Contents

Fluorine-containing Heterocycles. Part IV. Electrochemical Fluorination of Heterocyclic Compounds

GEORGII G. FURIN

Contributors

Numbers in parentheses indicate the pages on which the author's contribution begins.

Gabriela Cormos (205), Victor Papilian Faculty of Medicine, Lucian Blaga University, Str. Pompeiu Onofreiu 2-4, RO-550166, Sibiu, Romania

E.S.H. El Ashry (1), Chemistry Department, Faculty of Science, Alexandria University, Alexandria, Egypt

Georgii G. Furin (239), Novosibirsk Institute of Organic Chemistry, Siberian Division of the Russian Academy of Sciences, 630090 Novosibirsk, Russia

A.A. Kassem (1), Chemistry Department, Faculty of Science, Alexandria University, Alexandria, Egypt

V.P. Litvinov (125), N. D. Zelinsky Institute of Organic Chemistry, Academy of Sciences, Moscow, Russia

Daniela Carmen Oniciu (205), Department of Chemistry, University of Florida, Gainesville, FL 32611, USA

E. Ramadan (1), Chemistry Department, Faculty of Science, Alexandria University, Alexandria, Egypt

Ioan A. Silberg (205), Department of Organic Chemistry, Babes-Bolyai University, Str. Arany Janos 11, RO-400028, Cluj-Napoca, Romania

Preface

Volume 90 of Advances in Heterocyclic Chemistry contains four chapters and the indexes. The book commences with Part II of "Applications of Microwave Irradiation for Accelerating Reactions in Heterocycles." This continues Part I, which was published in Volume 88 of Advances in Heterocyclic Chemistry in 2005. Whereas Part I dealt with 3-, 4- and 5-membered heterocycles, the present Part II deals with 6- and 7-membered and spiro and fused heterocycles. Parts I and II have both been contributed by E. S. H. El Ashry, A. A. Kassem and E. Ramadan of Alexandria University, Egypt, and make available the large amount of recent work in this expanding area.

The chemistry of thienothiophenes, discussed by V. P. Litinov of the Zelinsky Institute of Organic Chemistry, Moscow, Russia, in the second chapter reflects a large number of recent publications in this important field.

Phenothiazines have been increasingly applied in recent years for the synthesis of new materials with desirable electrical and structural properties. Syntheses of phenothiazines have been covered comprehensively by Ioan Silberg (University of Cluj), Gabriela Cormos (University of Sibiu, Romania) and Daniela Oniciu (University of Florida, USA).

The final chapter comprises Part IV of the series on fluorine-containing heterocycles written by Georgii Furin of Novosibirsk, Russia. Part IV complements Parts I, II and III, respectively, published in Volumes 86, 87 and 88 of Advances in Heterocyclic Chemistry.

Volume 90 of Advances in Heterocyclic Chemistry is an "index volume" and closes with the following indexes: Cumulative Index of Authors, Volumes 1–90, Cumulative Index of Titles, Volumes 1–90 and the Volume 90 Subject Index.

Alan R. Katritzky
Department of Chemistry
University of Florida
Gainesville, Florida

Microwave Irradiation for Accelerating Organic Reactions – Part II: Six-, Seven-Membered, Spiro, and Fused Heterocycles

E.S.H. El Ashry, A.A. Kassem and E. Ramadan

Chemistry Department, Faculty of Science, Alexandria University, Alexandria, Egypt

I. Introduction

The use of microwave irradiation (MWI) as a nonconventional source of energy, a consequence of converting electromagnetic energy, had become very attractive for its applications to chemistry and material processing. In organic synthesis, the potential

ADVANCES IN HETEROCYCLIC CHEMISTRY
VOLUME 90 ISSN: 0065-2725 DOI: 10.1016/S0065-2725(05)90001-9

of microwave (MW) as a tool for heating attracted much interest soon after the work of Gedye (86TL279) and Giguere (86TL4945) in 1986. The terminology for the introduction of MW for organic reaction enhancement (MORE) and/or MW-assisted organic synthesis (MAOS) enabled access or parallel synthesis of various classes of compounds in organic chemistry. Although in the beginning some obstacles were faced by chemists using this technology, their desire led to the development of methods for the concurrent use of MW. One of these achievements involves the performance of organic reactions under solvent-free conditions: dry media in open vessels. Moreover, equipment and reactors have been developed and have become commercially available.

Nowadays, MW activations are widely used in organic chemistry as shown by the increased number of publications. Available reviews include (91OPP683, 95AJC1665, 95T10403, 97CSR233, 97MI1, 98CSR213, 98CJC525, 98S1213, 99AJC83, 99JHC1565, 99MI1, 99MI2, 99MI3, 99T10851, 00CSR239, 00MI1, 01MI1, 01MI2, 01T4365, 01T9199, 01T9225, 02ACR717, 02MI1, 02MI2, 02MI3, 02T1235, 03MI1, 03MI2, 04H903, 05AHC1).

The rapid expansion and popularity of assisting a wide range of organic reactions by exposure to MW have been accompanied by achieving reactions under solvent-free conditions, reducing reaction times, and increasing the yield of products and even selectivity. Moreover, in addition to the economic impact, there are additional advantages such as the use of noncorrosive, inexpensive, and environment-friendly catalysts, thus leading to eco-friendly approaches known as ''green chemistry''. All these have attracted our attention to review the available literature on the role of MW in the field of heterocyclic chemistry, but owing to the increased number of publications led us first to publish ''Microwave Irradiation for Accelerating Organic Reactions. Part I: Three, Four and Five Membered Heterocycles'' in a former volume (05AHC1). This new chapter will be the second part including six-, seven-membered, spiro, and fused heterocyclic ring systems. Our survey of the literature on the synthesis and reactions of these heterocycles has been divided according to the number of heteroatoms in the heterocycles. The fused heterocycles are located according to the heterocycle that was built under MWI or as a reaction of these heterocycles acting as precursors. Each type is reviewed by first presenting their methods of preparation of the desired ring followed by its reactions. Heterocycles having either fused benzene or other heterocyclic rings have been located under a separate title when enough literature has been reported.

II. Heterocycles with One Heteroatom

A. Pyrans

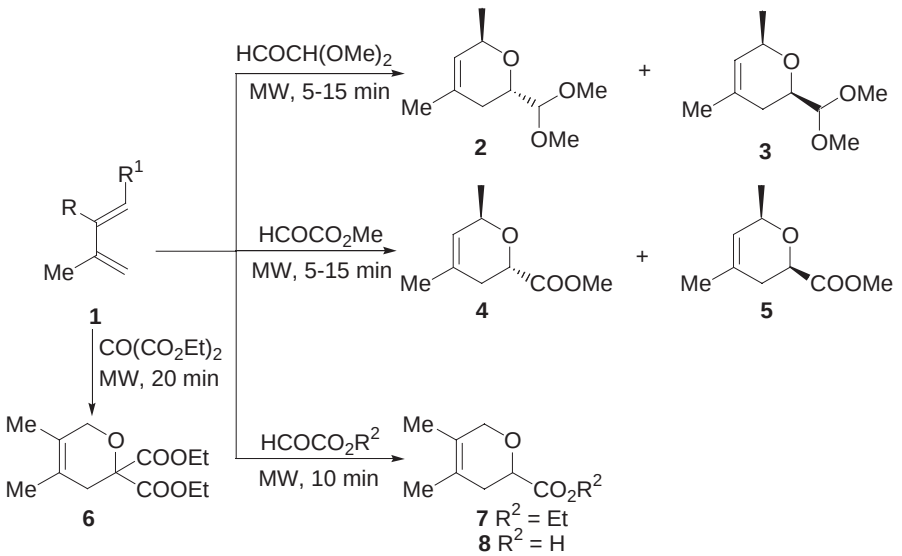
A large acceleration of some difficult Diels–Alder reactions was promoted under MWI on a graphite support (91TL1723, 96LA743). Thus, hetero Diels–Alder reactions of glyoxal monoacetal and methyl glyoxylate with 2-methyl-1,3-pentadiene **1** ($R = H$; $R^1 = Me$) have been carried out under pressure in an MW oven to give a

mixture of *cis*- and *trans*-isomers **2**–**5** in 54–96% yields after irradiation for 5–15 min. Compared to the conventional methods, reaction times were dramatically reduced and degradation as well as polymerization was avoided (91TL1723). 2,3-Dimethyl-1,3-butadiene **1** (R = Me; R^1 = H) reacted with ethyl mesoxalate without a catalyst under MWI for 20 min to give the expected adduct **6** in 75% yield; conventional heating at 150 °C in a sealed tube required 4 h. The ethyl glyoxylate gave adduct **7** in 87% yield after MWI for 10 min in the presence of a catalyst ($ZnCl_2$). Similarly, glyoxylic acid as dienophile afforded adduct **8** in 54% yield (Scheme 1), but it has not been examined by conventional heating (96LA743).

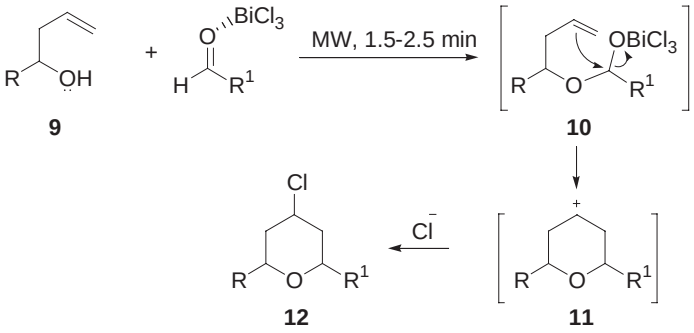
Reaction of several homoallyl alcohols **9** with aldehydes in the presence of bismuth trichloride under MWI for 1.5–2.5 min generated the respective 4-chlorotetrahydropyrans **12** in high yields (70–98%). Longer reaction times (4–7 h) were required at room temperature to achieve comparable yields. The reaction may proceed by the formation of hemi-acetal **10** whose cyclization gave **11** that could be attacked by the halide ion to give **12** (Scheme 2) (02SC1803).

Protection and deprotection of hydroxy groups with 3,4-dihydro-2*H*-pyran (DHP) are useful methods in synthesis. The tetrahydropyranylation has been conducted by mixing sulfuric acid adsorbed on finely ground silica gel with neat alcohols **13** and DHP. In most cases, the reactions were complete by simple mixing; however, gentle warming (1–2 min) by MW accelerated the reactions to give high yields (80–92%) and purities of **15** (99SC1013).

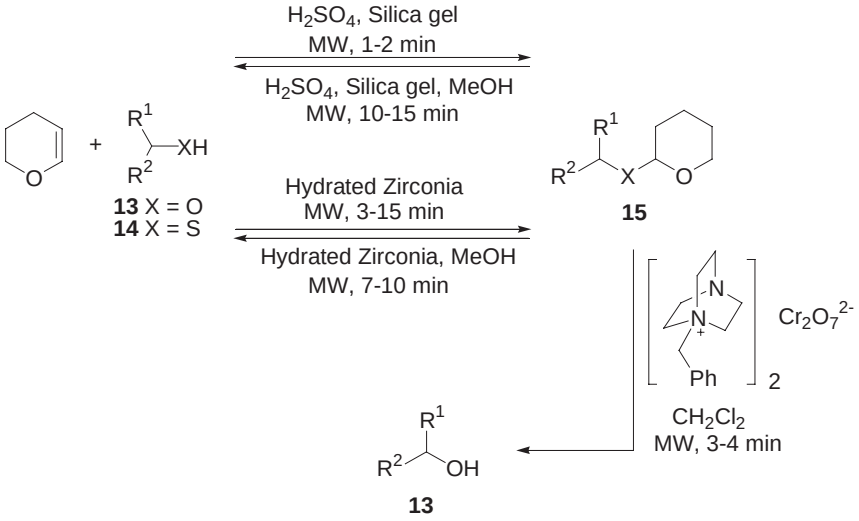
MW has also accelerated the tetrahydropyranylation of alcohols, phenols **13**, and thiols **14** in the presence of hydrated zirconia to give **15** in 80–98% yields within 3–15 min. This method has distinct advantages over the other existing methods, characterized by mild reaction conditions, absence of solvent, shorter reaction time, and easy as well as quick isolation of the products in excellent yields. The hydrated



Scheme 1



Scheme 2



Scheme 3

zirconia did not exhibit strong acidic sites, whereby the acid-sensitive groups were found intact under these conditions. Allylic and acetylenic alcohols could be protected without isomerization of double or triple bonds (02SC1549). An equally efficient reversal of tetrahydropyranylation, deprotection, took place under similar conditions, but in the presence of methanol, whereby the corresponding alcohols, phenols, and thiols were generated in 75–90% yields after irradiation for 7–10 min in a household MW oven (Scheme 3) (02SC1549). Similarly, deprotection was also completed in case of silica gel in the presence of methanol after irradiation for 10–15 min (99SC1013).

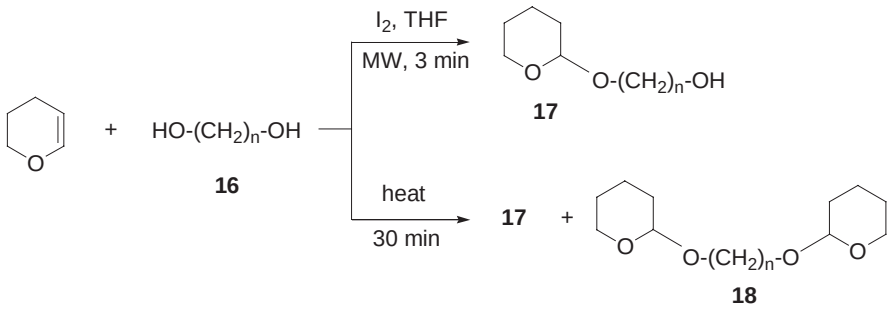
Selective cleavage of the tetrahydropyranyl group in **15** (X = O) was performed using 4-aza-1-benzyl azoniabicyclo[2.2.2]octane dichromate in dichloromethane to give the corresponding alcohols **13** in 84–96% yields by irradiation with MW for 3–4 min; no by-products were observed (Scheme 3). The method was claimed to be

very simple and efficient for the selective removal of the THP group without any change of the other functional groups in polyfunctional molecules (02SC611).

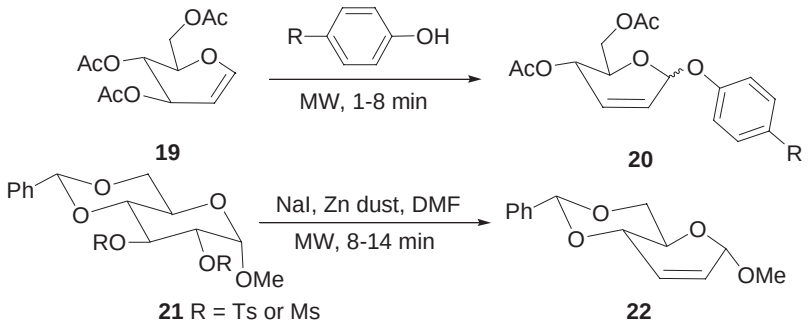
Selective monotetrahydropyranylation of symmetrical 1,*n*-diols **16** with DHP was achieved under MWI for 3 min in the presence of iodine as a catalyst to give the monoprotected diol **17** in 75% yield. The same reaction by conventional heating under reflux led to very poor selectivity whereby 43% yield of mono-THP-ether **17** and 51% yield of di-THP-ether **18** were obtained (Scheme 4) (01JOC1947).

Ferrier rearrangement of triacetyl glucal (**19**), upon reaction with phenols to give 2,3-unsaturated *O*-arylglucosides **20**, required a reflux in chlorobenzene for several hours. The MORE enabled a rapid access to **20** in 72–83% yields within 1–8 min, in the absence of a solvent (Scheme 5). The stereoselectivity and yields are fairly comparable with that under thermal conditions, but the reaction time was reduced by several fold (94SC2097).

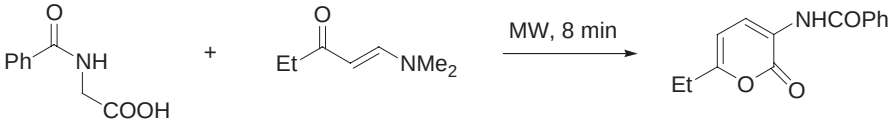
Unsaturated glycosides, versatile intermediates in the synthesis of a great number of natural products and in Diels–Alder reactions, were prepared by reacting *vicinal* di-*O*-sulfonates with sodium iodide and zinc dust in dimethylformamide (DMF) under MWI. The conversion was successful with different glycosides in the gluco and galacto series. Thus, glucosides **21** required 8–14 min to give high yields (88–89%) of **22**, while lower yields (35–53%) were obtained by conventional heating for 2–4 h (Scheme 5) (93TL8407).



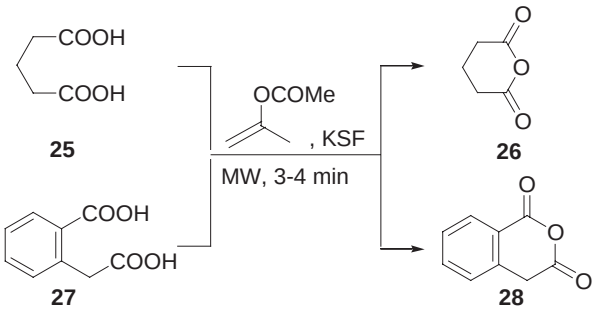
Scheme 4



Scheme 5



Scheme 6



Scheme 7

Pyranone **24** was prepared in 98% yield by the reaction of hippuric acid with enaminone **23** under MWI for 8 min (Scheme 6) (04JCR(S)174). The reaction required 4 h heating under reflux in acetic anhydride to give a 70% yield.

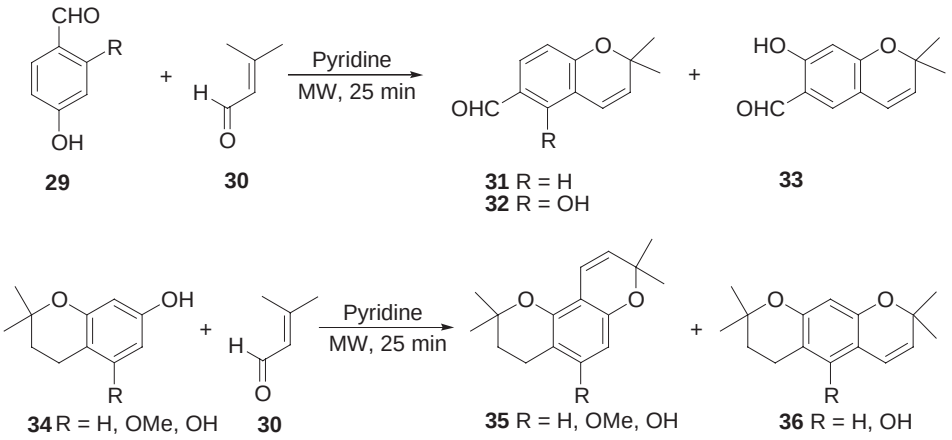
MWI of dicarboxylic acids **25** and **27** with isopropenyl acetate in the presence of KSF for 3–4 min gave the anhydrides **26** and **28** in 48% and 80% yields, respectively (Scheme 7) (93SC419).

Oxidation of the cyclic sulfide 4-oxothiophene to the respective sulfoxide 4-oxothiophenesulfoxide was achieved by heating with iron(III)nitrate impregnated on montmorillonite K_{10} clay in methylene chloride for 12 h to give a 79% yield. Much faster reaction took place using ''clayfen'' under MWI to give 83% yield within 60 min (98SC4087).

B. Benzopyrans

Subjecting 4-hydroxybenzaldehyde **29** (R = H) to 3-methyl-2-butenal (**30**) in the presence of pyridine in a sealed glass tube to MWI for 25 min yielded chromene **31** in 68% yield. Under similar conditions, the condensation of 2,4-dihydroxybenzaldehyde **29** (R = OH) with **30** gave chromenes **32** and **33** in 49% and 12% yields, respectively (99BCJ259).

Similarly, 2,2-dimethyl-7-chromanols **34** (R = H, OH) reacted with **30** to give the isomeric chromenes **35** (21–45%) and **36** (23–28%) but chroman **34** (R = OMe) gave only the respective chromene **35** (R = OMe) in 73% yield (Scheme 8), whose formation took nearly 48 h under conventional thermal conditions at 140 °C (99BCJ259).



Scheme 8

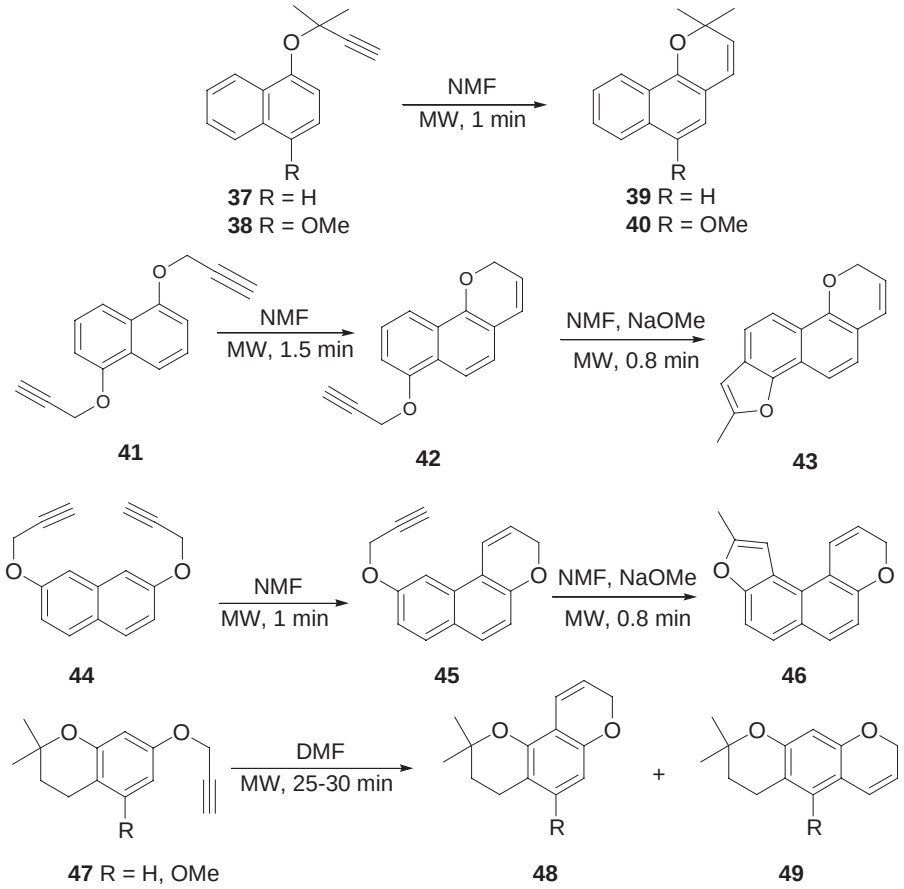
Irradiation of propargyl naphthyl ethers in *N*-methylformamide (NMF) either alone or in the presence of sodium methoxide in an MW oven gave naphthopyrans or naphthofurans, respectively, in good to excellent yields. Thus, conversion of 1,1-dimethylpropargyl naphthyl ethers **37** and **38** proceeded smoothly to produce 2,2-dimethylnaphtho[1,2-*b*]pyrans **39** (92%) and **40** (96%), respectively, by MWI for 1 min. Under conventional heating, ether **38** produced **40** in lower yield (80%) and longer reaction time (2 h) (Scheme 9) (96JCR(S)338).

In the case of *bis*-propargyl naphthyl ethers **41** and **44**, propargyloxynaphthopyrans **42** and **45** have been isolated, which could then be transformed by NaOEt to furonaphthopyrans **43** (81%) and **46** (85%), respectively (96JCR(S)338). Under MWI in DMF, compounds **47** were transformed into chromenes **48** and **49** in low yields (22–32%) within 25–30 min. However, thermal cyclization of **47** in dry xylene at 170 °C for 48 h gave only the angular chromenes **48** in 76–83% yields (Scheme 9) (97T12621). The later example is a case of greater selectivity by conventional heating than by MWI.

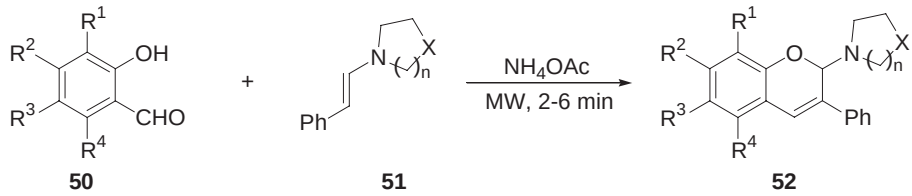
A one-pot synthesis of isoflav-3-enes **52** was achieved by the reaction of substituted salicylaldehydes **50** with enamines **51** in the presence of a catalytic amount of ammonium acetate under MWI for 2–6 min in 71–88% yields. The reaction of **50** with **51** in benzene under an inert atmosphere produced **52** in 45–55% yields (Scheme 10) (98JOC8038).

Intramolecular Diels–Alder cycloaddition in triene **53** was achieved by heating with toluene in a sealed glass tube in an MW oven for 2.5 h to afford (1*S*)(2*R*)(5*R*)(6*R*) (8*R*)(9*S*)(12*R*)-1,7,7-trimethyl-6-methoxy-4-oxatetracyclo[7.3.1.0]-10-tridecen-3-one (**54**) in 97% yield (93JOC2186). Compound **54** is a precursor in the synthesis of the sesquiterpene (+)-longifolene.

The pentacyclic compound **55**, supported on Florisil (activated magnesium silicate), was rearranged into **57** in 93% yield under MWI for 10 min. Conventional heating of **55**, up to 100 °C for 4 h, did not cause any change, but when it was supported on Florisil and heated for 5 h, it gave compounds **56** and **57** in 60% and



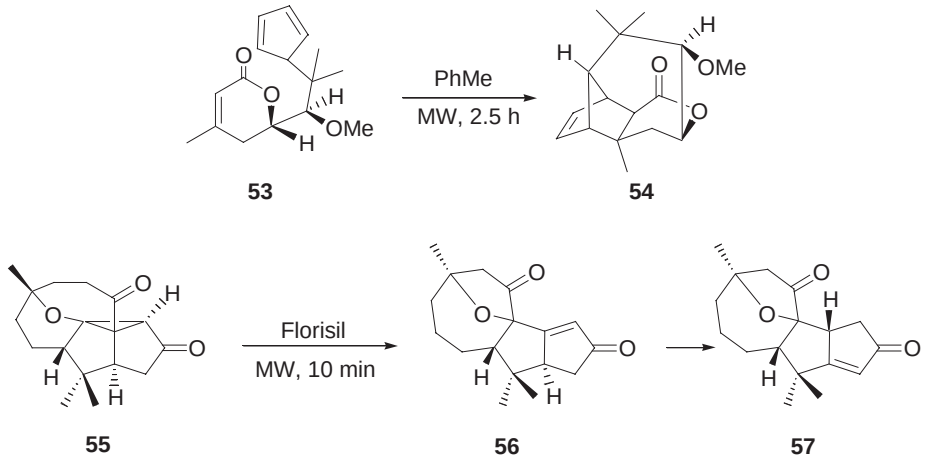
Scheme 9



Scheme 10

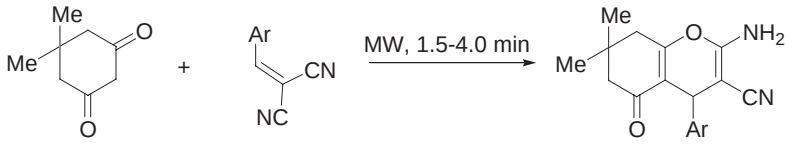
40% yields, respectively. Compound **56** had been suggested as an intermediate in the transformation of compound **55** to **57**, as proved by the transformation of **56**, supported on Florisil, to **57** by heating for 3 h (Scheme 11) (99T3209).

When a mixture of 5,5-dimethyl-1,3-cyclohexanedione (**58**) and arylidenemalononitrile **59** was subjected to MWI for 1.5–4.0 min under solvent-free condition, it gave



53 54 55 56 57

Scheme 11



58 59 60

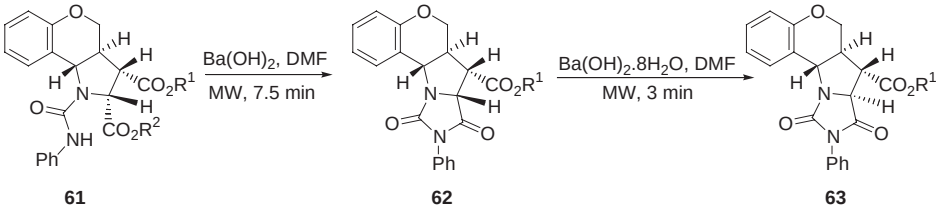
Scheme 12

2-amino-4-aryl-7,7-dimethyl-2,6,7,8-tetrahydro-5-oxo-4*H*-benzopyran-3-carbonitrile **60** in 89–96% yields (Scheme 12) (02SC2137).

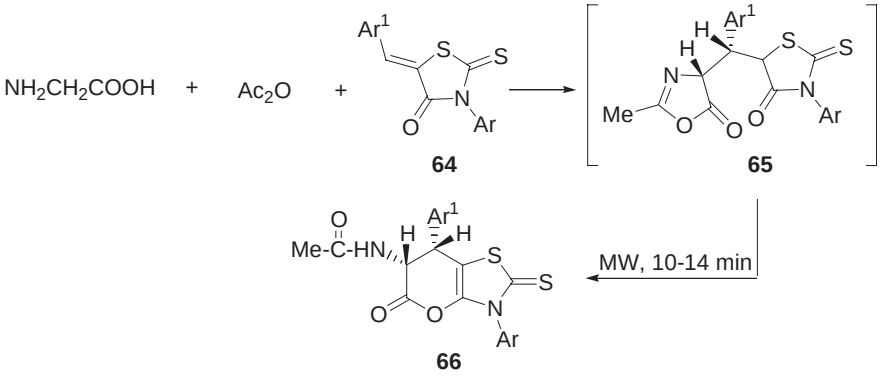
C. Fused Heterocycles Incorporating Pyran Rings

Intramolecular cyclization of **61** to give hydantoins **62** in 78–96% yields, in the presence of $Ba(OH)_2 \cdot 8H_2O$ as catalyst required 9–24 h, while under MWI (30 W) in DMF, compounds **62** were obtained in 81–91% yields within 7.5 min. Under lower power (20 W) and shorter reaction time (3 min), a mixture of the kinetic product **62** and the thermodynamic product **63** was obtained in 43–48% and 52–57% yields, respectively (Scheme 13). Moreover, epimerization of **62** took place in the presence of *N*,*N*-diisopropylethylamine in DMF under thermal conditions within 3 h to give 85–86% yields of **63**, while the epimerization required 3 min under MWI in the presence of $Ba(OH)_2 \cdot 8H_2O$ in DMF to give a comparable yield (98TL3379).

A diastereoselective synthesis of pyranothiazoles **66** was achieved in a one-pot reaction of the three components glycine, acetic anhydride, and 5-arylidenerhodanines **64** by employing MWI under solvent-free conditions. The yields of **66** were 73–86%, compared to 35–43% obtained from conventional heating. The formation of pyranothiazoles **66** occurred through the cyclization of Michael adducts **65**



Scheme 13



Scheme 14

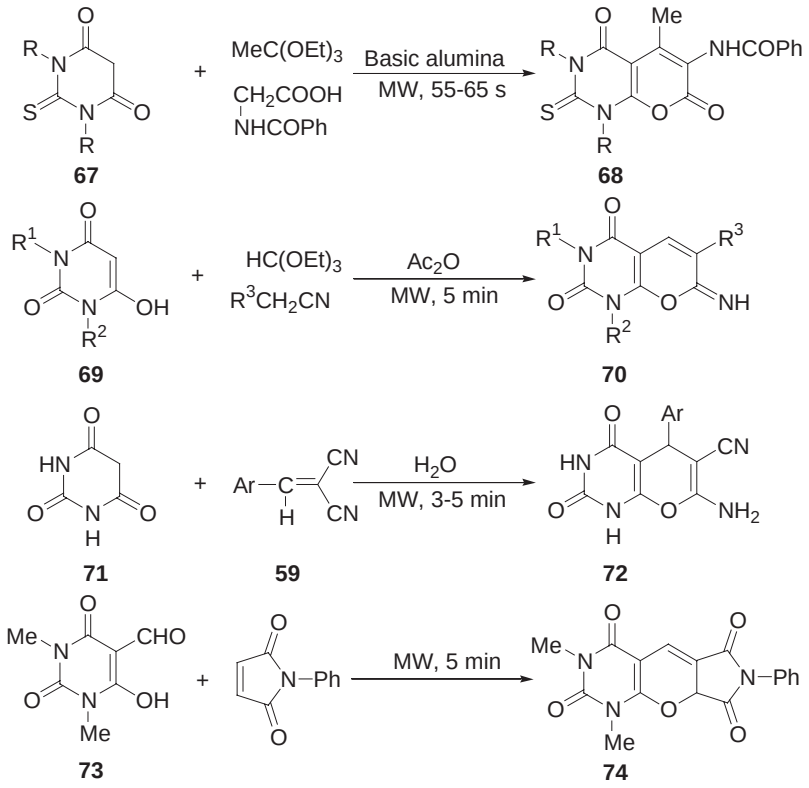
(Scheme 14). This ring closure was found to be highly diastereoselective in favor of the *cis*-isomers where the diastereomeric ratio of the *cis*/*trans* was 96:4 by using MWI whereas by conventional heating it was 57:43, as determined by ^{1}H-NMR spectroscopy. The higher diastereoselectivity toward the *cis*-isomers under MWI was explained by the formation of a more dipolar activated complex intermediate leading to the formation of *cis*- rather than *trans*-isomers, because MWI favors the reactions occurring *via* the more dipolar activated complex (03S2395).

Microwave assisted a simple and efficient route for the synthesis of pyranopyrimidines in excellent yields. Thus, cyclocondensation of 1,3-diarylthiobarbituric acids **67** with hippuric acid and triethyl orthoacetate on basic alumina was carried out under MWI to give pyranopyrimidines **68** in 92–95% yields within 55–65 s. More than 5 h were required under conventional heating at 110–120 °C to afford 60–70% yields (Scheme 15) (00JCR(S)586).

Cycloaddition of barbituric acids **69**, triethyl orthoformate, and malononitrile or alkylnitriles in the presence of acetic anhydride under MWI for 5 min afforded pyrano[2,3-*d*]pyrimidines **70** in excellent yields (75–85%) (04SL283).

Arylidenemalononitriles **59** reacted with barbituric acid **71** in water under MWI, without catalyst, for 3–5 min to give pyranopyrimidines **72** in good yields (86–94%) (Scheme 15) (04SC1295).

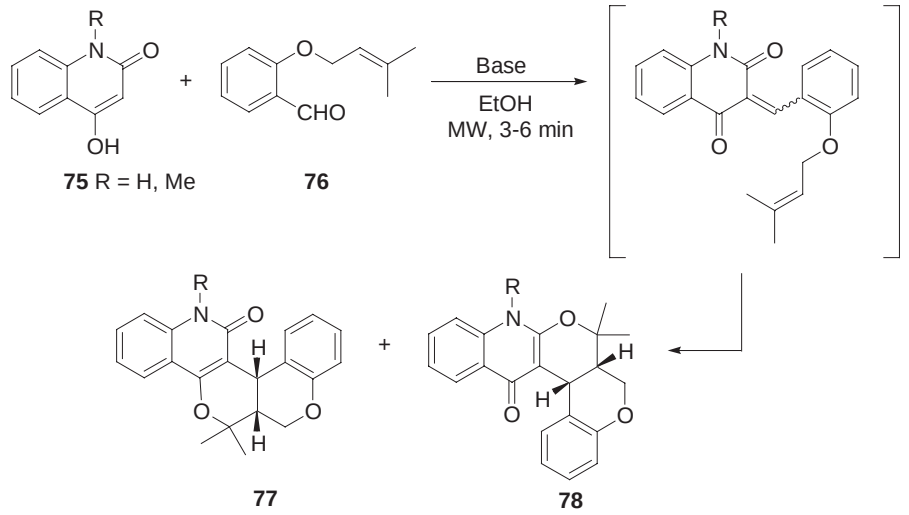
The pyrano[2,3-*d*]pyrimidine derivative **74** was obtained in 90% yield by reacting *N*,*N*-dimethyl-5-formyl barbituric acid **73** with *N*-phenyl maleimide in the solid state under MWI (04TL2405).



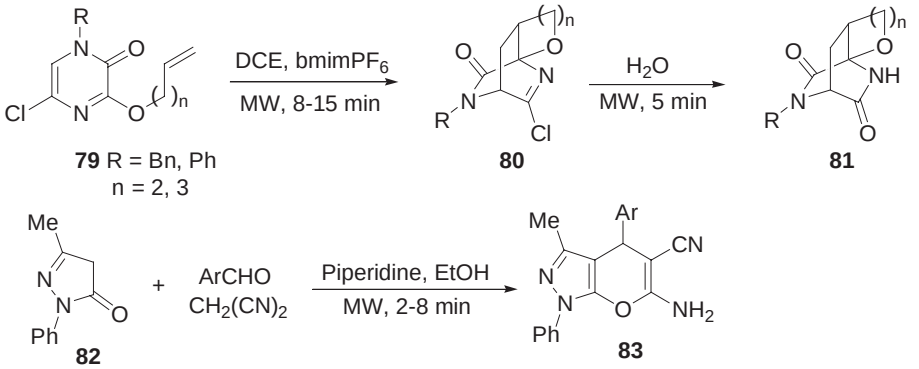
Scheme 15

The angular **77** and linear pyranoquinolinone **78** (R = H) derivatives were prepared *via* an intramolecular domino Knoevenagel hetero Diels–Alder pathway by the reaction of 4-hydroxy-1,2-dihydro-2-quinolinone (**75**) with 2-(3-methyl-2-butenyloxy)benzaldehyde (**76**) in the presence of ethylene diammonium diacetate (EDDA) in refluxing ethanol for 10 h. Both the keto and lactam carbonyls were involved in the cycloaddition to give a 53:47 ratio of **77** to **78** in 60% overall yield. The use of triethylamine or piperidine in place of EDDA afforded 50% and 67% yields, respectively, with no significant change in chemoselectivity. A better chemoselectivity and improved yields were achieved by performing the reaction using MWI and EDDA or triethylamine that gave 78% and 70% yields with a ratio 97:21 and 82:18, respectively, while using piperidine afforded a 79% yield with higer chemoselectivity (88:12) (Scheme 16) (02T8957). Similarly, **75** (R = Me) with **76** under MWI employing piperidine as base afforded the corresponding mixture of **77** and **78** in 66% yield with high selectivity (86:14) (02T8957).

Under MWI, intramolecular hetero Diels–Alder reactions of pyrazinones **79** in the presence of 1-butyl-3-methylimidazolium hexafluorophosphate (bmimPF_6) in 1,2-dichloroethane (DCE) gave imidolyl chloride **80** within 8–15 min. The cycloaddition products **80** were moisture sensitive and rapidly hydrolyzed to the more stable



Scheme 16



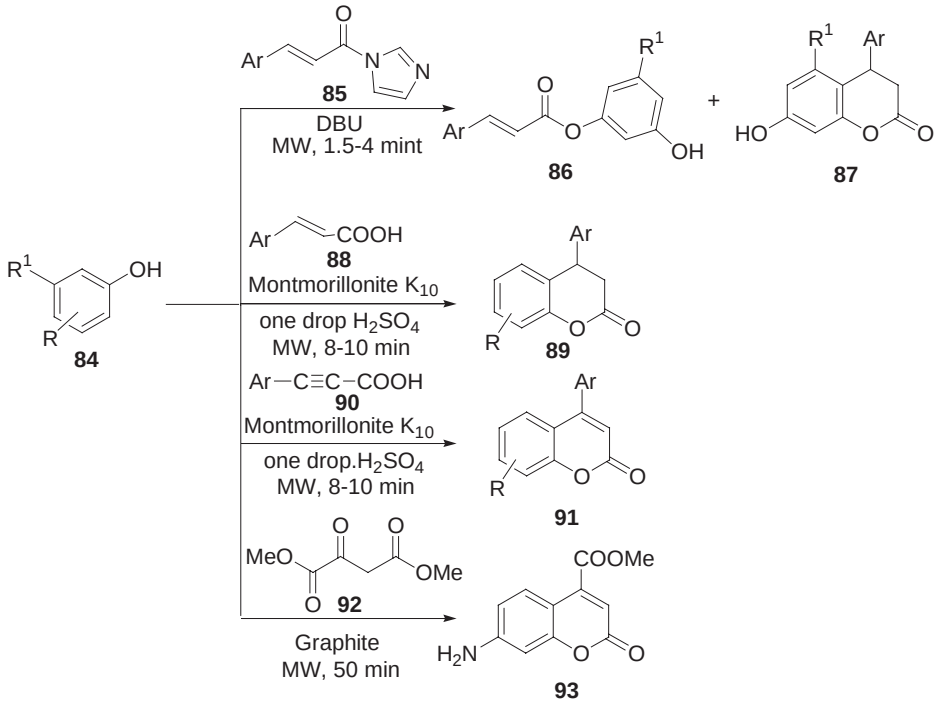
Scheme 17

bislactams **81** in 57–77% yields by the addition of water and under MWI for 5 min (02JOC7904). Conventional thermal conditions required 1–2 days of reflux in chlorobenzene to give **80**, which required 18 h stirring in chloroform in an open atmosphere to give **81** in comparable yields (Scheme 17) (02TL447).

MWI of a mixture of the pyrazolin-5-one **82**, aromatic aldehydes, and malononitrile in the presence of piperidine as a catalyst for 2–8 min gave **83** in 61–91% yields (Scheme 17) (02SC3363).

D. Coumarins

A mixture of 3-hydroxy phenolic derivatives **84** (R = OH) and *N*-cinnamoylazoles **85** in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) was subjected to



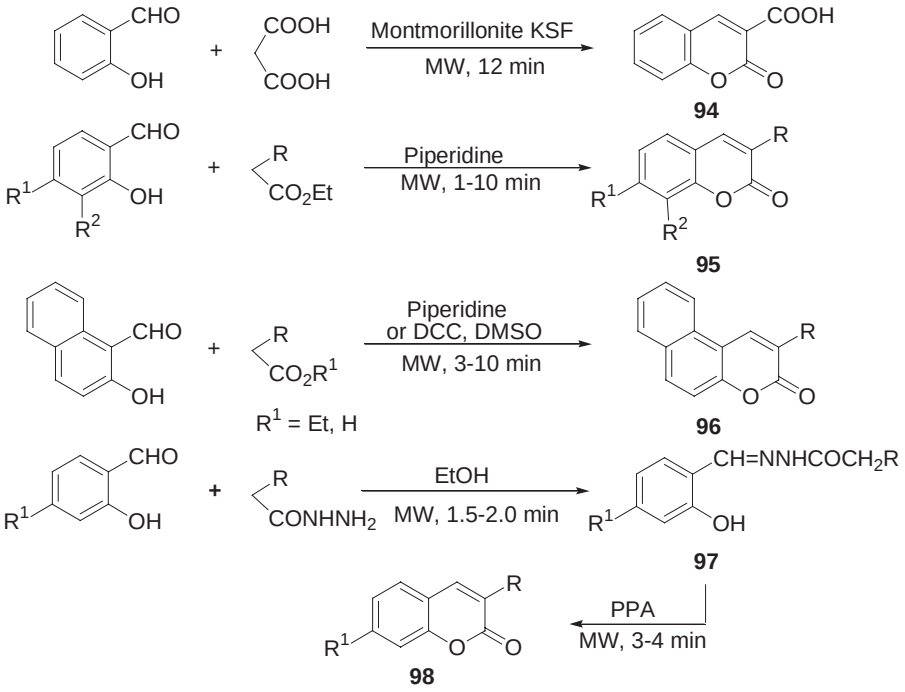
Scheme 18

MWI without a solvent to give a mixture of aryl cinnamoates **86** and chromanones **87**. The ratio of the products depended on the irradiation time; a longer time led mainly to the chromanones. When the irradiation time was 1.5 min, the ratio of **87**:**86** was 0.15, but increasing the time to 3–4 min changed the ratio to 2.1–11.8 (Scheme 18) (01JCR(S)78).

3,4-Dihydro-4-arylcoumarins **89** can be obtained in a single step and good yields (65–85%) by irradiating a mixture of phenols **84** and cinnamic acids **88** impregnated on activated montmorillonite K_{10} clay for 8–10 min. Similarly, 4-arylcoumarins **91** were prepared in moderate yields (55–69%) from phenols **84** and 3-arylpropynoic acids **90** (Scheme 18) (98JCR(S)280).

The synthesis of methyl 7-aminocoumarin-4-carboxylate (**93**) was reported by heating *m*-aminophenol (**84**) (R = H, $R^1 = NH_2$) with dimethyloxalacetate (**92**) at 130 °C for 2 h (84CPB3926). The yield of coumarin under such conditions was variable, sometimes low and accompanied by colored impurties that were very difficult to eliminate, even by column chromatography and recrystallization. This procedure in a focused MW reactor gave **93** in a similar yield (39%), but in less time (85 min). Moreover, a better yield (44%) and a shorter time (50 min) were achieved by irradiation of a mixture of **84** and **92**, adsorbed on graphite (Scheme 18) (01TL2791).

Condensation of salicylaldehyde with malonic acid in the presence of montmorillonite KSF clay as a catalyst gave, under MWI for 12 min (Scheme 19),



Scheme 19

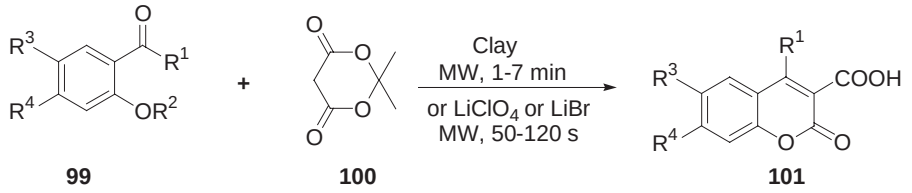
3-carboxycoumarin **94** in 60% yield instead of 89% after 24 h of heating under reflux (02S1578).

The condensation of salicylaldehyde or its derivatives with various derivatives of ethyl acetate in the presence of piperidine led to the synthesis of coumarins **95** in 55–94% yields under solvent-free conditions using MWI. Similarly, the benzo analogs **96** were prepared in 75–82% yields from 2-hydroxy-1-naphthaldehyde within 3–10 min (Scheme 19) (98JCR(S)468). However, naphtho[2,1-*b*]pyran-3-ones **96** were prepared in 58–67% yields from the same aldehyde and substituted acetic acids under MWI for 6–8 min but in the presence of DCC and using DMSO as a solvent (Scheme 19) (97JCR(S)178).

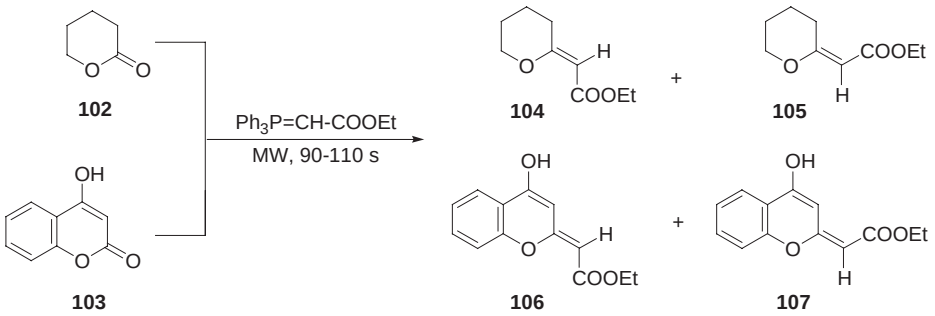
Condensation of *o*-hydroxyarylaldehydes with hydrazides in ethanol was carried out under MWI for 1.5–2.0 min to give the corresponding hydrazones **97** in 86–95% yields, the cyclization of which was achieved using polyphosphoric acid (PPA) under MWI for 3–4 min to afford coumarins **98** in 55–68% yields (Scheme 19) (97IJC(B)175).

Knoevenagel condensation under focused MWI for 1–7 min of 2-hydroxy or 2-methoxy-substituted benzaldehydes or acetophenones **99** and Meldrum's acid (**100**) using a solid catalyst combination of natural kaolinitic clay or Envirocats (EPZG, EPZ10) gave 3-carboxycoumarins **101** in 55–97% yields (Scheme 20) (99MI4).

Also, the condensation of *o*-hydroxy-ketones **99** with **100** can be achieved in the presence of a catalytic amount of $LiClO_4$ or LiBr under MWI to give **101** in 75–90%



Scheme 20



Scheme 21

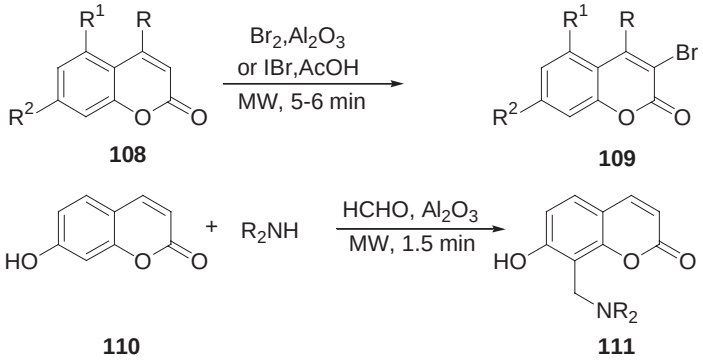
yields within 50–120 s (Scheme 20); this condensation did not take place in the absence of MW or catalyst even after stirring for 3 h (02JCR(S)40).

Phosphoranes failed even in refluxing toluene to undergo Wittig olefination of lactones, unlike other carbonyl compounds. However, under MWI for 90 s, lactone **102** reacted with ethoxycarbonyl methylidene triphenyl phosphorane on mixing a 1:1.2 ratio to give **104** and **105**. Similarly, **103** gave **106** and **107** after MWI for 110 s, each as a mixture of isomers in 80–82% yields. The *E*/*Z* product ratio was 20/80 for **104** and **105** and 15/85 for **106** and **107** (Scheme 21) (99TL165).

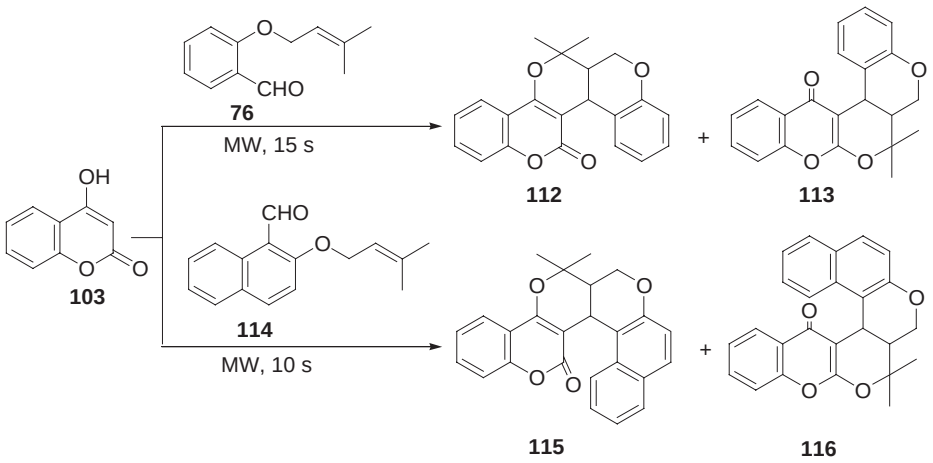
Bromination of coumarins **108** to give bromocoumarins **109** has been carried out by using bromine in acetic acid, *N*-bromosuccinimide, or copper(II) bromide adsorbed on alumina, but the drawbacks were the low yields of the products and the use of drastic conditions. However, MWI accelerated this bromination with either bromine adsorbed on neutral Al_2O_3 in a dry medium or iodine monobromide in acetic acid. Bromination took place selectively at the double bond in coumarins to give **109** in 63–92% yields (Scheme 22) (96SC887).

Aminomethylation of 7-hydroxycoumarin (**110**) with a secondary amine, formaldehyde, and acidic alumina gave **111** in 62–100% yields within 1.5 min upon irradiation by MW (Scheme 22) (00SC69).

Chemoselectivity has been achieved when MWI was used for the synthesis of pyrano[3,2-*c*]coumarins through intramolecular domino Knoevenagel hetero Diels–Alder reactions of 4-hydroxycoumarin (**103**). Thus, when the reaction of **103** with butenyloxyaldehyde **76** was carried out under MWI for 10–15 s, cycloadducts **112** and **113** were produced in 93:7 ratio, respectively, with 82% overall yield; and the cycloadducts **115** and **116** were obtained in a ratio 95:5, respectively, in 92%



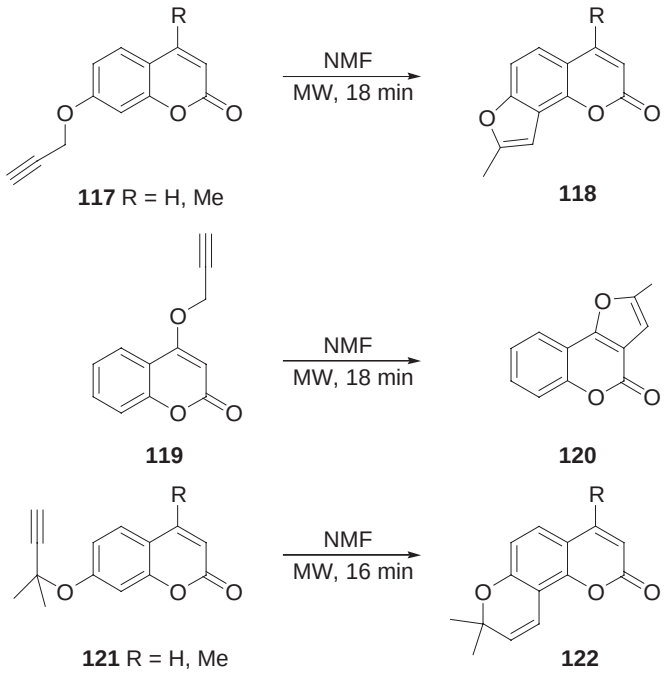
Scheme 22



Scheme 23

overall yield. On the other hand, the same reaction was carried out in refluxing ethanol for 4 h to afford pyrano[3,2-*c*]coumarin **112** and pyrano[2,3-*b*]chromone **113** in a ratio 68:32, respectively, in 57% overall yield; and the benzo analog **114** gave the cycloadducts **115** and **116** in a ratio 80:32, respectively, in 75% overall yield. The chemoselectivity and reduced reaction times were apparent (Scheme 23) (02T997).

Propargyl ethers of 7-hydroxy-, 4-methyl-7-hydroxy-, and 4-hydroxycoumarins **117** and **119** have been efficiently rearranged to furocoumarins **118** and **120** in 62–70% yields under MWI in NMF as a solvent. Under similar conditions, propargyl coumarin ethers **121** gave pyranocoumarins **122** in 71–82% yields (Scheme 24). The rearrangements required 16–18 min of MWI, while at boiling temperature (195–220 °C) in various solvents, such as *N*,*N*-diethylaniline or *N*-ethylformamide, they took place with lower yields (8–70%) and longer time (6–14 h) (98JCR(S)800).



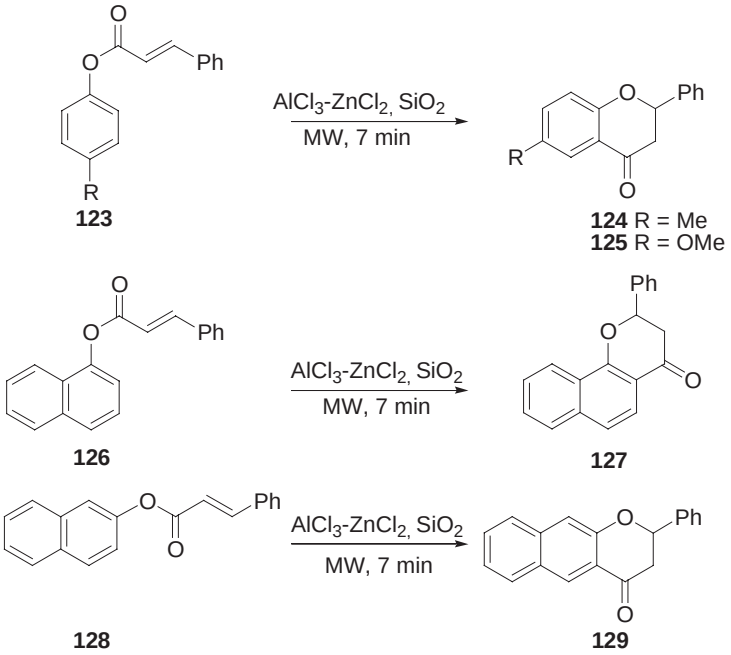
Scheme 24

E. Flavones

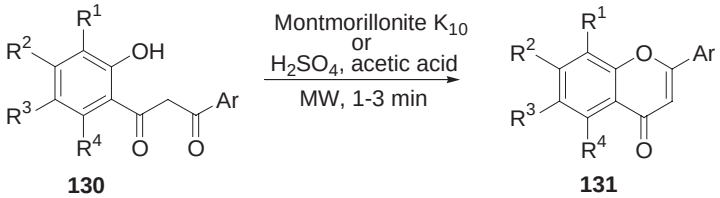
When the cinnamoyl esters **123** (R = Me or OMe), **126**, and **128** were supported with a $AlCl_3$–$ZnCl_2$ mixture on silica gel and exposed to MWI for 7 min, the resulting *ortho*-hydroxy rearranged products were spontaneously cyclized by intramolecular conjugate addition of the phenolic hydroxyl group to the α,β-unsaturated system to afford the flavanones **124**, **125**, **127**, and **129**, respectively, in excellent yields (73–87%) (Scheme 25) (99JCR(S)574).

o-Hydroxydibenzoylmethanes **130** were adsorbed on montmorillonite K_{10} and the mixture was irradiated for 1–1.5 min in an MW oven to give flavones **131** in 72–80% yields (98JCR(S)348). The MWI also caused the cyclization of **130** in the presence of conc. H_2SO_4 in acetic acid within 3 min to give flavones **131** in 60–81% yields (Scheme 26) (03H2775).

Diels–Alder reaction of (*E*)- and (*Z*)-3-styryl-chromones with *N*-methyl and *N*-phenyl maleimide as dienophiles under solvent-free conditions using MWI gave the corresponding cycloadducts in a stereoselective manner. Thus, the (*Z*)-isomer **132** gave stereoselectively *endo*-cycloadduct **133** in good yield (> 70%), when it was reacted with *N*-methyl maleimide. However, the reaction with *N*-phenyl maleimide gave the *endo*-cycloadduct **134** in 50–55% yields accompanied by a small amount of the *exo*-cycloadduct **135** (15–20%). This may be due to the low reactivity of *N*-phenyl maleimide and the isomerization of the (*Z*)-3-styryl-chromones **132** into



Scheme 25

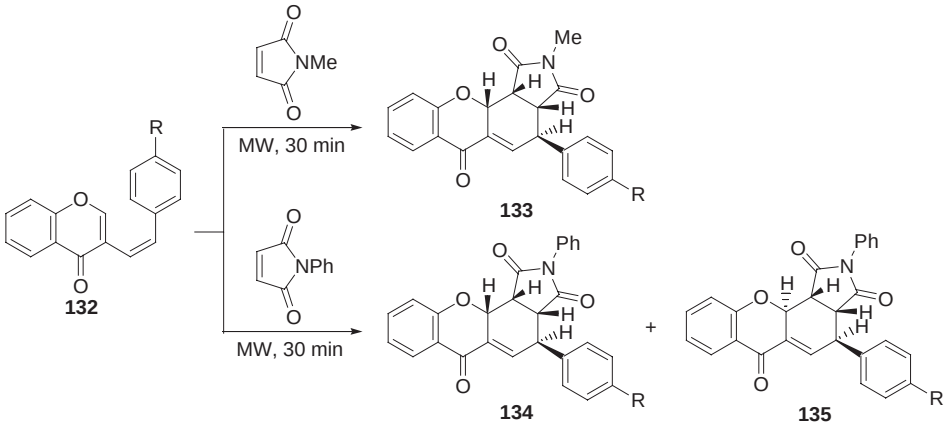


Scheme 26

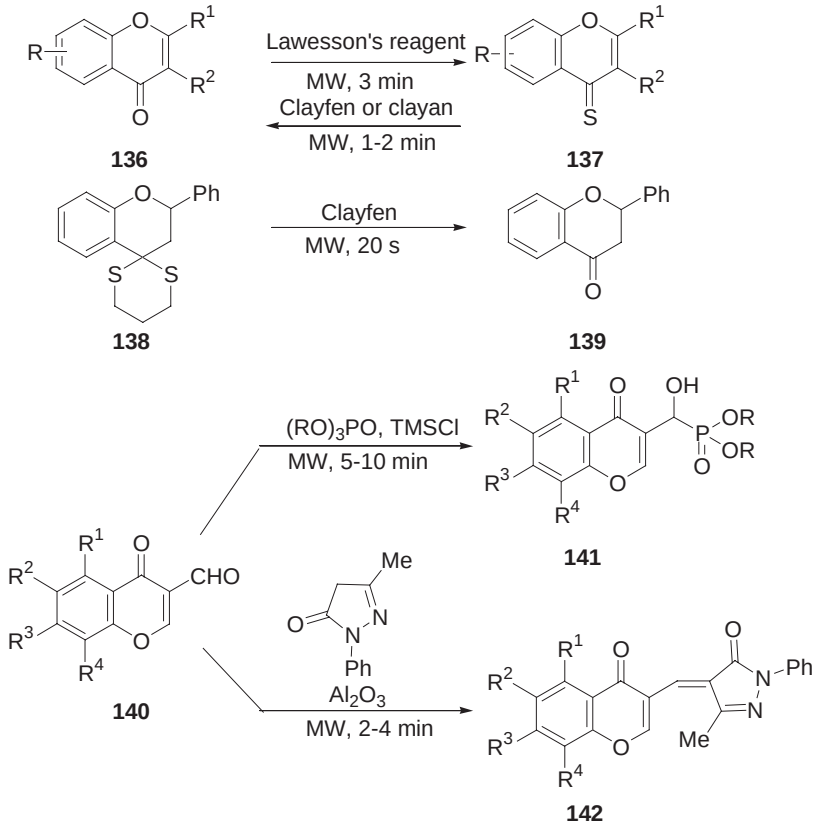
the corresponding (*E*)-isomer under MWI, the reaction of which gave the *exo*-cycloadduct **135** (Scheme 27) (03SL1415).

The naturally occurring plant phenolics, flavones, and isoflavones **136** that have an array of biological activities were transformed into their thio analogs **137** in 92–96% yields by using Lawesson's reagent [2,4-*bis*(*p*-methoxyphenyl)-1,3-dithiaphosphetane 2,4-disulfide] under solvent-free conditions and irradiation by MW for 3 min (Scheme 28) (99OL697). Under conventional heating in dry benzene or xylene for 2–25 h, compounds **137** were obtained in moderate yields (38–84%) by using phosphorous pentasulfide (82T993).

There are several reagents developed for the transformation of thioketones to ketones, but they have limitations such as the use of stoichiometric amounts of the oxidants, which often are inherently toxic, required long reaction time, or involved



Scheme 27



Scheme 28

tedious procedure. The use of supporting reagents as either clayfen or clayan under MWI for 1–2 min converted thioketones **137** rapidly into their parent ketones **136**; yields (88–95%) were comparatively higher in the case of clayfen (99SC1333). Similarly, the deprotection of the dithio ketal **138** was readily carried out on clayfen under MWI within 20 s to give **139** in 90% yield (Scheme 28) (97TL2623).

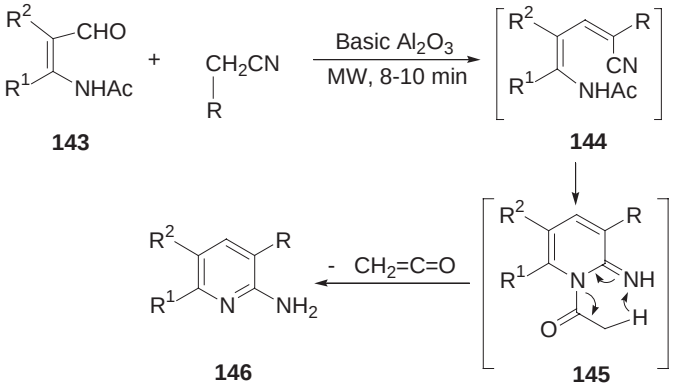
Various dialkyl-1-(chromon-3-yl)-1-hydroxymethylphosphonates **141** have been synthesized by the condensation of substituted 4-oxo-(4*H*)-1-benzopyran-3-carboxaldehydes **140** with trialkylphosphites mediated by TMSCl that acts as a trapping agent and prevents the intramolecular dealkylation, under solvent-free conditions using MWI. Compounds **141** were obtained in 70–95% yields within 5–10 min (02SC2633).

Condensation of **140** with 3-methyl-1-phenyl-pyrazolin-5-(4*H*)-one was carried out on alumina support and under solvent-free conditions using MWI to give 3-methyl-4-[(chromon-3-yl)methylene]-1-phenyl-pyrazolin-5-(4*H*)-ones **142** in 59–87% yields within 2–4 min (Scheme 28). The same reaction in refluxing dioxane using a catalytic amount of triethylamine required 45 min to give lower yields (02SC497).

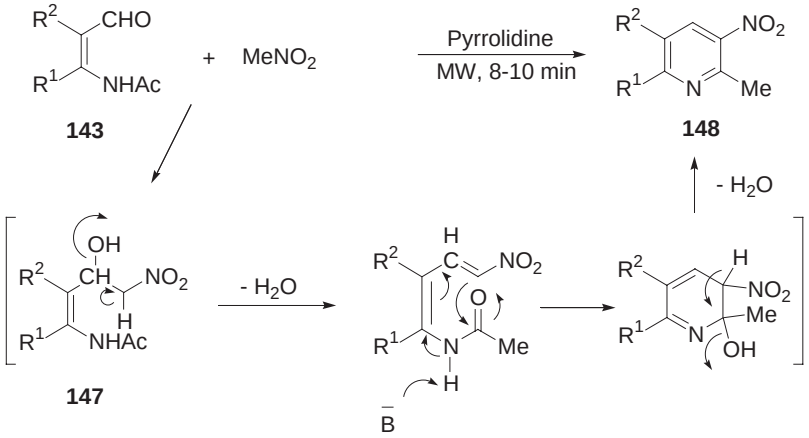
F. Pyridines

The *β*-formyl enamides **143** were condensed with cyanomethylenes under MWI in the presence of basic alumina in dry media to give excellent yields (81–88%) of the pyridine derivatives **146** within 8–10 min. The reaction has been envisaged to occur *via* Knoevenagel condensation of cyanomethylenes with **143** to give intermediate **144**, followed by intramolecular cyclization into **145**, which then underwent a hydride shift from the *N*-acetyl group to the imino group followed by the loss of ketene to give **146** (Scheme 29) (00TL3493).

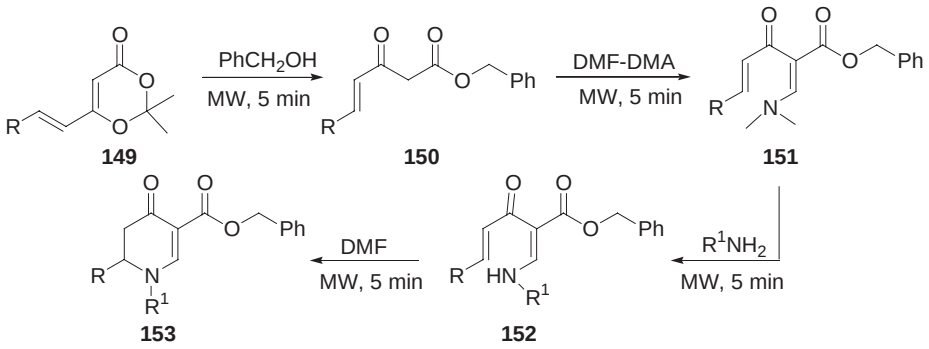
The base-catalyzed solid-phase condensation through a Henry reaction of *β*-formyl enamides **143** with nitromethane in the presence of pyrrolidine produced pyridine derivatives **148** in 80–90% yields under MWI for 8–10 min. The conventional heating in toluene for 8–10 h gave lower yields (62–74%). The mechanism



Scheme 29



Scheme 30

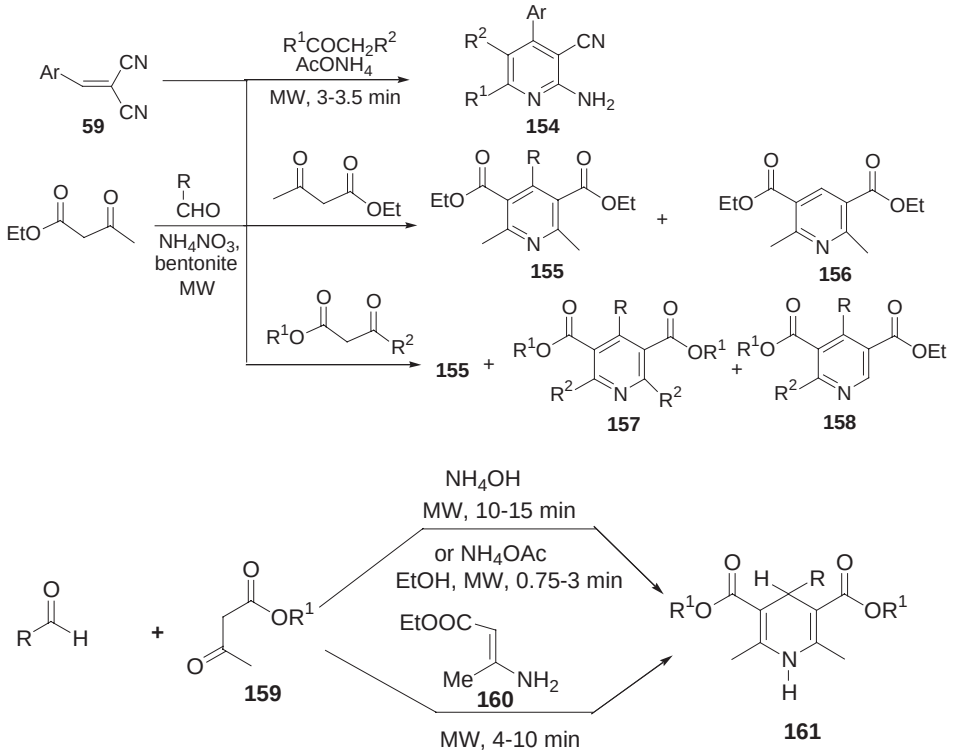


Scheme 31

involved a reaction of nitromethane with the formyl group of **143** to give the intermediate **147**, which underwent dehydration, followed by base-catalyzed cyclization and aromatization with loss of water to afford **148** (Scheme 30) (04SL1309).

Ring opening of 1,3-dioxin-4-one derivatives **149** by benzyl alcohol under MWI in a Synthewave system gave the expected benzyl esters **150** in quantitative yields, which upon reaction with dimethylformamide–dimethylacetal (DMF–DMA) gave the dimethylaminomethylene derivatives **151** in 40–80% yields. Treatment of **151** with amines under MWI gave compounds **152**, which upon MWI in DMF cyclized to give 1,6-disubstituted-4-oxo-1,4,5,6-tetrahydro-pyridine-3-carboxylic acid benzyl esters **153** in 54–86% yields (Scheme 31) (04SC345). The sequence from the adduct **149** to **153** was also performed with classical heating, but the reaction times were longer, yields were lower, and solvents were necessary (04SC345).

Derivatives of 2-amino-3-cyanopyridines **154** have been synthesized from the reaction of arylidenemalononitriles **59** with α-methylene ketones in the presence of ammonium acetate and traces of solvent under both classical heating for 5–6 h in



Scheme 32

refluxing benzene to give 46–69% yields, and in *o*-dichlorobenzene under MWI for 3–3.5 min to give 69–78% yields (Scheme 32) (98JCR(S)330).

A one-pot synthetic method for pyridines on a multigram scale was achieved from a condensation between 2 moles of a β-keto ester and 1 mole of aldehyde under MWI using bentonite clay as a support and ammonium nitrate as the source of ammonia and oxidant. However, good yields of C-4 substituted pyridines **155** could only be obtained when the aldehydes were aliphatic, but only 5% yield of **155** (R = Ph) and 75% yield of **156** were obtained when benzaldehyde was used. A number of 1,3-dicarbonyl compounds including β-keto esters were used as building blocks for the multicomponent Hantzsch synthesis (95T6511) whereby symmetrical **155** and **157** and nonsymmetrical pyridines **158** were synthesized (Scheme 32) (98TL1117).

Since the discovery of the pharmacological effects of the 1,4-dihydropyridines as calcium channel blockers, a great deal of work has been directed toward the synthesis of novel 1,4-dihydropyridines acting as calcium antagonists. The original Hantzsch dihydropyridine synthesis under conventional conditions has been carried out by heating aliphatic or aromatic aldehydes, a β-keto ester **159**, and ammonia for prolonged reaction times, 10 h or more, to afford **161** in moderate yields (58JA992, 49JA4003, 91TL3839). Moreover, the same reaction using ammonia in boiling acetic acid or alcohol gave moderate yields (47–77%) after long reaction times (8–24 h)

(Scheme 32) (64MI1, 01SC425). MWI has assisted the condensation of aldehydes with **159** (R^1 = Et) and ammonia to give 1,4-dihydropyridines **161** in higher yields (51–92%) and less reaction time (10–15 min) (Scheme 32) (01SL1296). The same reactants but in the presence of ammonium acetate under MWI gave the substituted 1,4-dihydropyridines **161** in 66–96% yields within 0.75–3 min (02SC659), and in another report the yields were 85–90% after 2.0–5.5 min (Scheme 32) (02JCS(P1)1845).

The 1,4-dihydropyridines **161** were also obtained in 60–77% yields when MWI was used to induce the condensation of ethyl 3-aminocrotonate (**160**) with methyl acetoacetate (**159**, R^1 = Me) and aldehydes without a solvent for 4–10 min. The substituents attached to the benzene ring of benzaldehyde may facilitate or retard the condensation through their electronic effects (Scheme 32) (95SC857).

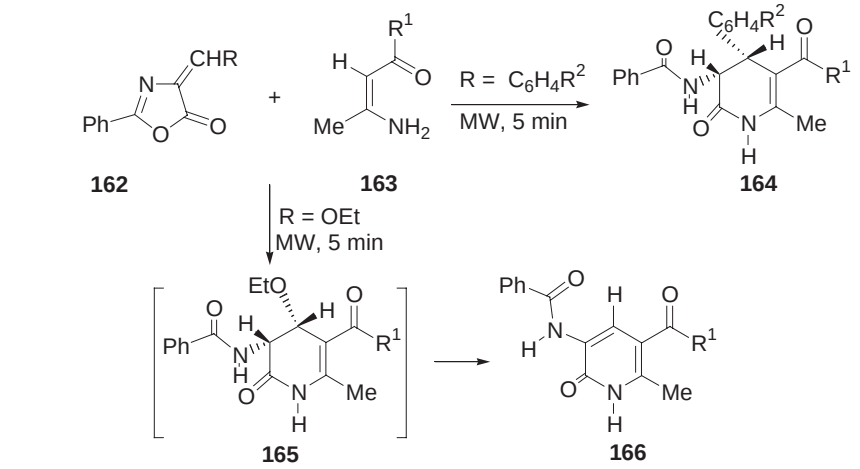
The reactions between enaminocarbonyl compounds and 4-ylidene-2-phenyloxazol-5-(4*H*)-ones **162** yielded pyridine derivatives, but the experimental conditions were restricted and required prolonged heating in chlorobenzene (85BSB849, 76MI1). When a mixture of **162** and ethyl 3-amino-2-butenoate **163** (R^1 = OEt) was irradiated in a domestic MW oven for 5 min, a quantitative yield of **164** was obtained. The reaction was monitored by recording IR spectra so that optimization of the power and time settings enabled the production of a quantitative yield of **164**. No solvent was employed and it was unnecessary to support the reagents on a porous solid. When 4-ethoxymethylene-2-phenyloxazol-5(4*H*)-one **162** (R = OEt) was used, the dihydropyridinone derivatives **165** bearing an ethoxy group in the 4-position lost ethanol and yielded pyridinones **166** (Scheme 33) (97SC3683).

Oxidation of 4-substituted 1,4-dihydropyridines **167** into the corresponding pyridine derivatives **155** has been carried out using nitric acid supported on bentonite without a solvent, under MWI. When the substituents (R) were hydrogen, methyl, ethyl, *n*-propyl, and aryl groups, only dehydrogenated products **155** were obtained within 1 min, in 51.3–98.6% yields. Nitration of the aryl group did not occur as under conventional thermal conditions, which required longer time and gave lower yields. On the other hand, when the substituents (R) were isopropyl and benzyl groups, aromatization occurred, accompanied by dealkylation to produce **156** in 87.4–91.4% yields (Scheme 34) (93TL623).

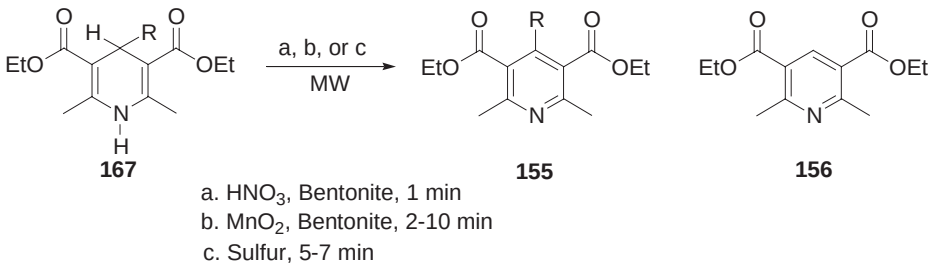
The oxidation of **167** with MnO_2/bentonite was performed without a solvent to give a mixture of **155** and **156**, depending on the alkyl substituent in 9–100% yields after irradiation for 2–10 min (Scheme 34). The ease of oxidation of the 4-substituted dihydropyridines was found to be in the order R = H > alkyl > aryl (91SC2137).

A solid-phase oxidative method for the conversion of 1,4-dihydropyridines to pyridines in good yields (76–90%) was carried out by employing phenyliodine(III) *bis*(trifluoroacetate) (PIFA) at room temperature. The dealkylation at the 4-position in the case of ethyl-, isopropyl-, and benzyl-substituted dihydropyridine derivatives with PIFA was circumvented by using elemental sulfur in solvent-free conditions under MWI for 5–7 min, compared to 35 min for the traditional heating to yield products **155** and **156** in 68% and 85% yields, respectively (Scheme 34) (99JCS(P1)1755).

When 2-iodopyridine **168** was treated with sulfur, oxygen, and carbon nucleophiles (PhSNa, MeSNa, PhONa, $PhCH_2OH$, and $PhCH_2CN$) in an appropriate



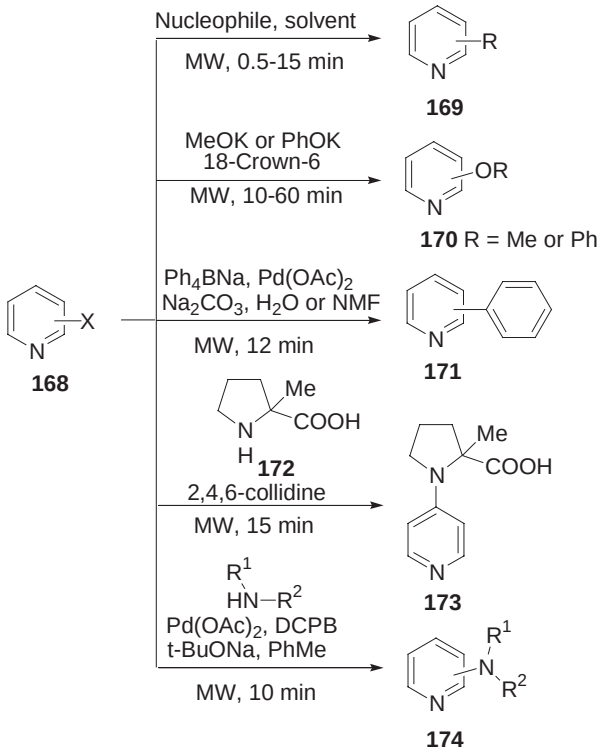
Scheme 33



Scheme 34

solvent under irradiation in a monomode MW reactor, the corresponding 2-substituted pyridines **169** were obtained in 36–99% yields (Scheme 35). Nucleophilic-displacement reactions of 2-bromo-, 2-chloro-, and 2-fluoropyridines were similarly carried out. In order to compare the efficacy of MWI with conventional heating, an HMPA solution of 2-bromopyridine and PhSNa was heated at 110 °C in an oil bath for 40 s, whereby no traces of 2-phenylthiopyridine was found (02T4931). It is well known that 3-halopyridines are less reactive than 2-halopyridines in nucleophilic reactions; however, high yields (97–99%) of 3-phenylthiopyridine were attainable by MWI of 3-iodopyridine or 3-bromopyridine with PhSNa in HMPA for 1–2.5 min. Moreover, the reaction of 3-fluoropyridine with $PhCH_2OH$ afforded 3-benzyloxypyridine in 65–88% yields. Under MWI, 4-iodopyridine also reacted with nucleophiles to give the corresponding 4-substituted pyridines in varied yields (28–99%) (02T4931).

An efficient method for an aromatic nucleophilic-substitution reaction using a solid–liquid transfer catalysis coupled with MWI was applied to the reaction of halogenopyridine **168** with alkoxides or phenoxides in the presence of 18-crown-6 as



Scheme 35

a phase transfer agent (PTA) to give the corresponding alkoxy- or phenoxy-substituted pyridines **170** in 34–95% yields within 10–60 min (Scheme 35) (04H297). Under classical heating, the substitution needed 4 h to give 10–70% yields (91H1947, 88TL773).

Suzuki coupling of halopyridines **168** with the nontoxic sodium tetraphenylborate as phenylating agent and palladium acetate as catalyst in water or NMF as solvent was performed in a Teflon closed vessel under MWI for 12 min to give 73–85% yields of the respective 2- or 3-phenylpyridines **171** (Scheme 35). Better yields were obtained in NMF, perhaps because the temperature gradient and the ionization of the solvent are higher. Lower yields (42–53%) were obtained on heating in an oil bath (01TL635).

N-(4-Pyridinyl)proline (**173**) was synthesized from α-methyl-L-proline (**172**) and 4-chloropyridine hydrochloride (**168**) in the presence of 2,4,6-collidine under MWI; the yield was 40% within 15 min (Scheme 35). Conventional heating up to 180 °C for prolonged periods in the presence or absence of a base gave no more than a 7% yield (02TL6001).

Palladium-catalyzed aminations of aryl chlorides required reaction times ranging from hours to 1 day; however, it can proceed in few minutes to give higher yield of products by MWI. Rapid palladium-catalyzed aminations of azaheteroaryl chlorides **168** with arylamines have been achieved using temperature-controlled MW heating,

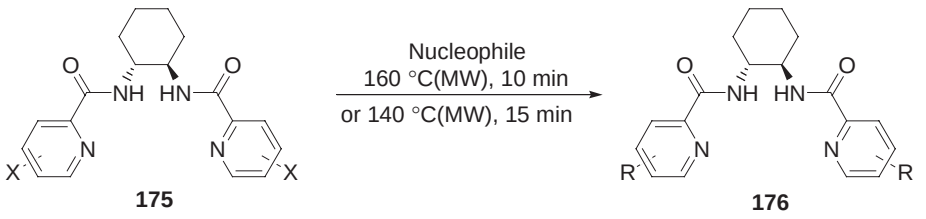
to give **174** in good yields (75–89%) within 10 min. 2-(Dicyclohexylphosphanyl)biphenyl (DCPB) was used as a ligand for the palladium catalyst and $Pd(OAc)_2$ was selected as the Pd(0) source (Scheme 35) (03SL1822).

The 4- and 6-substituted *bis*-pyridylamides **176** were prepared by direct nucleophilic substitution of the 4- and 6-halo *bis*-pyridyl derivatives **175** by heating with an appropriate nucleophile under MWI. Thus, a solution of the 4-chloro derivative was heated with pyrrolidine in an MW cavity at 160 °C for 10 min to give the respective 4-pyrrolidyl derivative in quantitative yield. Similarly, a suspension of the 6-bromo derivative was heated with MeONa in MeOH in the MW cavity at 140 °C for 15 min to give 6-methoxy *bis*-pyridylamide derivative in a quantitative yield (Scheme 36) (02S1601).

Pyridylthioglycosides **179** were prepared in 40–88% yields by MWI of 2-chloropyridines **178** with isothiouronium salts **177** in the presence of triethylamine (Scheme 37). The reaction required 2–3 min instead of 6–8 h under classical heating (05UP1).

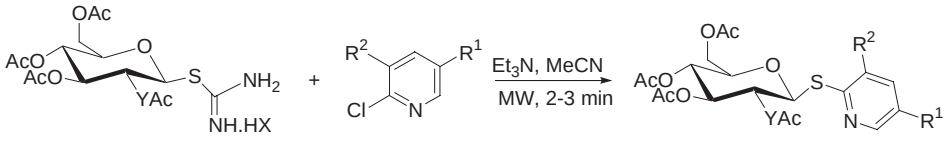
The effect of MWI on aromatic nucleophilic substitutions of activated halobenzenes **181** with piperidine **180** (R = H) at atmospheric pressure and in a homogeneous medium was studied. The reactions were carried out in DMSO solvent and the products **182** were obtained in 9–93% yields within 6 min–15 h (Scheme 38). The reaction rates were 3.8–5.0 times faster than conventional heating with comparable yields (98TL2471).

A number of piperidine derivatives **180** have been rapidly methylated under MWI using formic acid–formaldehyde mixtures in DMSO to give the *N*-methyl derivatives **183**. Methylation was extremely rapid and was complete within 1–3 min, while it required 24 h at 80 °C under conventional thermal conditions. The method was used for the preparation of the corresponding deuterated compounds (Scheme 38) (02TL9487).



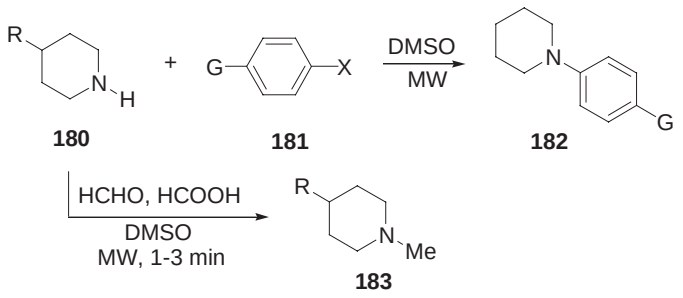
175 **176**

Scheme 36

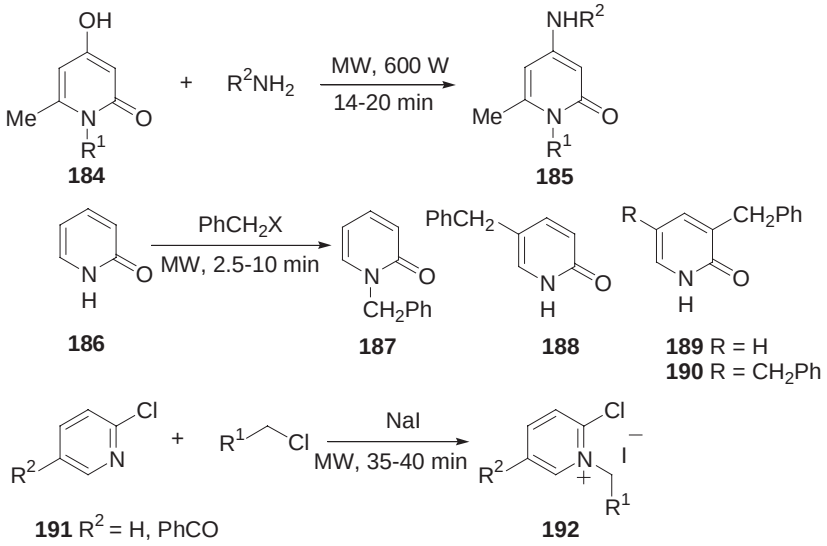


177 Y = O, NH **178** **179**

Scheme 37



Scheme 38



Scheme 39

Nucleophilic substitution of the hydroxyl group in 4-hydroxy-6-methyl-2(1*H*)-pyridones **184** using an excess of aralkyl amine without any solvent under MWI for 14–20 min gave the 4-aralkylamino-2(1*H*)-pyridones **185** in 60–91% yields. However, under the same conditions, aliphatic and aromatic amines gave no reaction (Scheme 39) (99SL1747).

Regiospecific N- or C-benzylations of 2-pyridone (**186**) in solvent-free conditions and in the absence of base were found to be controlled by the emitted power of the MWI and the halide group in benzyl halide. With benzyl chloride, N-alkylation was the only reaction occurring after irradiation for 5 min at 780 W. Using benzyl bromide, a drastic change in selectivity occurred whereby C-benzylation took place at 450 W to give **188**, **189**, and **190** (Scheme 39), whereas the N-benzylation to give **187** took place on reducing the power to 150 W or by conventional heating. With benzyl iodide, MWI led to exclusive C-benzylation with increased amounts of C-3 versus C-5 but no reaction occurred under the same conditions using conventional heating (96CL333).

Imidazo[1,2-*a*]pyridine derivatives are potent antirhinoviral agents, and the N-alkylation reaction of 2-halopyridines has been considered as a route for the preparation of 2-amino-imidazo[1,2-*a*]pyridine derivatives *via* 2-chloropyridinium salts. When N-alkylation of 2-chloropyridines **191** occurred using chloromethyl alkylating agents in the presence of sodium iodide by irradiation in a focused MW reactor for 35–40 min, the corresponding pyridinium salts **192** were obtained in 48–91% yields (Scheme 39). The same reaction required heating at 165–170 °C for 20–100 h to give the corresponding pyridinium salts in 10–48% yields (99T2317).

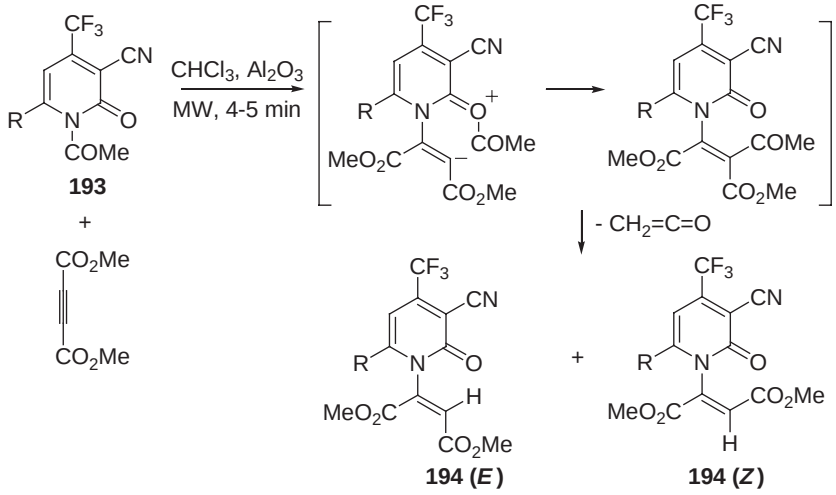
Michael-type addition of 2(1*H*)-pyridones **193** to dimethyl acetylenedicarboxylate (DMAD) was achieved by MWI for 4–5 min to afford the corresponding *E*- and *Z*-isomers of *N*-adducts **194** in 28–37% and 9–15% yields, respectively (Scheme 40) (02JFC133).

The proposed mechanism suggested that the *N*-acyl group in **193** migrated to the oxygen, and then a reaction *in situ* with DMAD took place at the nitrogen, followed by a loss of ketene to give **194** (Scheme 40) (92T9111).

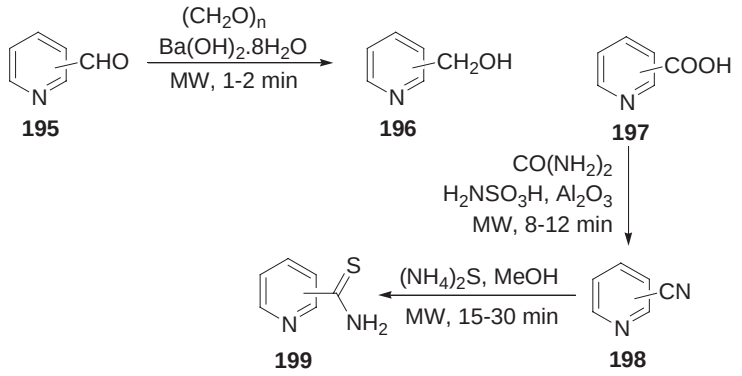
Pyridine 2- and 3-carboxaldehydes **195** with barium hydroxide and paraformaldehyde under MWI for 1–2 min gave the respective alcohols **196** as the major products (97%), in addition to the carboxylic acids **197** as minor ones (3%) (Scheme 41) (98TL8437).

The important industrial pyridine nitriles **198** were prepared in 77–90% yields under MWI of the corresponding carboxylic acids **197** in the presence of urea and sulfamic acid, adsorbed on alumina support in dry media (Scheme 41) (96SC4545).

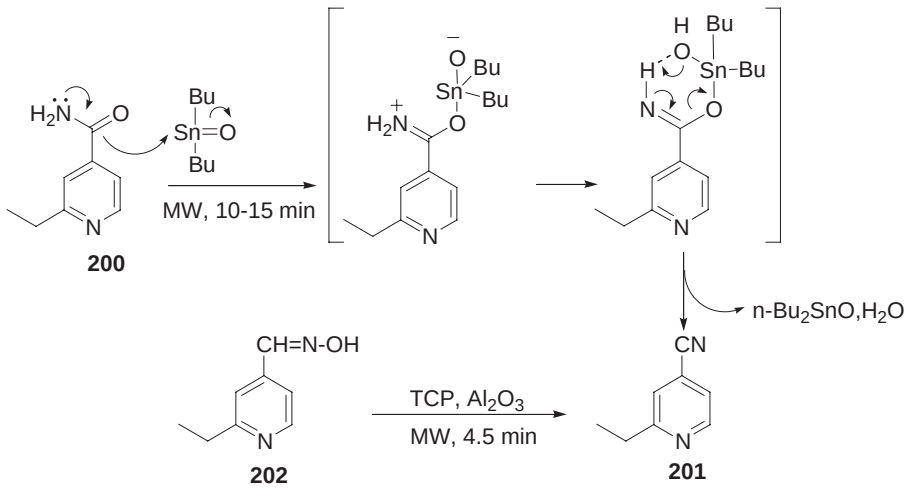
Thionation of 2- or 3-cyanopyridines **198** to the corresponding thioamides **199** was carried out under MWI at 80 or 130 °C by using either NaSH or $(NH_4)_2S$ in methanol within 15–30 min.Ammonium sulfide provided thioamides in essentially quantitative yield rather than sodium hydrogen sulfide, which gave 30–46% yields, although its reactions have a less unpleasant smell (Scheme 41) (04SL2615). At room temperature, these transformations were achieved by stirring for 18 h.



Scheme 40



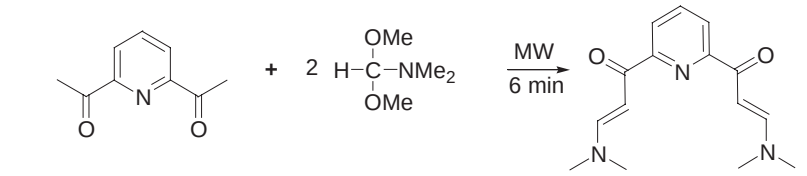
Scheme 41

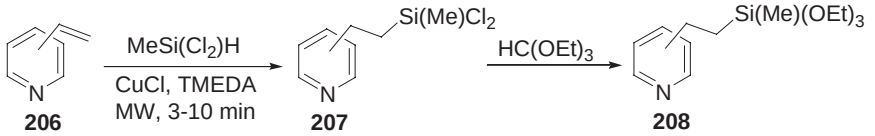


Scheme 42

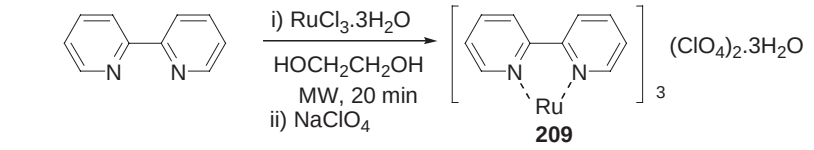
A heterogeneous mixture of primary amide **200** and a catalytic amount of dibutyltin oxide in dry toluene was subjected to MWI for 10–15 min to give nitrile **201** in 95% yield (Scheme 42). Under conventional heating, the reaction required a reflux overnight in toluene. In contrast to the thermal conditions, dehydration under MWI did not need strong dehydrating or expensive reagents and the reaction could be easily performed in a large scale under neutral conditions. The reaction occurred with the production of *n*-Bu_2SnO as by-product, again introduced in a catalytic cycle (99JOC1713).

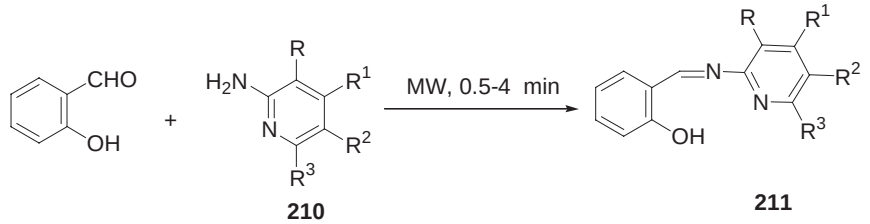
Dehydration of aldoximes to nitriles is an important transformation in organic synthesis. Most of the classical methods of dehydration required an excess of solvents and the catalyst remains as a waste (78S702, 80S659). However, zeolites or clay are reported as reusable catalysts but they required harsh reaction conditions and longer reaction time (92S943). Recently, nitrile **201** was isolated in 60% yield when a mixture of the aldoxime **202** and tetrachloropyridine (TCP) adsorbed on alumina in a Pyrex test tube was subjected to MWI for 4.5 min (Scheme 42). TCP represented a





Scheme 43





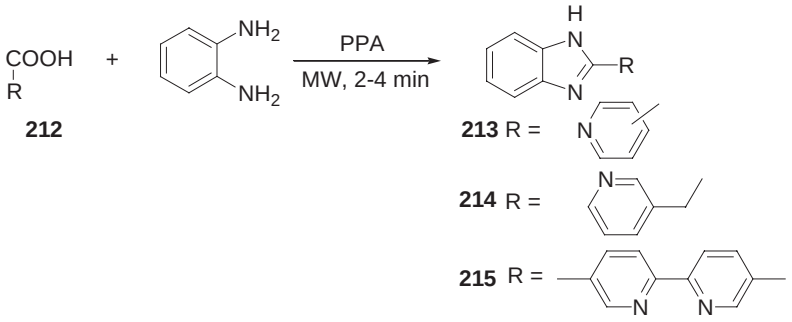
Scheme 44

new catalyst for the dehydration of aldoximes to nitriles and it can be recovered and reused (02SC2391).

Reaction of 2,6-diacetylpyridine (**203**) with two equivalents of *N*,*N*-dimethylformamide dimethyl acetal (**204**), under MWI for 6 min, gave 2,6-*bis*(3-dimethylamino-1-oxoprop-2-enyl)pyridine **205** in >95% yield (Scheme 43). This reaction was usually performed by refluxing the reactants for several hours (01S55).

Hydrosilylation of 2-vinylpyridine **206** with methyldichlorosilane and CuCl in the presence of TMEDA (18 h at 180 °C) with or without Et_3N gave a low yield (5%) of **207**, whereas the reaction with MWI for 3 min afforded the product, isolated as the diethoxysilane derivative **208** in a good yield (75%). Similarly, 4-vinylpyridine **206** gave product **208** in 71% yield after 10 min as opposed to 50% yield after 16 h of conventional heating (Scheme 43) (91TL5251).

A facile synthesis of tris(2,2′-bipyridine)ruthenium(II) perchlorate trihydrate **209** in 86% yield has been developed by a reaction of 2,2′-bipyridine with ruthenium(III) chloride trihydrate in ethylene glycol within 20 min under MWI, followed by a reaction with $NaClO_4$ (Scheme 44) (94CL2443); conventional heating required 4 h.



Scheme 45

A MW-assisted condensation of heterocyclic amines **210** and salicylaldehyde under solvent-free conditions afforded the corresponding salicylaldimines **211** within 0.5–4 min in 65–95% yields (Scheme 44) (02SC2395).

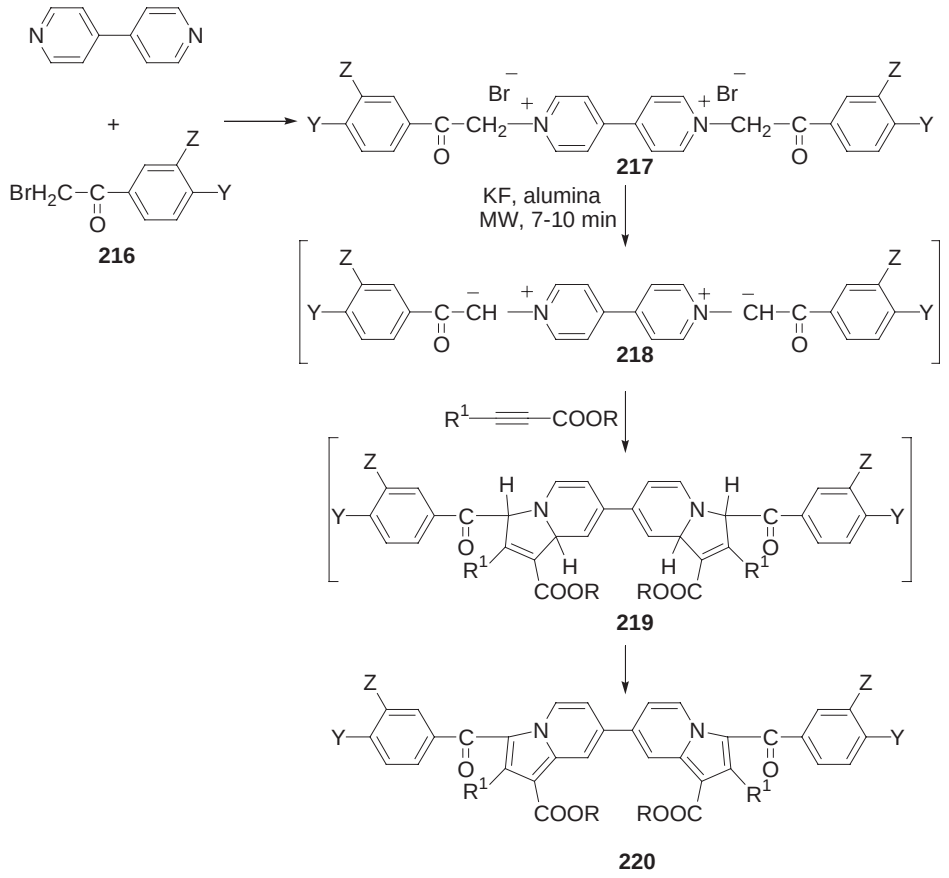
Pyridyl substituents linked to benzimidazoles were prepared by the condensation of hetero arylcarboxylic acids **212** with 1,2-phenylenediamine in the presence of PPA. When the reaction mixtures were subjected to MWI for 2–4 min, imidazoles **213**–**215** were obtained in 61–97% yields (Scheme 45). Conventional heating gave comparable yields, but after a longer time (4–16 h) and with twice the amount of PPA (03H1457).

G. Fused Heterocycles Incorporating Pyridine Rings

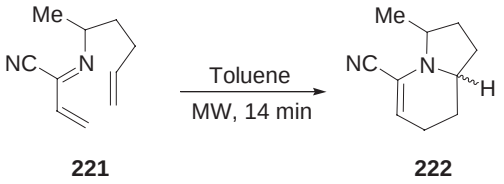
[3 + 2]-Cycloaddition of 4,4′-bipyridinium ylides **218**, generated *in situ* from 4,4′-bipyridine and substituted phenacyl bromides **216** *via* 4,4′-bipyridinium diquaternary salts **217**, with activated alkynes has been achieved under solvent-free conditions and in the presence of basic catalyst KF on alumina within 7–10 min by MWI to give 7,7′-*bis*-indolizines **220** in 81–93% yields *via* intermediate **219** (Scheme 46). On heating in benzene (or in benzene and *N*-methylpyrrolidone (NMP)), the reaction times were longer (3–6 h) and the yields were lower (50–59%) (00SL1013).

Intramolecular Diels–Alder reaction of the 2-cyano-substituted *N*-alkyl azadiene **221** to indolizidine **222** (70%) was carried out under MWI within 14 min (Scheme 47). This conversion took place on heating in benzene overnight in a sealed tube to give a 90% yield (97JOC2098).

The reaction of pyridinium *N*-dicyanomethylide **223** with ethyl phenylpropiolate **224** (R = CO_2Et), under solvent-free conditions using MWI afforded a mixture of the two possible regioisomers **225** and **227**. Reaction was performed in a monomode reactor in order to have an accurate control of temperature to prevent the decomposition of **223**. The best results (84–87%) were obtained using a molar ratio of ylide:dipolarophile 1:1.5 or 1.5:1 and irradiation at 120 W over 25 min at 150 °C (Scheme 48). Yields were increased from 61% to 87% when compared with conventional heating. Reactions in the presence of different supports were performed under MWI; the best selectivity was obtained using neutral bentonite or silica gel.



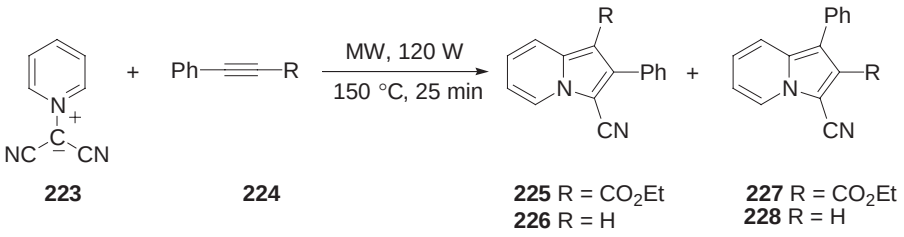
Scheme 46



Scheme 47

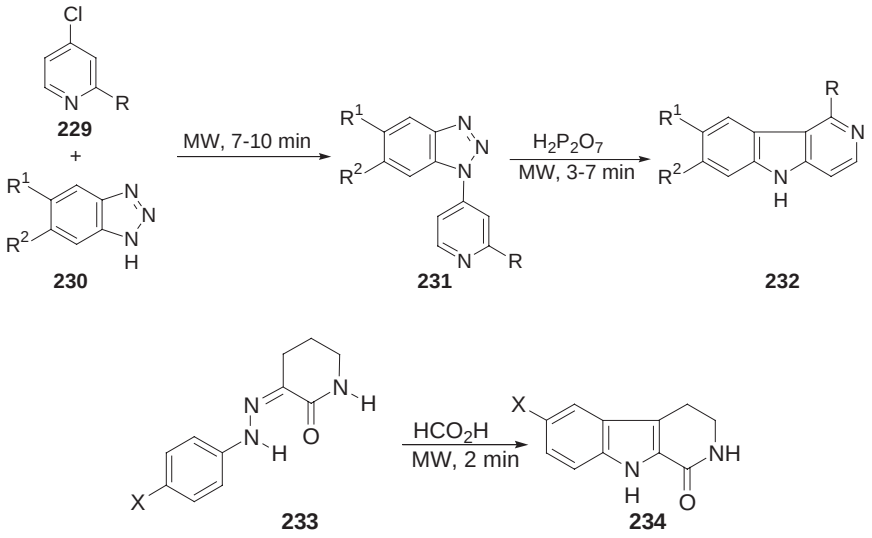
The reaction with phenylacetylene **224** (R = H) under similar conditions gave a mixture of regioisomers **226** and **228** in 24% yield (Scheme 48), which increased up to 46% with increasing irradiation time to 60 min (94H785).

A one-pot γ-carboline synthesis was carried out by MWI of 4-chloroazines **229** with benzotriazoles **230** in the absence of a solvent to give **231** within 7–10 min. Subsequent irradiation for 4–6 min in the presence of pyrophosphoric acid gave γ-carboline **232** in 30–81% yields (Scheme 49). Under conventional heating at



223 **224** **225** R = CO_2Et **226** R = H **227** R = CO_2Et **228** R = H

Scheme 48

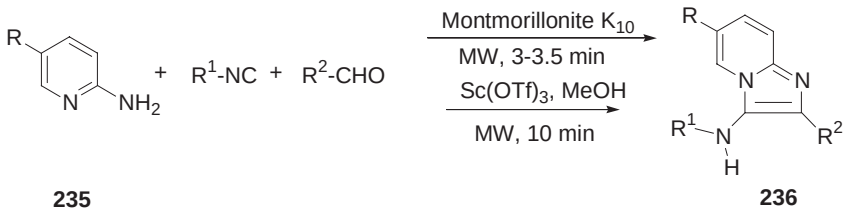


Scheme 49

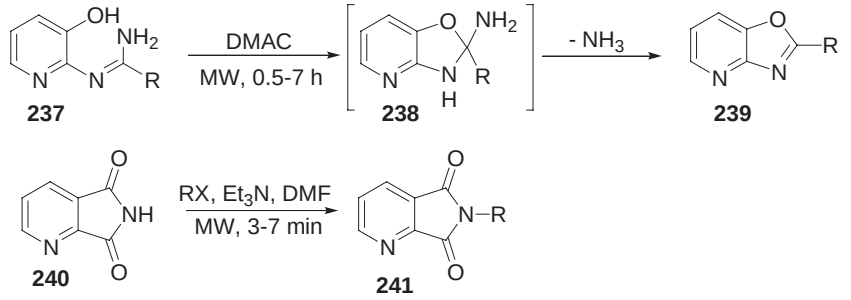
150–210 °C, the formation of **231** and **232** took 15–30 min and 1.5–2 h, respectively, to give comparable yields (93TL2673).

Dry media conditions were found to be unsuitable for effecting Fischer cyclizations of preformed arylhydrazones **233** in an MW oven. Thus, when **233** (X = H) was heated in an MW oven with montmorillonite KSF or silica gel, either in a sealed glass vessel or in an open vessel, only the starting material was isolated. However, the reaction can be achieved by heating **233** with formic acid in the Teflon cup of a Parr MW bomb in an MW oven for 2 min to give **234** in 73–88% yields (Scheme 49) (92SL795).

A solventless one-pot reaction to generate imidazo[1,2-*a*]pyridines was done by MWI of a mixture of aldehyde, alkyl isocyanide, and 2-aminopyridine **235** (R = H) in the presence of montmorillonite K_{10} clay. The products **236** (R = H) were obtained within 3–3.5 min in 82–88% yields (Scheme 50). However, under conventional conditions by stirring in acetic acid overnight, some unreacted starting materials were obtained and also in a traditional oil bath no products were obtained owing to the volatile nature of the reactants, especially isocyanides (99TL7665).



Scheme 50



Scheme 51

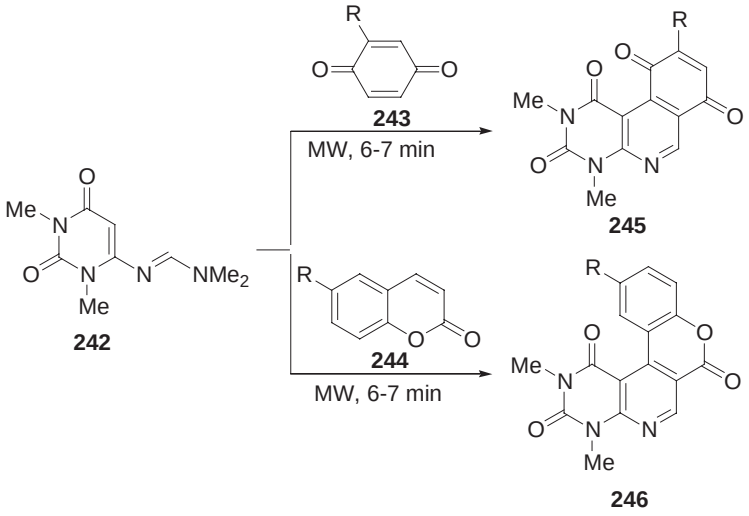
A variety of fused 3-aminoimidazoles were synthesized under MWI by an Ugi three-component coupling reaction. Thus, the reaction of 2-amino-5-methyl or 2-amino-5-bromopyridine **235** (R = Me, Br) with 2-naphthaldehyde or pyridine-2-aldehyde and isocyanide using scandium triflate as catalyst was carried out in methanol solvent under MWI for 10 min to afford the respective imidazo[1,2-*a*]pyridine **236** in 50–93% yields (03TL4369).

Oxazolopyridines **239** have been prepared by intramolecular cyclization of hydroxyamidines **237** in dimethylacetamide (DMAC) *via* intermediate **238**; 55–88% yields were obtained by classical heating (5–15 h) or MWI (0.5–7 h) (Scheme 51) (03S2033).

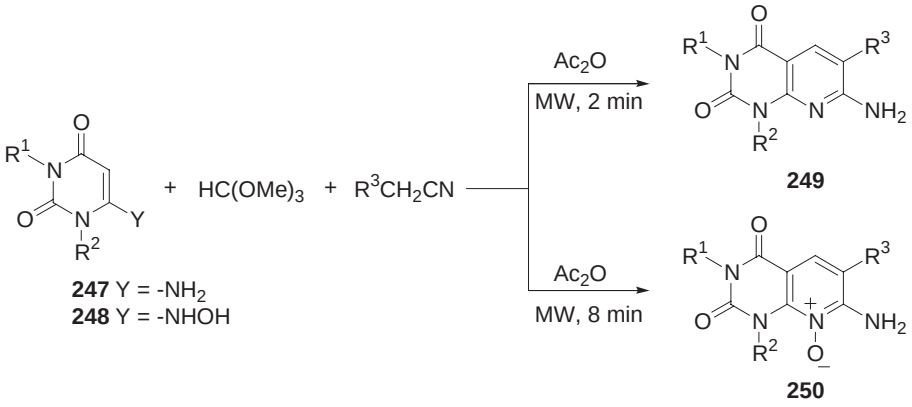
A mixture of **240**, alkyl halide, and triethylamine was exposed to MWI in dry DMF to afford **241** in 70–89% yields within 3–7 min (Scheme 51). Conventional heating at 140 °C gave **241** in 15–29% yields within 40–48 h (02H1881).

[4 + 2]-Cycloaddition between electron-rich 6-[(dimethylamino)methylene]amino-1,3-dimethyl uracil **242** and various electron-deficient substrates such as quinones **243** and coumarins **244** was considered to take place by elimination of dimethylamine from the respective cycloadducts, followed by oxidative aromatization in a highly regiospecific manner to give pyrido[2,3-*d*]pyrimidines **245** and **246**, respectively (Scheme 52). Heating in DMF/nitrobenzene required 4–5.5 h, but under MWI and solvent-free conditions, the times were reduced to 6–7 min and the yields were increased from 70–80% to 85–94% (04SL1179).

The 6-aminouracils **247** or 6-hydroxyaminouracils **248** reacted with triethyl orthoformate and R^3CH_2CN in the presence of acetic anhydride to give pyrido[2,3-*d*]pyrimidines **249** or pyrido[2,3-*d*]pyrimidines *N*-oxides **250**, respectively, in 55–90%



Scheme 52

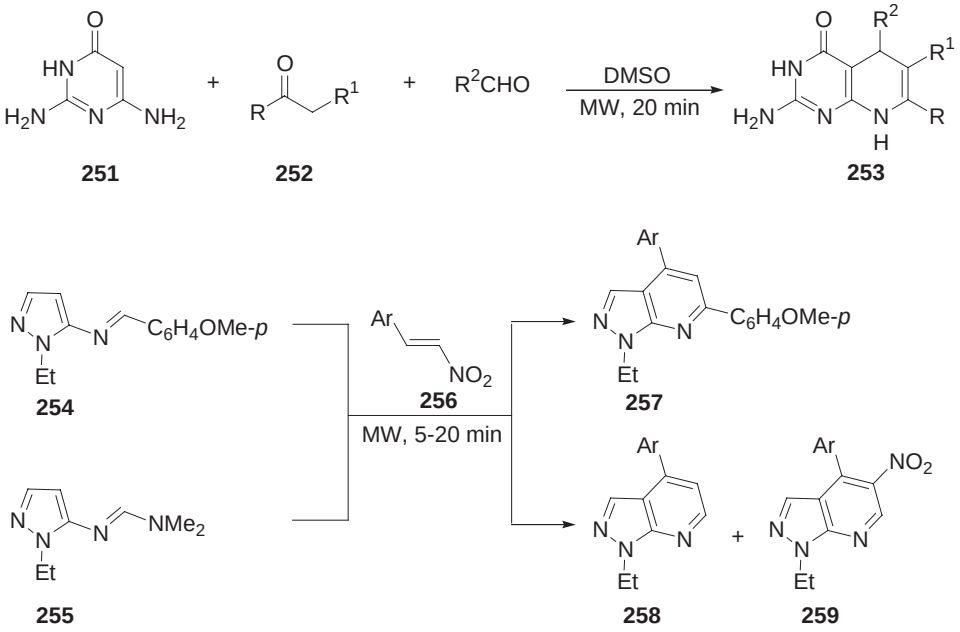


Scheme 53

yields within 2–8 min (Scheme 53), while it required 3–6 h under thermal conditions to give 35–50% yields (04SL283).

The 5-deaza-5,8-dihydropterins **253** were synthesized by the cyclocondensation of 2,6-diaminopyrimidin-4-one (**251**) with carbonyl compounds **252** and different aldehydes in the presence (for aromatic aldehydes) or absence (for aliphatic aldehydes) of $ZnBr_2$. Under MWI, compounds **253** were obtained in 43–91% yields within 20 min at 160 °C, but under conventional heating at 110 °C, **253** were obtained after 3 days in 14–86% yields (Scheme 54) (02SL1718).

The pyrazolo[3,4-*b*]pyridines **257**, **258**, and **259** were constructed by Diels–Alder cycloaddition of the 2-azadienes, alkylidene derivatives of 5-aminopyrazole **254** or **255**, with nitroalkenes **256** as electron-poor dienophiles under MWI and solvent-free

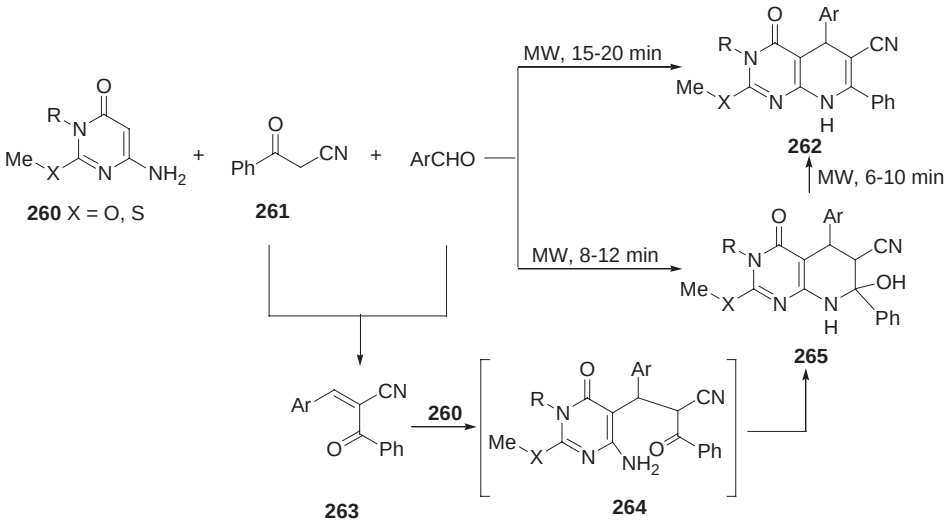


Scheme 54

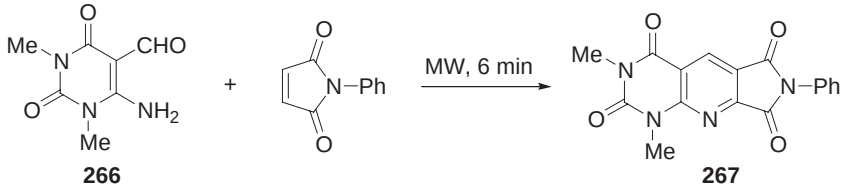
conditions at atmospheric pressure in a focused MW reactor. They were obtained in good yields within 5–20 min, avoiding the polymerization or decomposition of the diene pyrazole, which occurred on classical heating. Cycloaddition of **255** with **256** took place preferentially by loss of H_2 to afford **258** as a major product whereas adduct **259**, obtained from the loss of HNO_2, was a minor product (Scheme 54). Changing the irradiation time to favor the elimination of HNO_2 was unsuccessful and a similar product ratio was obtained in all attempts. The method was extended to other derivatives (98SL1069, 00T1569).

Equimolar amounts of compounds **260**, **261**, and aryl aldehydes were irradiated in an MW oven for 15–20 min to give dihydropyrido[2,3-*d*]pyrimidin-4(3*H*)-ones **262** in 70–75% yields. Under reflux in absolute ethanol for 40–48 h, products **262** were produced in 21–25% yields. Formation of **262** was assumed to take place through a Michael-type addition of **260** to the activated double bond of the benzylidenebenzoylacetonitrile **263**, produced *in situ* by a Knoevenagel condensation between **261** and aryl aldehydes to give adduct **264**, which upon cyclization gave **265**; dehydration produced **262**. Compound **265** was isolated as a stable hydrated intermediate when aminopyrimidines **260**, benzoylacetonitrile **261**, and aryl aldehyde were irradiated under MW for 8–12 min, but further irradiation for 6–10 min gave compound **262** (Scheme 55) (01TL5625).

The reaction of 6-amino-1,3-dimethyl-5-formyluracil **266** with *N*-phenylmaleimide under MWI for 6 min gave pyrido[2,3-*d*]pyrimidine **267** in 85% yield (Scheme 56) (04TL2405).



Scheme 55

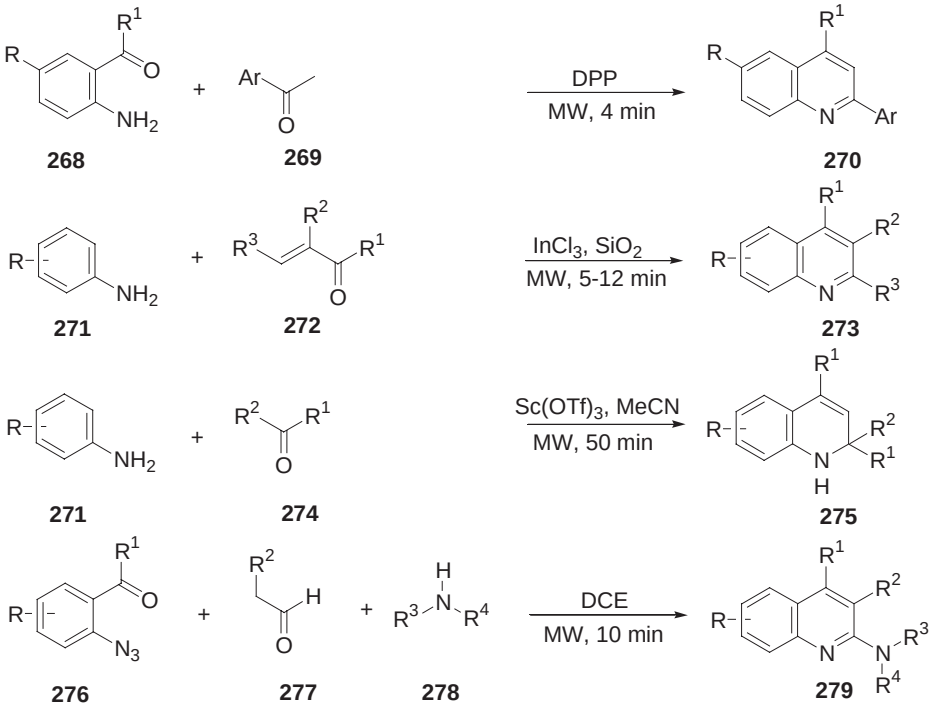


Scheme 56

H. Quinolines, Isoquinolines, and their Fused Rings

The condensation between acetophenones **269** and 2-aminoacetophenones or benzophenones **268** under MWI in the presence of diphenylphosphate (DPP) as acidic catalyst gave the corresponding quinolines **270** in 50–85% yields within 4 min. When the reaction of **269** (Ar = Ph) with **268** (R = R^1 = H) was carried out in a preheated oil bath for the same time (4 min) (Scheme 57), it proceeded slowly at 108 °C to give 15–24% yields, whereas a 70% yield was obtained after 330 min at 136 °C (03TL255).

Michael addition of the aromatic amines to the vinyl ketones followed by subsequent cyclization and aromatization under catalysis by silica gel impregnated with indium(III)chloride has been successfully achieved under MWI to give the corresponding quinolines. Conventional heating produced polymerization of the vinyl ketones that drastically reduced the yield (00TL531). Thus, quinolines **273** were prepared in 55–87% yields by reacting anilines **271** with alkyl vinyl ketones **272** by irradiation in an MW oven for 5–12 min (Scheme 57).

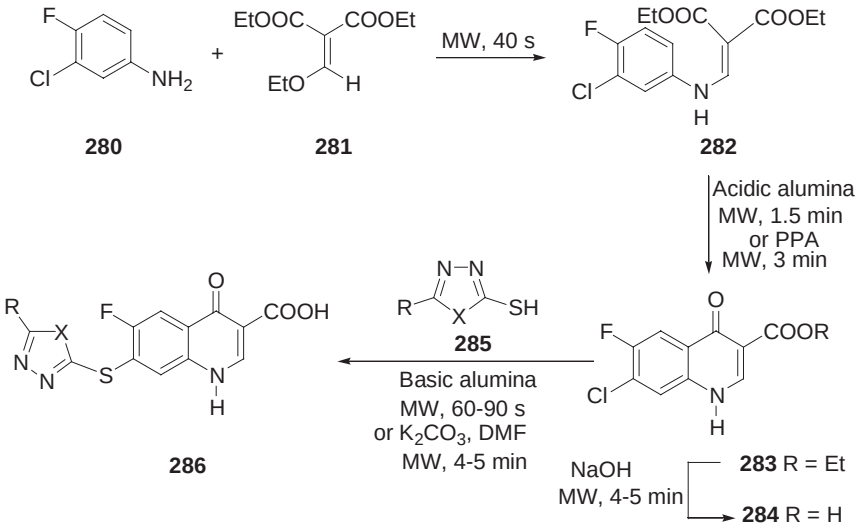


Scheme 57

The cyclization of a variety of substituted anilines **271** with ketones **274** in the presence of scandium trifluoromethane sulfonate under MWI at 150 ºC produced 2,2,4-substituted 1,2-dihydroquinolines **275** within 50 min in 30–79% yields. Under conventional conditions at room temperature for about 2–6 h, the yields were 59–98% (Scheme 57) (02TL3907).

The conversion of 2-azidobenzophenones **276** into the corresponding 2-amino-quinolines **279** in 57–100% yields was achieved by irradiating a mixture of **276**, aldehydes **277**, and secondary amines **278** in DCE under MW for 10 min (Scheme 57). Thermal heating in *p*-xylene or toluene for 4–24 h produced the products in 10–52% yields (02TL581).

The functionalized amine **282** was prepared in 96% yield under MWI from 3-chloro-4-fluoroaniline (**281**) and diethyl ethoxymethylenemalonate within 40 s; conventional heating required 6–7 h. It was cyclized to quinolone **284** using acidic alumina within 1–1.5 min (00M1207). On the other hand, the cyclization of **282** in PPA under MWI for 3 min yielded the respective ester **283**, which upon alkaline hydrolysis under MWI for 4–5 min afforded **284** in 78% yield (Scheme 58) (98M961). Nucleophilic substitution of the chlorine in **284** with mercapto-substituted 1,3,4-thiadiazoles and oxadiazoles **285** on a solid phase using basic alumina under MWI gave the substituted-carboxylic acids **286** within 60–90 s in 90–96% yields (Scheme 58). This nucleophilic reaction needed longer time (3–5 min) and gave lower yields



Scheme 58

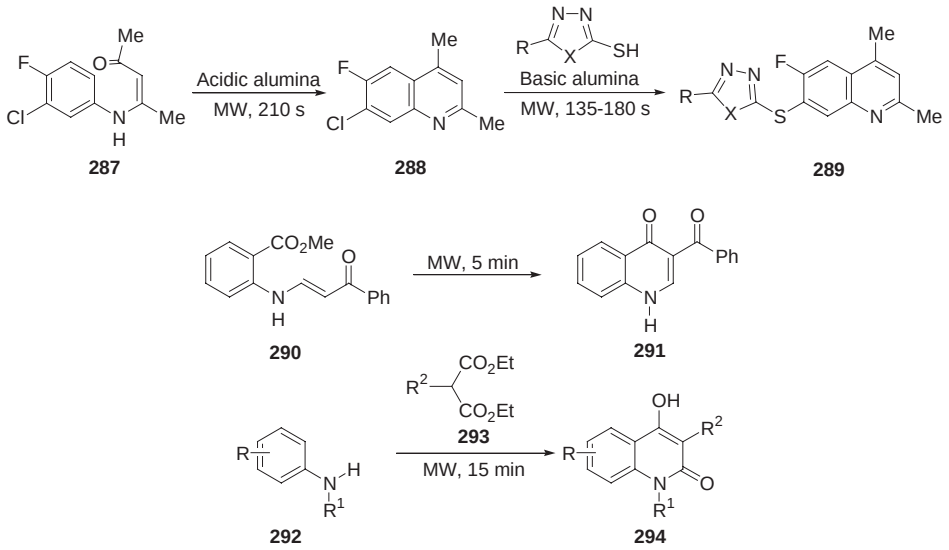
(70–78%) in solution (00M1207). The reaction in the presence of K_2CO_3 and DMF under MWI required 4–5 min to give 50–72% yields (98M961). Under conventional conditions, it took 9–15 h to give 59–65% yields (80TL5011).

Intramolecular cyclization of 4-(3-chloro-4-fluoroanilino)pent-3-en-2-one (**287**), adsorbed on acidic alumina, under MWI for 210 s gave 7-chloro-6-fluoro-2,4-dimethylquinoline (**288**) in 94% yield. Displacement of chlorine in **288** with mercaptothiadiazolyl or oxadiazolyl group to give quinolines **289** in 94–98% yields was carried out by irradiation under MW for 135–180 s in the presence of basic alumina (Scheme 59) (00MI2).

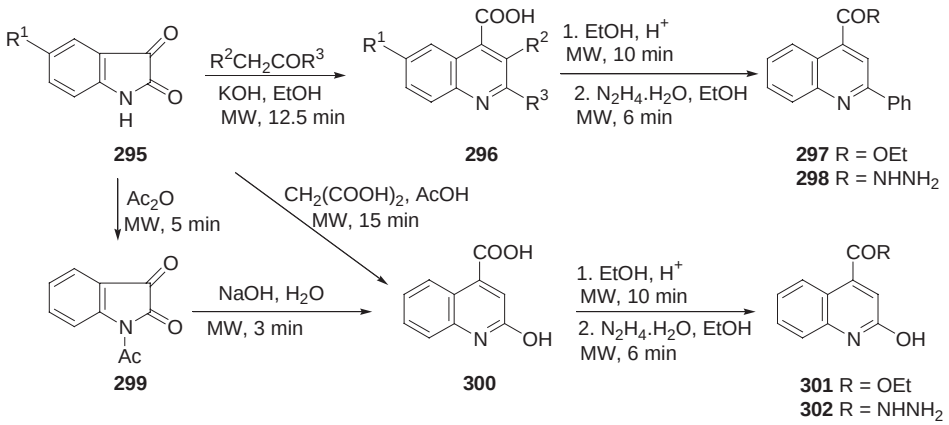
Classical heating failed to cyclize methyl 2-(3-oxo-3-phenylpropenylamino)benzoate (**290**) into 3-benzoyl-1*H*-quinolin-4-one **291**. However, the cyclization was successfully achieved by heating **290** for 5 min in an MW oven to give **291** in a 70% yield (Scheme 59) (04JHC1).

MW-assisted synthesis provided an efficient way to prepare a variety of 3-aryl-4-hydroxyquinolin-2(1*H*)-ones **294** by irradiating a mixture of aniline derivatives **292** and malonic ester **293** under solvent-free conditions in an MW oven. Optimal conditions for the irradiation were found to be 15 min at 500 W. The yields (13–94%) were found to be strongly dependent on the relative amounts of the starting materials and on the presence of electron-donating or -withdrawing groups on the aniline ring (Scheme 59) (01TL1367). This reaction required many hours at reflux in a high boiling organic solvent (88JHC857).

MWI has successfully accelerated the condensation of isatins **295** with a number of ketones in alcoholic KOH, whereby quinoline-4-carboxylic acids **296** were obtained in 50–96% yields within 12.5 min. Esterification of **296** ($R^1 = R^2 = H$; $R^3 = Ph$) with ethanol in the presence of a catalytic amount of conc. H_2SO_4 under MWI took 10 min to give ethyl 2-phenylcinchoninate **297** in 94% yield. Under MW activation, the ester **297** was transformed into the hydrazide **298** in 80% yield after 6 min

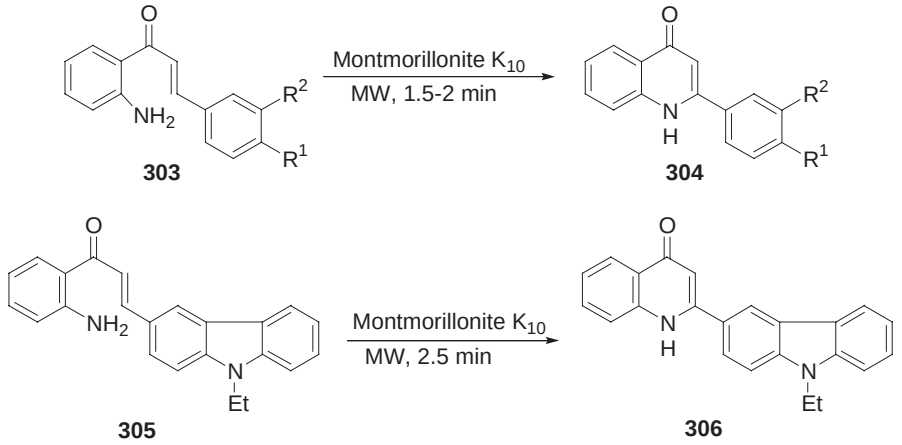


Scheme 59

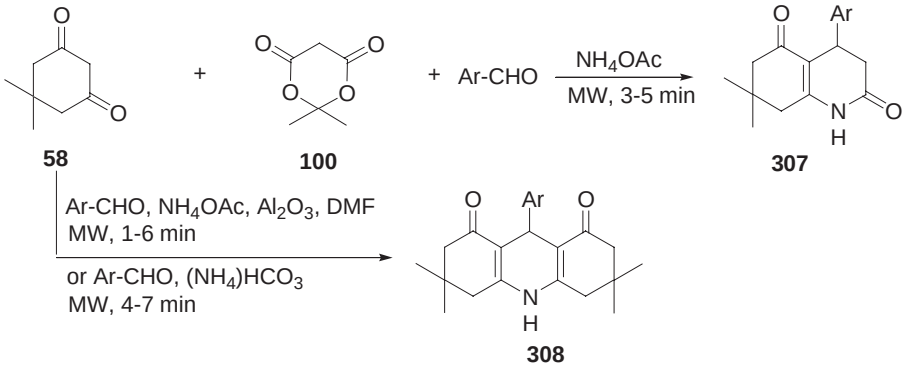


Scheme 60

(Scheme 60). On the other hand, isatin **295** ($R^1 = H$) was acetylated with acetic anhydride by irradiation for 5 min to give *N*-acetylisatin **299** in 70% yield, which then was irradiated by MW for 3 min with aqueous NaOH to give 2-hydroxyquinoline-4-carboxylic acid (**300**) in 65% yield. When a mixture of **295** and malonic acid in the presence of acetic acid was irradiated for 15 min, **300** was obtained in 68% yield. Esterification of **300** to the ethyl ester **301** and its subsequent transformation to hydrazide **302** were carried out under MWI within 6–10 min to give 99% and 92% yields, respectively (Scheme 60) (05SC2243).



Scheme 61



Scheme 62

Upon MWI of 2′-aminochalcones **303** adsorbed on montmorillonite K_{10} clay for 1.5–2 min, exclusive formation of 2-aryl-1,2,3,4-tetrahydro-4-quinolones **304** took place in high yields (70–80%) (Scheme 61) (97SL857). Similarly, the carbazolylquinolone **306** was prepared in 75% yield by the cyclization of **305**. Under conventional conditions and in the presence of catalysts ($InCl_3$, $In(OTf)_3$, $KHSO_4$ or $PPh_3 \cdot HClO_4$), longer reaction times (1–2 h) were required to give lower yields (41–55%) (04S1269).

The 4-substituted 7,7-dimethyl-2,5-dioxo-1,2,3,4,5,6,7,8-octahydroquinolines **307** were obtained in 60–75% yield by heating equivalent amounts of dimedone (**58**), aromatic aldehyde, Meldrum's acid **100**, and ammonium acetate in acetic acid for 8 h. When the reactants without acetic acid were MW irradiated for 3–5 min, higher yields of **307** (72–86%) were obtained (Scheme 62) (01SC2657).

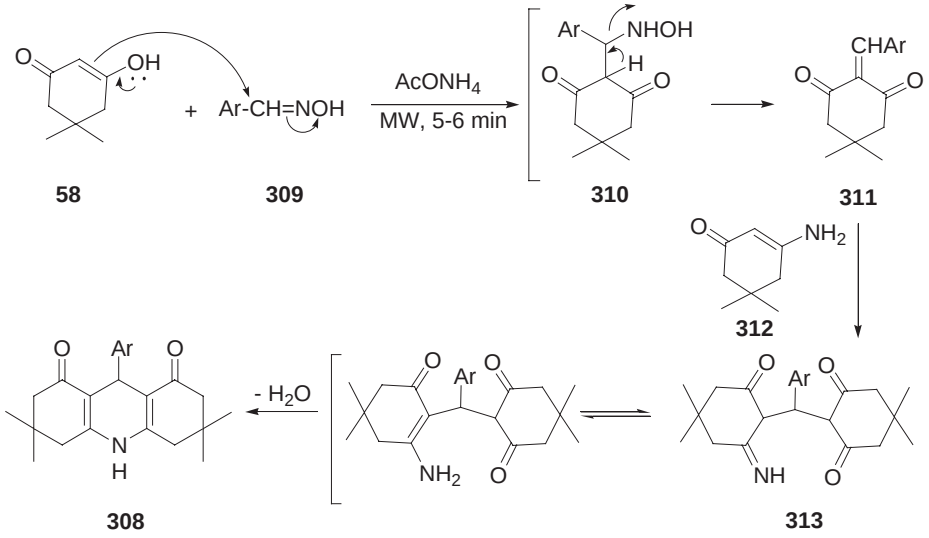
On the other hand, decahydroacridine derivatives **308** were obtained under MWI and solvent-free conditions by the reaction of 2 moles of dimedone (**58**) with 1 mole of the aromatic aldehyde in the presence of ammonium acetate supported on neutral

or basic alumina and a catalytic amount of DMF. The products were obtained in good yields (50–90%) within 1–6 min (Scheme 62), whereas conventional heating under reflux in ethanol required 1–2 h to give comparable yields (99H21).

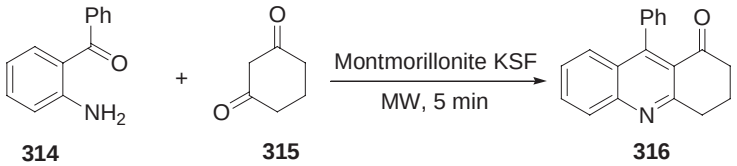
However, higher yields (85–92%) of **308** were obtained within 4–7 min under MWI in the presence of $(NH_4)HCO_3$ without solid supports and an energy transfer medium (Scheme 62) (02SC2181).

When aldoximes **309** reacted with dimedone **58** in the presence of ammonium acetate under MWI, they gave acridines **308** in 80–92% yields within 5–6 min. These reactions may occur through a Michael addition of dimedone **58** to **309** to give the intermediate **310**, which on elimination of hydroxylamine gave **313**. Then Michael addition between **311** and **312**, resulting from dimedone **58** and ammonium acetate, produced **313**, which isomerized and cyclodehydrated to give **308** (Scheme 63) (04SC1289).

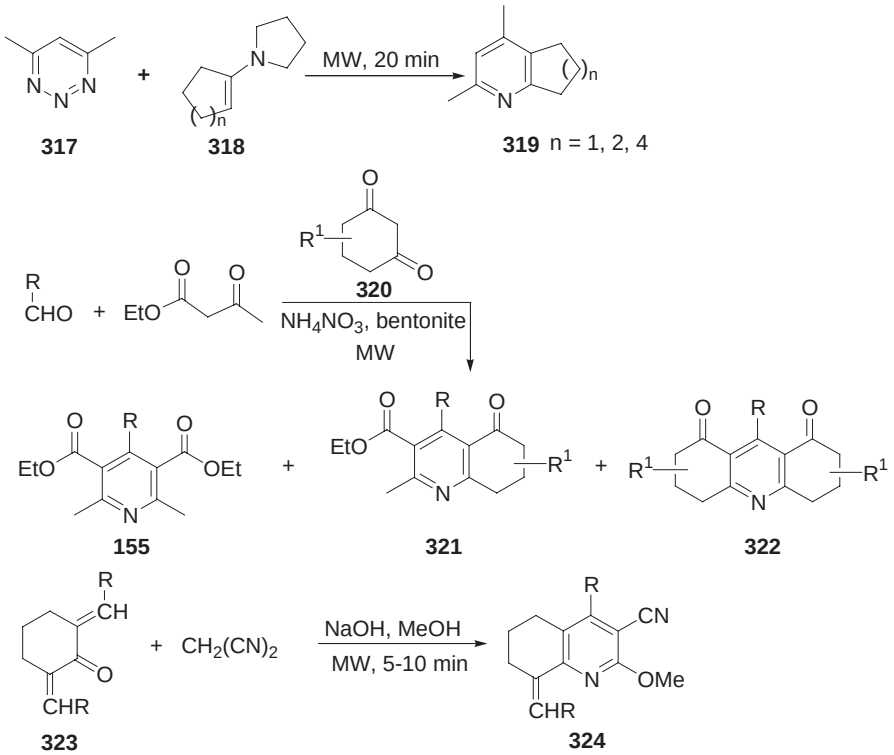
When a mixture of 2-aminobenzophenone (**314**) and 1,3-cyclohexanedione (**315**) was adsorbed on montmorillonite KSF clay and irradiated in an MW oven for 5 min, acridine derivative **316** was obtained in 62% yield (Scheme 64). The yield was reduced on prolonged irradiation owing to thermal decomposition (99SC4403).



Scheme 63



Scheme 64



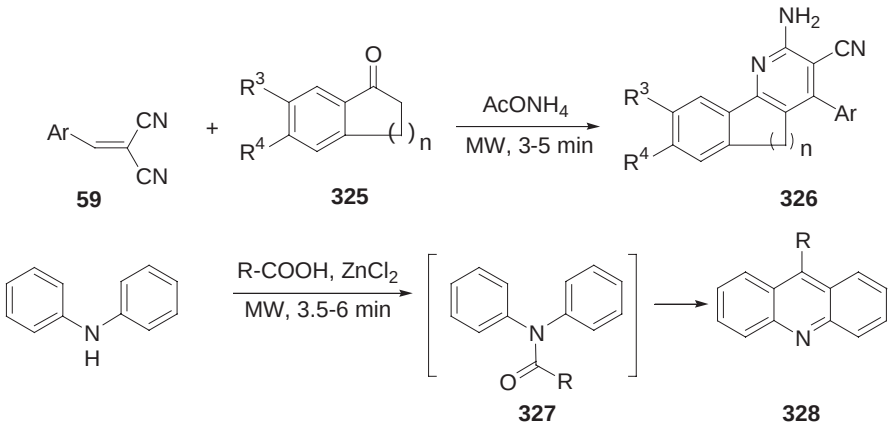
Scheme 65

Diels–Alder cycloaddition of 4,6-dimethyl-1,2,3-triazine (**317**) with enamines **318** was performed under MWI at 140–150 °C in a focused MW reactor to give the corresponding heterocyclic products **319** within 20 min and in 32–71% yields (Scheme 65); the conventional method needed 1–2 h. The relatively modest yields were explained by the poor thermal stability of the 1,2,3-triazines and enamines (01SL236).

Pyridine derivatives **155**, **321**, and **322** were obtained in one step by the reaction of aldehydes, *β*-keto ester, and cyclic 1,3-diketones **320** under MWI by using bentonite clay as a support and $NH_4(NO_3)$ as the source of ammonia and as oxidant (Scheme 65) (98TL1117).

Cyclization of 2,6-diarylidenecyclohexanone **323** with malononitrile in the presence of sodium hydroxide in methanol was carried out under MWI for 5–10 min to give quinoline derivatives **324** in 91–98% yields (Scheme 65). The reaction required 3 h under classical heating to afford **324** in 70–85% yields (01MI3).

A simple and efficient synthesis of 2-amino-3-cyanopyridines **326** was carried out through the reaction of arylidenemalononitriles **59** with cyclic ketones **325**. The reaction under MWI in the presence of $AcONH_4$, without or with a trace of solvent, gave **326** in 42–78% yields within 3.5–4.5 min (Scheme 66), while the synthesis required 5.5–6 h, in refluxing benzene, to give lower yields (46–55%) (98JCR(S)330).



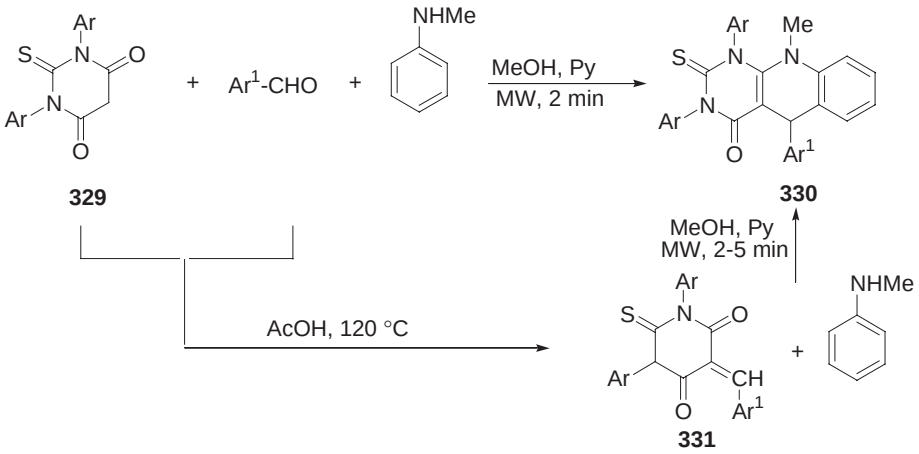
Scheme 66

A general method of producing 9-alkyl and 9-arylacridines involved the Bernthsen reaction by heating diphenylamine, an aliphatic or aromatic carboxylic acid, and $ZnCl_2$ at 200–220 °C over a long period; the yields were rather low, up to 30% (1884MI1). Graef modified this method by using esters or chlorides of dicarboxylic acids (46JOC257). MWI has successfully assisted the synthesis of 9-substituted acridine derivatives **328** from diphenylamine and the appropriate dicarboxylic acids or arylacetic acids, catalyzed by zinc chloride, in a much shorter reaction time, from 20–40 h to 3.5–6 min, to afford good yields (50–80%) (Scheme 66) (02SC729).

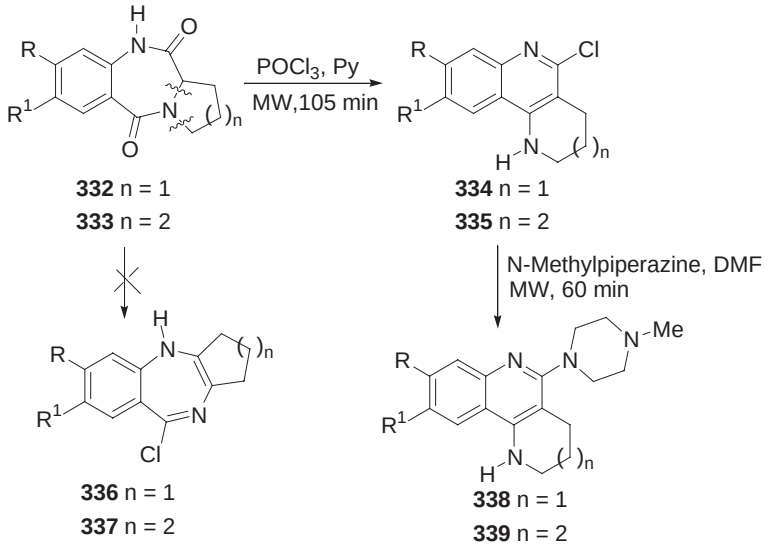
Meantime, similar results were achieved in another publication by reacting diphenylamine with a series of alkylcarboxylic acids in the presence of zinc chloride under MWI for 5–6 min to give the corresponding 9-alkylacridines **328** in 63–87% yields (02H1299). Long-chain octadecanoic acid has a longer reactivity that upon irradiation for 22 min resulted in only a 37% yield of **328**. Moreover, arylcarboxylic acids are less reactive than alkylcarboxylic acids. In particular, the reaction of 2,6-dimethoxybenzoic acid with diphenylamine did not produce the corresponding acridine. The possible mechanism may involve the formation of the amide **327**, followed by the rearrangement of its acyl group to the *o*-position of the phenyl ring and subsequent dehydrative cyclization to afford **328** as a final product (Scheme 66) (02H1299). For comparison, the reaction of diphenylamine with acetic acid in the presence of zinc chloride under conventional heating at 200 °C gave **328** (R = Me) in 82% yield after 8 h, while under MWI it required only 5 min (Scheme 66) (02H1299).

A one-pot synthesis of pyrimido[4,5-*b*]quinolines **330** under MWI involved the reaction of 1,3-diaryl-2-thiobarbituric acids **329**, the appropriate aldehyde, and *N*-methylaniline to give 72–88% yields after 2 min, compared to 1.5–2 h under conventional thermal conditions. However, compounds **330** were prepared by cyclizing the arylidene derivatives **331** with *N*-methylaniline under MWI for 2–5 min (Scheme 67) (97JCR(S)266).

Rearrangement of pyrrolo[2,1-*c*][1,4]benzodiazepine-5,11-diones **332** ($n = 1$) and pyrido[2,1-*c*][1,4]benzodiazepine-6,12-diones **333** ($n = 2$) into 5-chloro-1,2,3,4-tetrahydro-benzo[*h*][1,6]naphthyridine **334** and 6-chloro-2,3,4,5-tetrahydro-1*H*-azepino

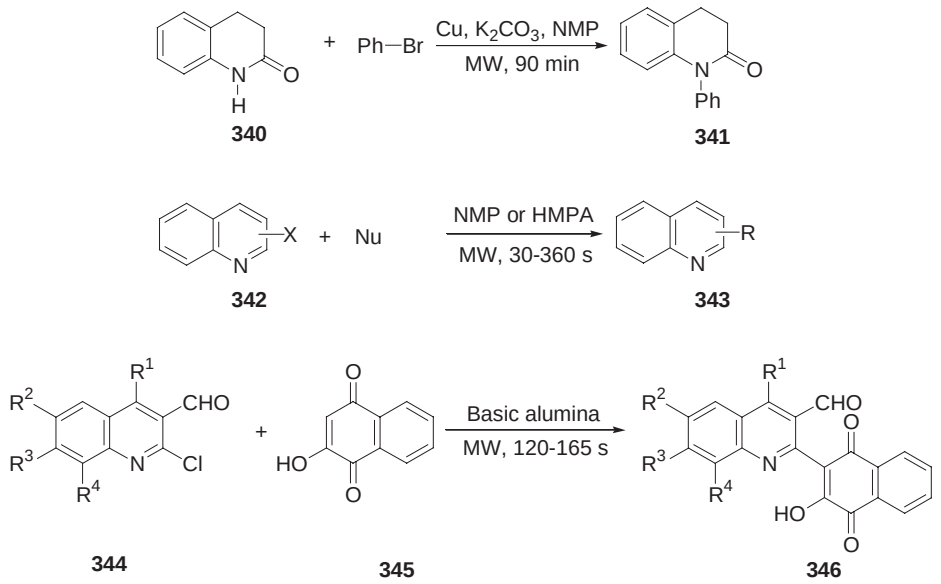


Scheme 67



Scheme 68

[3,2-*c*]quinoline **335** in 43–53% and 28–45% yields, respectively, occurred in the presence of $POCl_3$ and a catalytic amount of pyridine under MW heating for 105 min (Scheme 68). The rearrangement occurred also under conventional heating conditions, but with a significantly lower rate (5 h) (00T1361). Based on analytical data, the structures cyclopentabenzodiazepine **336** and dibenzodiazepine **337** were initially proposed for the rearranged products (95TL6673). However, X-ray diffraction analysis revealed that the structures have a quinoline and not a benzodiazepine skeleton and demonstrated benzonaphthyridine and azepinoquinoline structures **334** and **335**,



Scheme 69

respectively. Treatment of **334** and **335** (R = R^1 = H) with *N*-methylpiperazine in DMF at 240 °C in a sealed tube under MWI for 60 min gave amidines **338** and **339** in 68% and 40% yields, respectively (00T1361).

The MW-enhanced Goldberg reaction of 3,4-dihydro-1*H*-quinolin-2-one (**340**) with bromobenzene produced 1-phenyl-3,4-dihydro-1*H*-quinolin-2-one **341** within 30 min at 200 °C, followed by 1 h at 190 °C (Scheme 69) (02TL1101); 4 h were required under conventional heating.

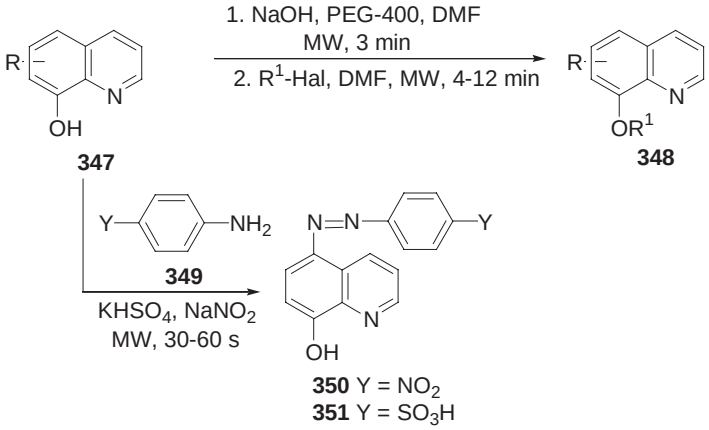
The substitution reaction of 2-chloroquinoline **342** with 1.2–4.0 equivalents of PhSNa, MeSNa, EtONa, MeONa, and $PhNH_2$ in NMP or HMPA solvent was carried out by heating in a monomode MW reactor at 70–120 °C for 30–360 s to give the corresponding 2-substituted quinolines **343** in 66–99% yields (Scheme 69). Similar reactions were performed on 3-bromoquinoline **342** by MWI at 90–120 °C for 35–240 s to give 3-substituted quinolines in 30–98% yields (02T1125); the substitution reaction of 3-bromoquinoline with PhSNa by conventional heating at 165 °C for 7.5 h gave a low yield (18%) of 3-phenylthioquinoline (83JOC4214).

Basic alumina catalyzed C–C bond formation between 2-hydroxy-1,4-naphthoquinone **345** and 2-chloroquinoline derivative **344** in CH_2Cl_2 under MWI for 120–165 s to give **346** in 94–98% yields (Scheme 69) (00MI2). Conventional heating required 4–6 h to give 70–82% yields (80TL5011).

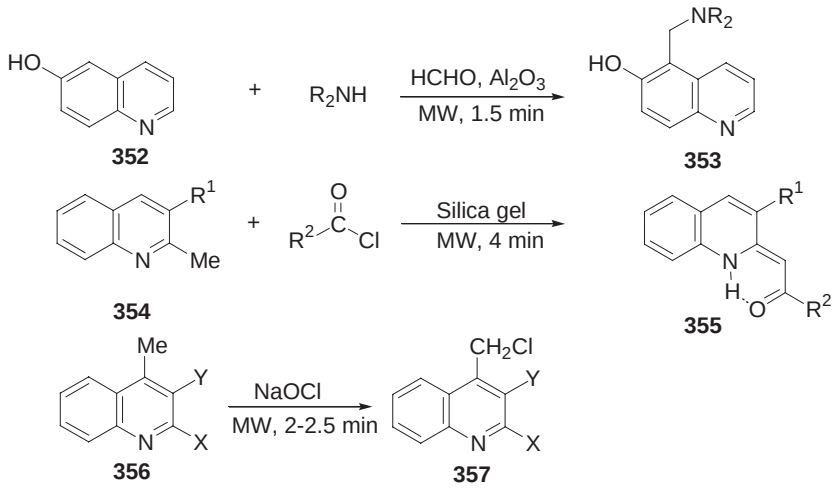
Ethers are generally prepared by the Williamson reaction. Although the phase transfer catalysis technique has been successfully used, it required a long reaction time. However, when MWI was applied to the reaction of 8-hydroxyquinolines **347** with organic halides, it proved to be very simple and afforded fair to good yields (54–91%) of the respective ethers **348** (Scheme 70) (98SC2407).

A one-pot method for the synthesis of azo dyes in high yields by using MWI for a very short time in the absence of solvent was developed. Thus, an equimolar mixture of the aniline derivatives **349**, sodium nitrite, potassium hydrogen sulfate, and 8-hydroxyquinoline **347** (R = H) was irradiated for 30–60 s in an MW oven, followed by addition of a drop of water to give about 80–85% yields of the azo dyes **350** and **351** (Scheme 70) (00SC829).

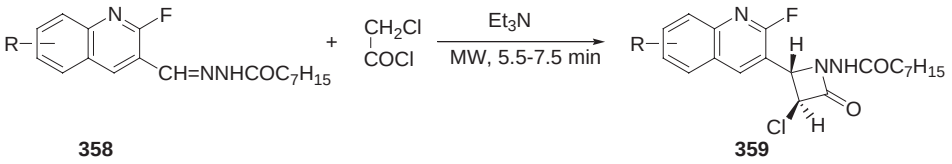
The Mannich reaction involving the aminomethylation of electron-rich compounds without any solvent in the presence of acidic alumina under MWI gave good to excellent yields (00SC69). Thus, a mixture of 6-hydroxyquinoline (**352**) with a secondary amine, formaldehyde, and acidic alumina was irradiated 3 times, each time for 30 s and with 5 min intervals to give the aminomethylated products **353** in 46–98% yields (Scheme 71).



Scheme 70

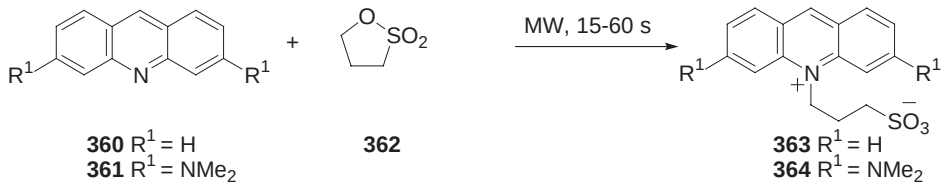


Scheme 71



358 **359**

Scheme 72



360 R^1 = H
361 R^1 = NMe_2

362

363 R^1 = H
364 R^1 = NMe_2

Scheme 73

Silica gel catalyzed the reaction of 2-methylquinolines **354** with acyl chlorides under solvent-free conditions using MWI to give 2-ketomethylquinolines **355** in 53–91% yields within 4 min (Scheme 71). The reaction of 2-methylquinoline **354** (R^1 = H) with benzoyl chloride without irradiation was unsuccessful at room temperature and at 200 °C (01TL4363).

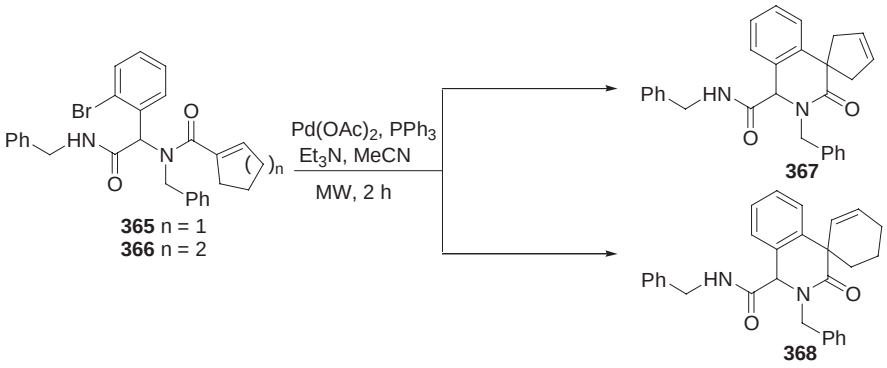
The chlorination of a side-chain methyl group of substituted quinolines **356** by using sodium hypochlorite under MWI gave the corresponding chloromethyl derivative **357** in 90–96% yields (Scheme 71) (98JCR(S)586).

The reaction of the acylhydrazones **358** with chloroacetyl chloride in the presence of triethylamine under MWI gave the corresponding *β*-lactams **359** in 70–78% yields within 5.5–7.5 min (Scheme 72). Under conventional heating, it required longer times (5–8 h) to give lower yields (55–62%) (00M85).

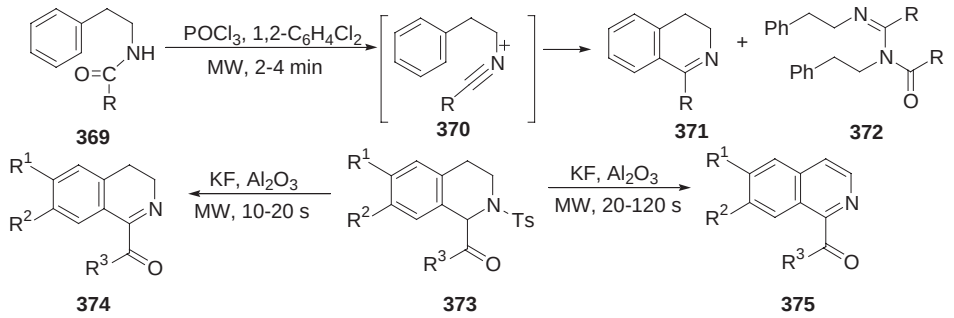
Acceleration of the N-alkylation of acridine derivatives **360** and **361** with 1,3-propane sultone (**362**) took place on irradiation for 15–60 s in an MW oven to give the *N*-(3-sulfonatopropyl)acridinium inner salts **363** and **364**, respectively. The yields (68–81%) were good to excellent with minimal side reactions (Scheme 73), while the conventional conditions required heating at >100 °C for 1–4 h (98TL9587).

The MW-assisted Heck reaction of **365** and **366** in MeCN and in the presence of $Pd(OAc)_2$, PPh_3, and Et_3N at 125 °C for 2 h gave the spirocyclic products **367** and **368**, respectively, in excellent yields (91–98%), with high diastereoselectivity (Scheme 74) (04TL417). Under conventional conditions, analogs of such spirocyclic systems have been prepared with longer times (18 h) and lower yields (73–76%) (87JOC4130).

The Bischler–Napieralski reaction (1893CB1903) of the amides of β-phenethylamides **369** gave 3,4-dihydroisoquinolines **371** in high yields on heating in toluene or xylene for several hours in the presence of $POCl_3$ or P_2O_5. When a toluene solution of amide **369** and $POCl_3$ was irradiated in an MW oven for several minutes, acylamidine **372** (R = Ph) and only traces of the desired 3,4-dihydroisoquinoline **371** were obtained (Scheme 75). On the other hand, when a chlorobenzene solution was



Scheme 74

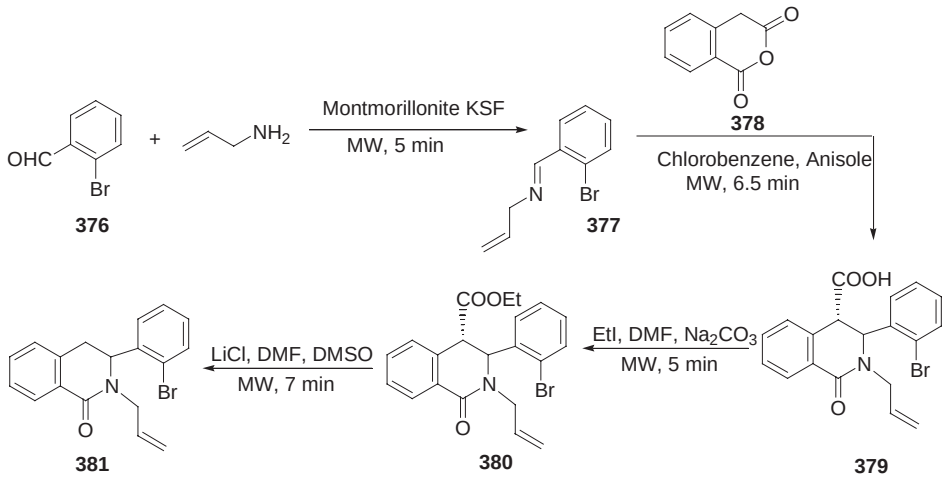


Scheme 75

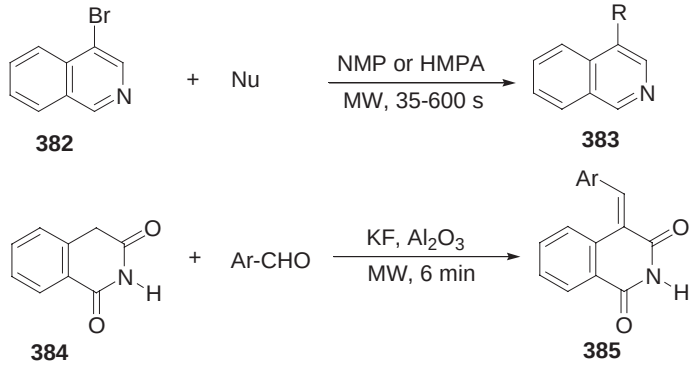
irradiated for 2–4 min at 110–120 °C, the product was a mixture of **371** and **372** in a ratio 40:60. That ratio was reversed to 90:10 by using *o*-dichlorobenzene solvent to give **371** in 72% yield (91JOC6968).

Selective formation of 3,4-dihydroisoquinolines or isoquinolines from *N*-sulfonyl tetrahydroisoquinolines **373** supported on KF/alumina was achieved under solvent-free conditions using MWI depending on the irradiation time. When the irradiation time was 10–20 s, dihydroisoquinolines **374** were obtained in 60–92% yields while increasing irradiation time to 20–120 s, isoquinolines **375** were obtained in 49–86% yields (Scheme 75). Conventional heating of **373** with KF/Al_2O_3 in toluene afforded the corresponding 3,4-dihydroquinoline after 48 h reflux (02SL907).

o-Bromobenzaldehyde (**376**) reacted with allylamine under solvent-free conditions in the presence of montmorillonite KSF with MWI to give the corresponding Schiff base **377** in a quantitative yield within 5 min. It was then reacted with homophthalic anhydride in chlorobenzene/anisole under MWI to afford **379** after 6.5 min. The carboxylic group was esterified with EtI under MWI to give **380** in 61% yield within 5 min. De-esterification under MWI using LiCl in DMF/DMSO was accompanied by decarboxylation to give **381** in 68% yield within 7 min (Scheme 76) (02S1578). Under conventional heating at 115 °C, the process required an hour (98H639).



Scheme 76

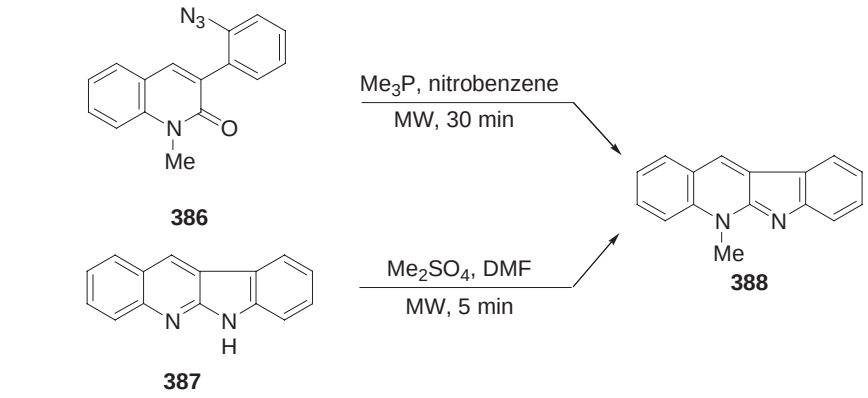


Scheme 77

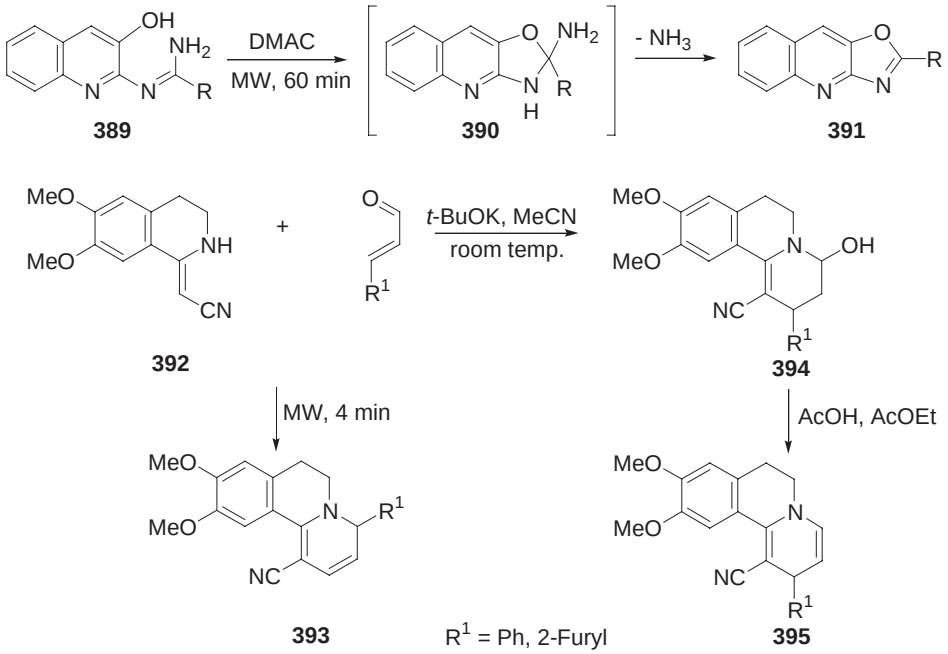
Nucleophilic-substitution reactions of 4-bromoisoquinoline (**382**) with thiolate and alkoxy ions were completed within 35–600 s under MWI to give the corresponding 4-substituted isoquinoline **383** in 53–98% yields (Scheme 77) (02T1125).

The reaction of 1,2,3,4-tetrahydroisoquinoline-1,3-dione (**384**) with aromatic aldehydes on the basic catalyst KF on alumina without a solvent, under focused MWI gave 4-(arylmethylene)-1,2,3,4-tetrahydroisoquinoline-1,3-dione **385** as the only *Z*-isomer within 6 min in 72–94% yields (Scheme 77). This stereochemistry corresponded to the thermodynamically more stable isomer according to AM1 calculations. However, the reaction was slow with hindered aldehydes such as 2,6-dichlorobenzaldehyde whereas prolonged MWI caused degradation of the product (98SC3195). The reaction took place slowly at room temperature, but it was generally incomplete after 24 h.

An intramolecular aza-Wittig reaction in 3-(*o*-azidophenyl)-1-methyl-1*H*-quinolin-2-one (**386**) by using trimethylphosphine in refluxing nitrobenzene for 24 h gave



Scheme 78



Scheme 79

the alkaloid cryptotackieine **388** in 24% yield. A better yield (40%) and shorter reaction time (30 min) were achieved under MWI (Scheme 78) (99TL7275, 01T6197).

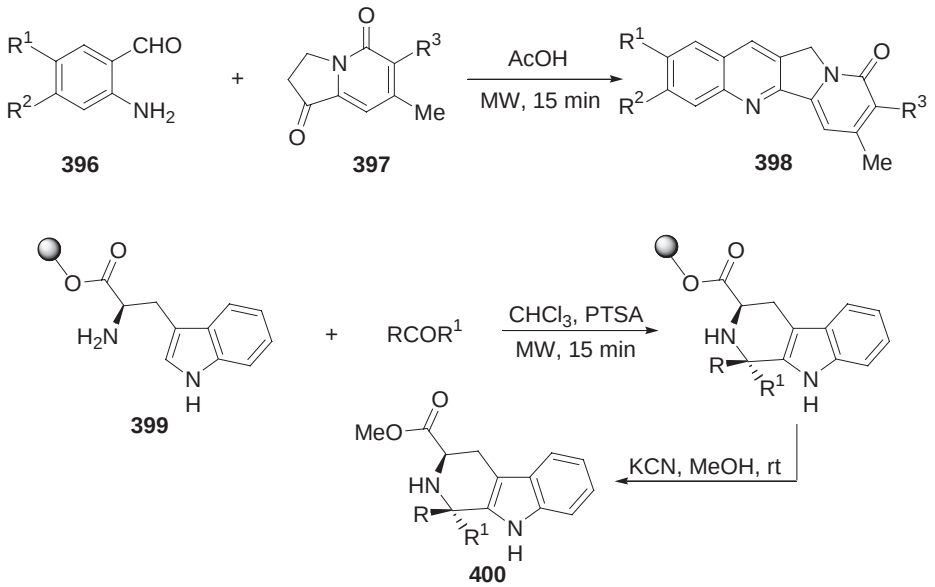
MW promoted methylation of 6*H*-indolo[2,3-*b*]quinoline (**387**) with dimethyl sulfate in DMF at 140 °C to provide **388** in 75% yield within 5 min (Scheme 78) (99S326).

Intramolecular cyclization of hydroxyamidines **389** by heating or MWI gave the oxazoloquinolines **391** in 85–96% yields (Scheme 79). The reaction time was reduced under MWI from 5 to 1 h without significantly affecting the yields (03S2033).

Cyclocondensations of 1-cyanomethylene tetrahydroisoquinoline (**392**) with α,β-unsaturated aldehydes were assisted by MWI to afford 6,7-dihydro-4*H*-benzo[*a*]quinolizines **393** in 72–85% yields within 4 min (Scheme 79). But under conventional conditions, compounds **393** were produced in 65–70% yields after 2–5 h heating. On the other hand, base-catalyzed cyclization of **392** with α,β-unsaturated aldehydes was carried out at room temperature to give **394**, which underwent acid-catalyzed dehydration to **395** on treatment with AcOH/AcOEt. The marked difference between the two reactions may be due to the different nucleophilic character of the nitrogen and the C-1′ carbon atoms in **392**, whereby in the absence of the base, the nucleophilic addition of the carbon atom to the carbonyl group was favored and the ring closure gave **393** (03SL250).

Tetrahydroindolizinediones **397** reacted with 2-aminobenzaldehydes **396** on heating under reflux in acetic acid for 8 h to give indolizino[1,2-*b*]quinolines **398** in 31–51% yields. Under MWI, the yields were improved (57–91%) perhaps owing to the shortened reaction times (15 min) that limited any degradation of unstable reactants (Scheme 80) (02SL2077).

1,2,3,4-Tetrahydro-β-carbolines, important structural elements of many tryptophan-derived natural alkaloids, showed a broad spectrum of pharmacological activities. One-pot cyclocondensation of polymer-bound tryptophan **399** with different aldehydes and ketones in $CHCl_3$ in the presence of *p*-toluenesulfonic acid (PTSA) as catalyst were carried out under MWI to give polymer-bound 1,2,3,4-tetrahydro-β-carboline derivatives within 15 min. Subsequent reaction with KCN in MeOH at room temperature gave **400** in 87–96% yields (Scheme 80). When cyclization was carried out under reflux in $CHCl_3$ for 15 min using identical stoichiometry, no



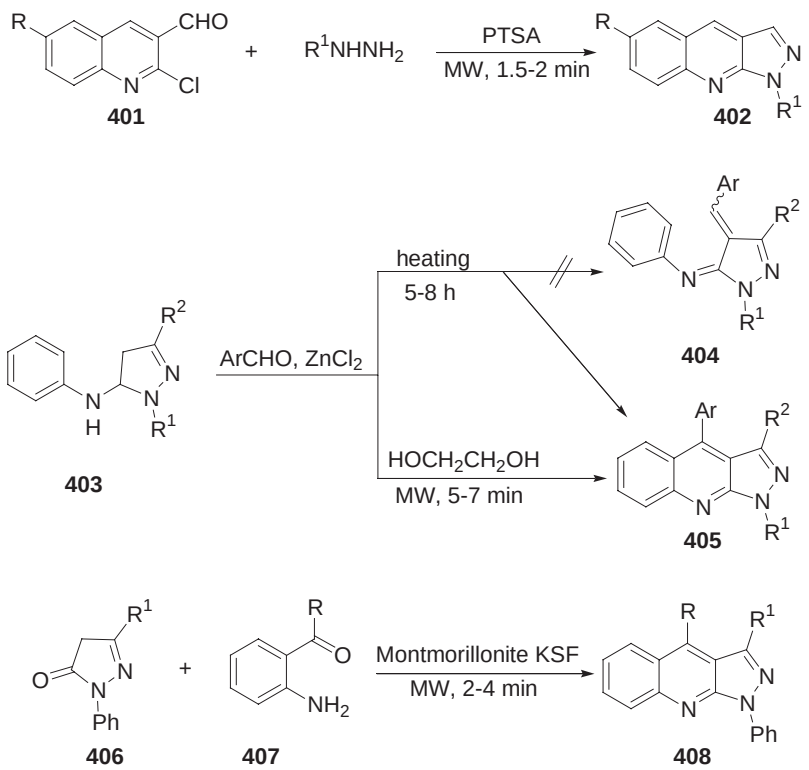
Scheme 80

product was formed, but the cyclized products were produced in a quantitative yield after 6 h reflux (02SL1709).

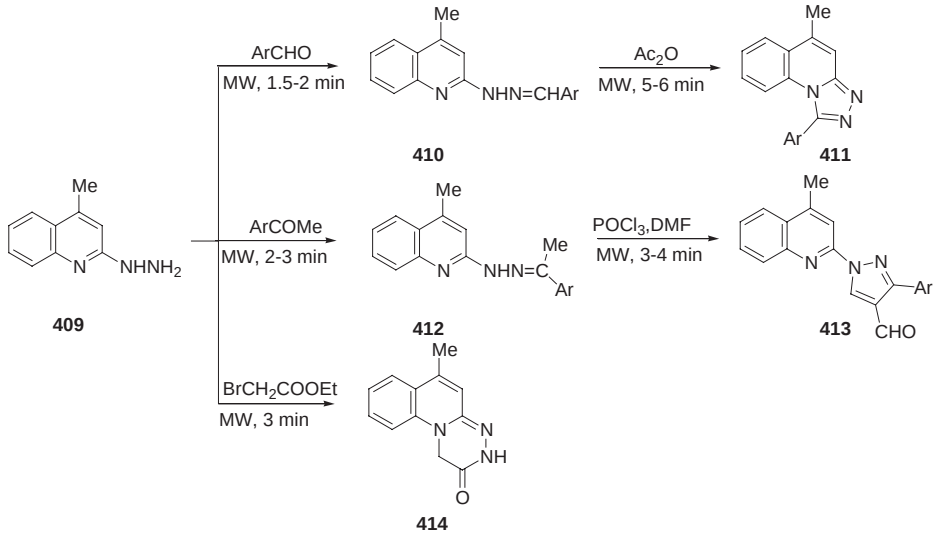
A common method for the synthesis of condensed pyrazoles involves the reaction of *β*-chlorovinylaldehydes with hydrazine hydrate or phenylhydrazine. Thus, pyrazolo[3,4-*b*]quinolines **402** were prepared in 44–82% yields from 2-chloro-3-formylquinolines **401** and hydrazine hydrate or phenylhydrazine in refluxing ethanol within 5–7 h (94OPP383). The reaction in the presence of PTSA and MWI gave higher yields (78–97%) within shorter times (1.5–2.5 min) (Scheme 81). When solid supports, including silica gel, alumina, montmorillonite K_{10}, or $HCOOH/SiO_2$ were used, lower yields (10–43%) were obtained (01TL3827).

Condensation of **403** with aromatic aldehydes in the presence of $ZnCl_2$ produced the corresponding 4-arylidenepyrazole derivatives **404** in 50–75% yield after 5–8 h heating at 140–150 °C. However, when the reaction was done under MWI for 5–7 min, the products were identified as 1*H*-pyrazolo[3,4-*b*]quinolines **405** and not **404** albeit in lower yields (40–71%) (Scheme 81) (00MI4). Reaction of **407** with pyrazolones **406** gave **408** (99SC4403).

Condensation of 2-hydrazino-4-methylquinoline (**409**) with aromatic aldehydes under MWI led to 2-arylidenehydrazino-4-methylquinolines **410** in 95–98% yields; cyclization to 1,2,4-triazolo[4,3-*a*]quinoline derivatives **411** (85–92%) was also



Scheme 81



Scheme 82

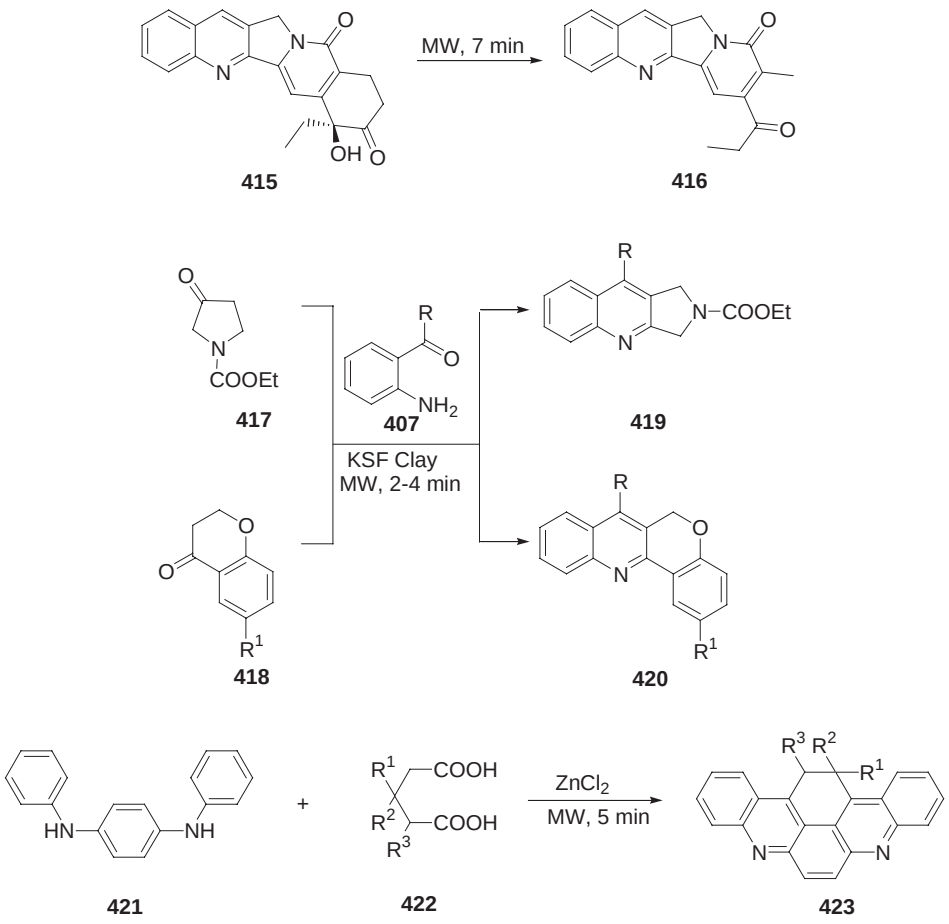
achieved under MWI for 5–6 min (Scheme 82). Similarly, **409** with aromatic ketones under MWI gave hydrazones **412** in 94–98% yields. Reaction of which with $POCl_3$ in DMF under MW heating for 3–4 min gave 2-pyrazolyl-quinoline derivatives **413** in 70–77% yields. MWI of **409** with ethyl bromoacetate gave **414** in 84% yield (Scheme 82) (98IJC(B)174).

A naturally occurring pyrrolo[3,4-*b*]quinoline alkaloid **415**, named camptothecin, has a promising antineoplastic activity in animal tumor models. When **415** was irradiated with MW under solvent-free conditions, it gave mappicine ketone **416** in 96% yield within 7 min (Scheme 83); **416** was found to be an antiviral lead compound. Under conventional conditions, **415** reacted with borontrifluoride etherate in THF at room temperature for 1.5 h to give **416** in 65% yield (98TL431).

Polycyclic quinoline derivatives can be prepared in good yields by the Friedländer synthesis: an acid- or base-catalyzed condensation, between 2-aminobenzaldehyde or 2-aminoarylketones **407** and ketones possessing an active methylene group followed by cyclodehydration. Thus, the condensation of **407** with *N*-carbethoxy-3-pyrrolidone (**417**) or 4-chromanone **418** catalyzed by montmorillonite KSF under MWI and solvent-free conditions gave quinolines **419** and **420**, respectively (Scheme 83) (99SC4403).

One-pot synthesis of helical aromatics **423** was achieved under MWI by the reaction of *N*,*N*′-diphenyl-*p*-phenylenediamine (**421**) and dicarboxylic acids **422** under solvent-free conditions in the presence of a Lewis acid. Compounds **423** were obtained within 5 min in 34–84% yields (Scheme 83), but conventional heating required 9 h to give 18–80% yields (04JOC7794).

2-Amino-3-(*p*-chlorophenyl)-1,8-naphthyridine (**424**) reacted with HNO_2 to give 1,2-dihydro-3-(*p*-chlorophenyl)-1,8-naphthyridin-2-one (**425**), whose reaction with $POCl_3$ under MWI for 3 min gave 2-chloro-3-(*p*-chlorophenyl)-1,8-naphthyridine

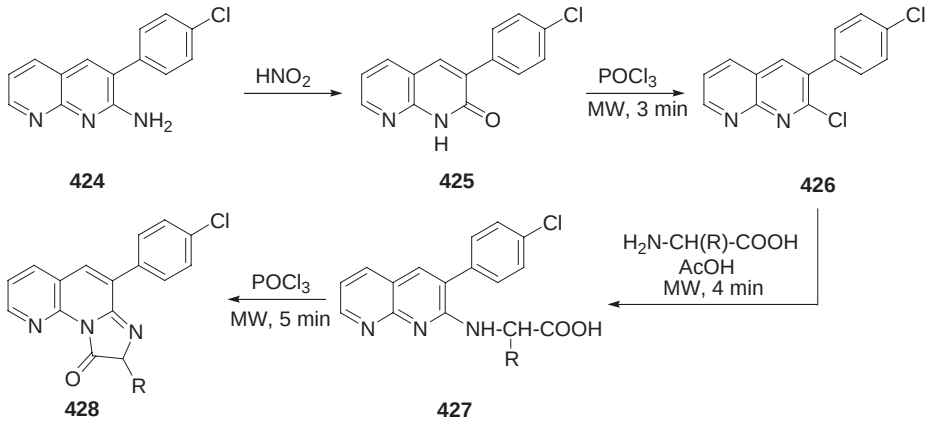


Scheme 83

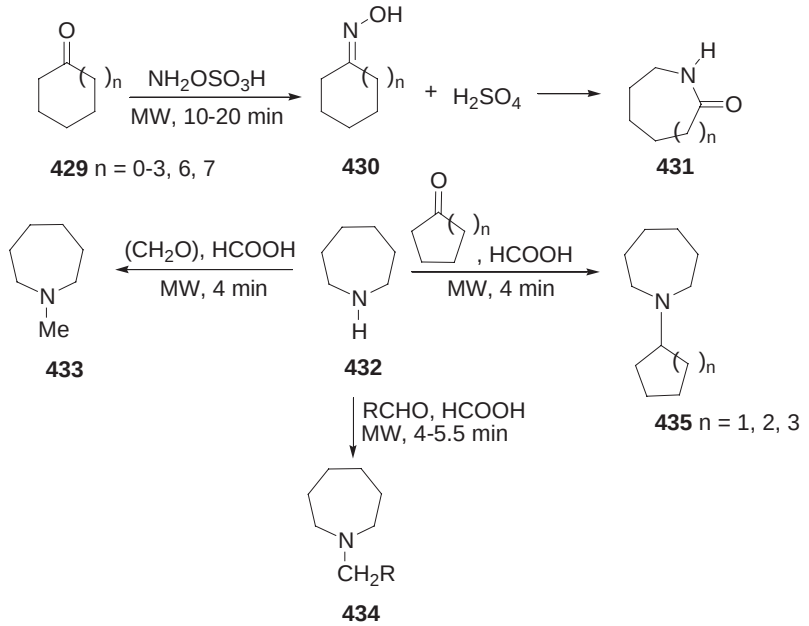
(**246**) in 88% yield (Scheme 84). Reaction of **246** with α-aminoacids in glacial acetic acid under MWI gave 2-carboxyalkylamino-3-(*p*-chlorophenyl)-1,8-naphthyridines **427** in 86–94% yields within 4 min. Treatment of **427** with $POCl_3$ under MWI afforded imidazo[1,2-*a*][1,8]naphthyridin-1(2*H*)-ones (**428**) in 93–90% yields within 5 min (Scheme 84), instead of 6–7 h under conventional heating (02SC857).

I. Azepines

Formation of lactams **431** was achieved in good yields (60–86%) by allowing a mixture of alicyclic-ketones **429** and hydroxylamine-*O*-sulfonic acid adsorbed on SiO_2 to be irradiated in a focused MW oven for 10–20 min (Scheme 85). The reaction proceeded by forming the oxime **430** and sulfuric acid, which promoted a Beckmann rearrangement of **430** to give lactams **431** (95JCS(CC)1101).



Scheme 84



Scheme 85

Reductive amination, a suitable method for N-alkylation of amines, can be carried out using methanolic pyridine-borane under conventional conditions at room temperature for 3–16 h (95JOC5995). Under MWI, alkylation of hexahydroazepine **432** with paraformaldehyde and formic acid gave 70% of *N*-methylhexahydroazepine **433** after 4 min of irradiation (Scheme 85) (01JCR(S)292). Similarly, *N*-alkyl and *N*-cycloalkylhydroazepines **434** and **435** were obtained in 28–81% yields.

III. Heterocycles with Two Heteroatoms

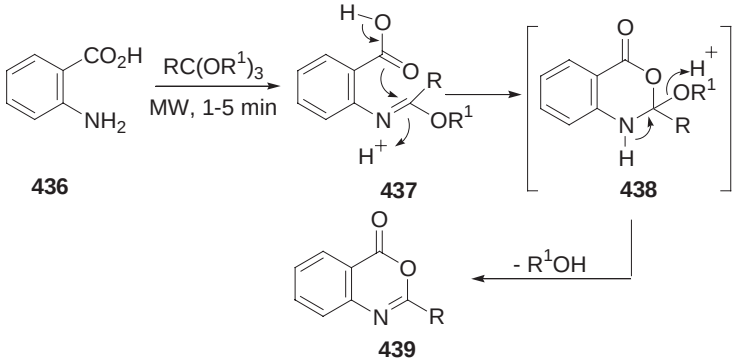
A. Oxa(thia)zines and their Fused Rings

An efficient method for the synthesis of 2-substituted benzoxazin-4-ones was performed by the condensation of anthranilic acid (**436**) with various orthoesters by classical heating for 1–2 h to give 75–91% yields. But under MWI in an open vessel, a rapid formation of benzoxazin-4-ones **439** in high yields (76–94%) took place within 1–5 min (Scheme 86). The reaction may proceed through the imidic ester intermediate **437**, which upon nucleophilic attack by the carboxyl oxygen produced the cyclized intermediate **438** that then eliminated a molecule of alcohol to give **439** (97JCR(S)286).

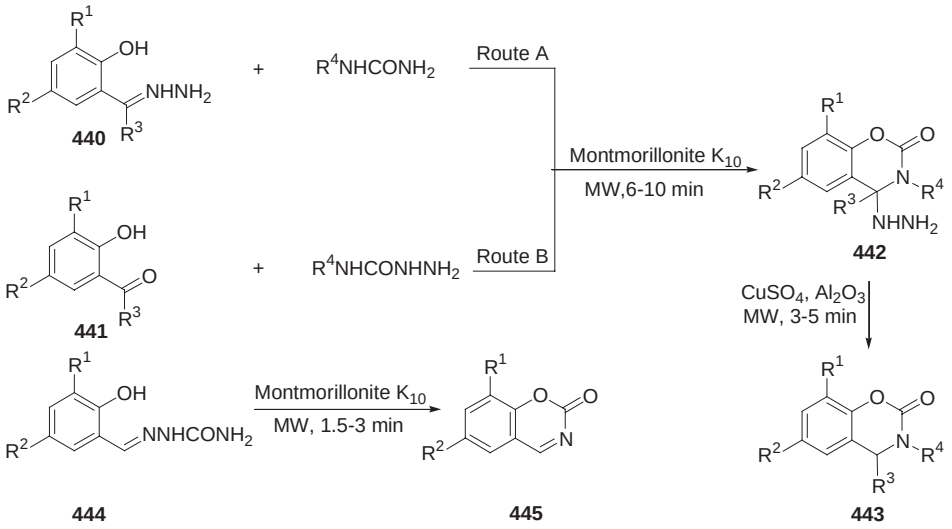
Various potentially useful benzoxazin-2-ones were prepared by the reaction of hydrazones **440** with aryl-/alkyl-ureas (route A) and by salicylaldehyde or 2-hydroxyacetophenones **441** with 4-aryl-/alkyl-semicarbazides (route B), in the presence of montmorillonite K_{10}, under MWI for 6–10 min to give 4-hydrazinobenzoxazin-2-ones **442** in 78–89% yields (Scheme 87). On heating in an oil bath, compounds **442** were obtained in lower yields (40–53%) and required more time (3–6 h). When **442** were irradiated by MW for 3–5 min on alumina-supported copper(II) sulfate without a solvent, the corresponding benzoxazin-2-ones **443** were obtained in 68–80% yields (Scheme 87); this reductive dehydrazination required 2–4 h to give **443** in 34–39% yields by conventional heating (04JOC8118).

Dehydrazinative cyclization of salicylaldehyde semicarbazones **444** was affected under solvent-free conditions on montmorillonite K_{10} using MWI to give 2*H*-benz[*e*]-1,3-oxazin-2-ones **445** in 83–94% yields within 1.5–3 min (Scheme 87). Employing conventional heating in an oil bath, this cyclization could not be completed (only 60% conversion) after 20 h (02TL8551).

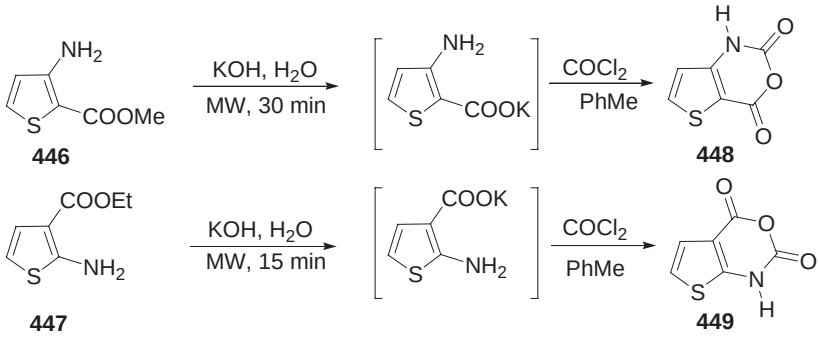
Thiaisatoic anhydrides have been considered as precursors for the synthesis of tricyclic compounds containing thiophene ring. Syntheses of these anhydrides have a major problem owing to the instability of their precursors thiophene *o*-aminoacids, which easily decarboxylate at room temperature. Under MWI, alkaline hydrolysis of



Scheme 86



Scheme 87



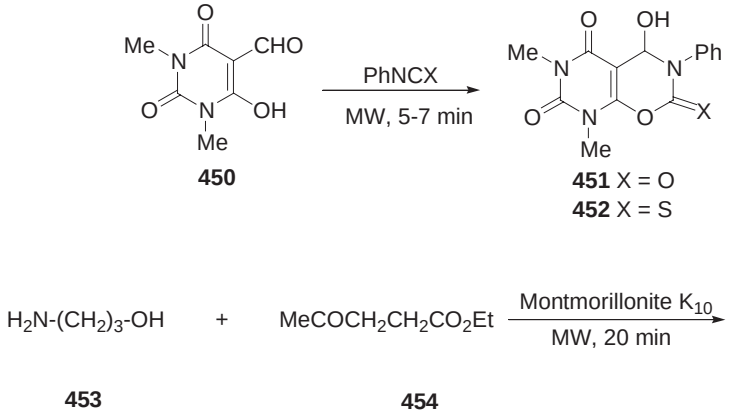
Scheme 88

o-aminoesters **446** and **447** gave the corresponding potassium carboxylates on a large scale within 15–30 min; further, on treatment with phosgene in toluene gave 85% and 67% yields of 2- and 3-thiaisatoic anhydrides **448** and **449**, respectively (Scheme 88) (98T10789).

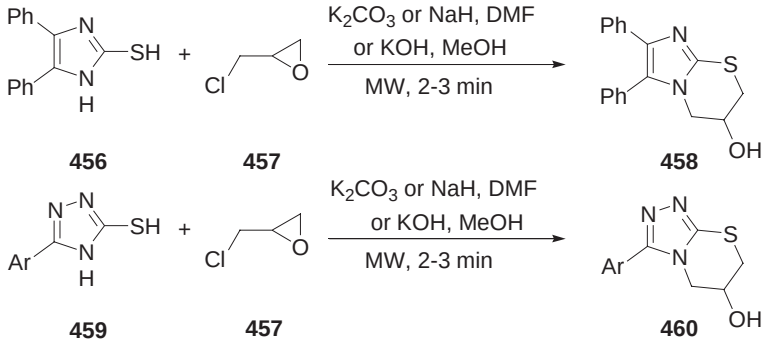
Reaction of **450** with phenyl isocyanate under MWI for 5 min in the absence of a solvent gave the corresponding oxazino[4,5-*d*]pyrimidine **451** in 87% yield. Under similar conditions, **450** reacted with phenyl isothiocyanate to afford the corresponding thio-oxazino[4,5-*d*]pyrimidine analog **452** in 85% yield (Scheme 89) (04TL2405).

Fused oxazine with bridge-head nitrogen **455** can be prepared in 60% yield from the reaction of aminoalcohol **453** adsorbed onto montmorillonite K_{10}, with ethyl levulinate (**454**) under MWI for 20 min (Scheme 89) (92SL219).

Imidazolo[2,3-*b*]thiazine **458** and triazolo[3,4-*b*]thiazine **460** were prepared in 80–85% yields by base-catalyzed reaction of imidazole **456** or triazole **459** with



Scheme 89



Scheme 90

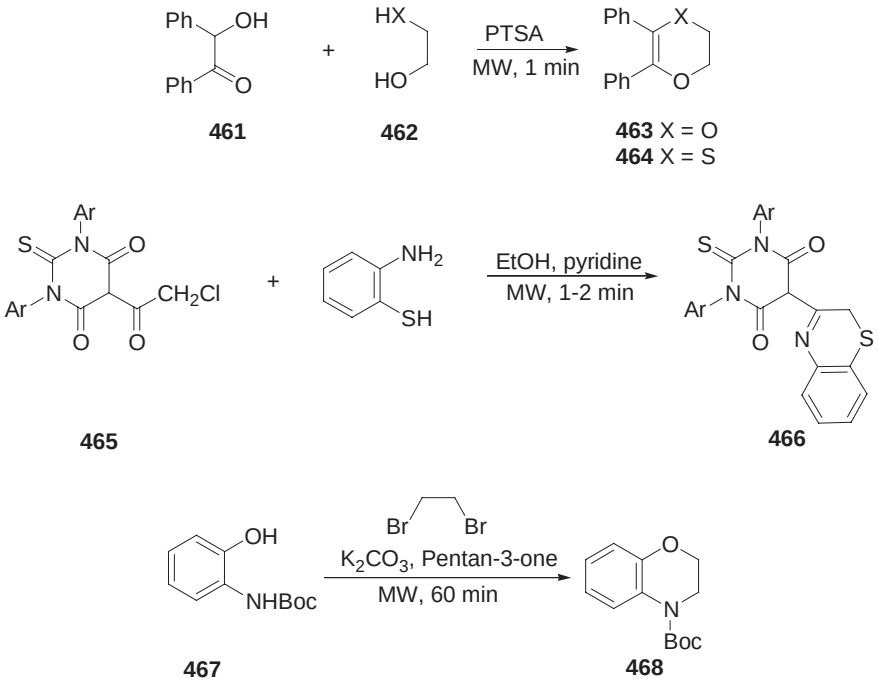
epichlorohydrin **457** in DMF or MeOH solvent after 2–3 min of MWI (Scheme 90) (05UP2, 05UP3).

Condensation of benzoin (**461**) with ethylene glycol or 2-mercaptoethanol **462** in the presence of PTSA as a catalyst under MWI for 1 min gave 5,6-dihydro-2,3-diphenyl-1,4-dioxene **463** and 5,6-dihydro-2,3-diphenyl-1,4-oxathiin **464** in 95% and 65% yields, respectively (Scheme 91) (01MI4).

Reaction of **465** with 2-aminobenzenethiol in absolute ethanol in the presence of pyridine, under both MWI and classical conditions, gave the benzothiazines **466** in 63–77% yields (Scheme 91). The reaction was 180 times faster using MWI (97JCR(S)16).

The 2,3-dihydrobenzoxazine **468** was obtained in 75% yield by heating **467** with 1,2-dibromoethane in refluxing acetone in the presence of excess K_2CO_3 for 18 h. This reaction was performed under MWI for 1 h in pentan-3-one to give 76% yield (Scheme 91) (00T605).

Several methyl aryl ketones reacted with sulfur and morpholine (**469**) under solvent-free conditions in a domestic MW oven for 3.5–6 min to give thiomorpholides



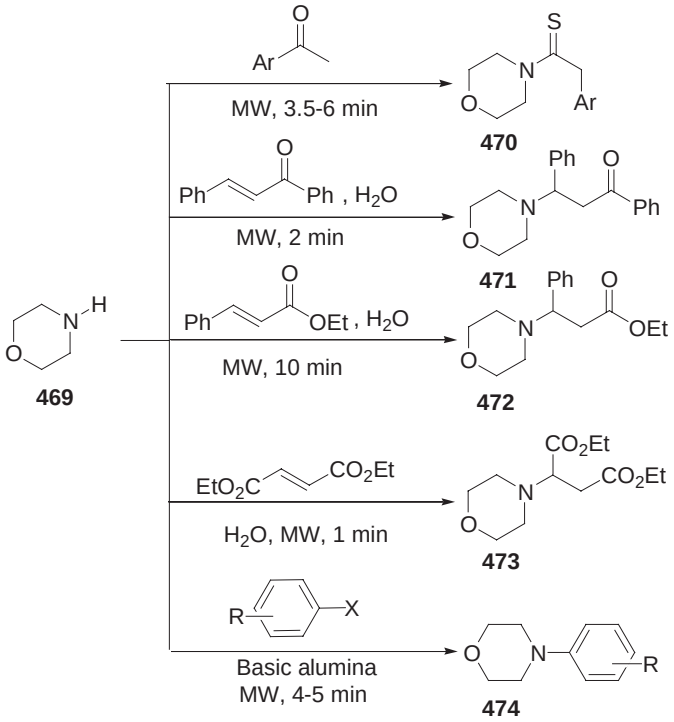
Scheme 91

470 in good yields (55–81%) (Scheme 92). This, the Willgerodt–Kindler reaction, needed high temperature and long reaction time (several hours) to give low to moderate yields (99TL7549).

The Michael addition of secondary amines to α,β-unsaturated carbonyl compounds under MWI essentially required the presence of water to drive the amine addition to completion and the presence of at least 10 mole equivalents of the amine. Besides increasing the polarity and possibly some micellar effect, water facilitates protonation of the resulted enolate from amine addition. In a typical procedure, benzalacetophenone was mixed with morpholine (**469**) and water in a teflon flask and subjected to MWI for 2 min to yield 93% of the 1,4-adduct **471** (Scheme 92). The method was also extended to other morpholine derivatives **472** and **473** in 30% and 100% yields, respectively (00SC643).

The synthesis of *N*-arylamines **474** by amination of aryl halides with morpholine (**469**) was carried out in the presence of basic alumina under MWI. This required 4–5 min of irradiation to give 88–89% yields (Scheme 92). Conventional heating at 120 °C required 8 h for completion to give 65–69% yields (00MI3).

Although some solution-phase Ugi reactions were known to proceed rapidly, reaction times from 24 h to several days have been usually required for the solid phase. However, MWI-assisted solid-phase Ugi condensations of 2-morpholinoethyl isocyanide **475**, aldehydes, and carboxylic acids in a mixture of dichloromethane and methanol (2:1) on amino-functionalized TentaGel S Ram as support gave



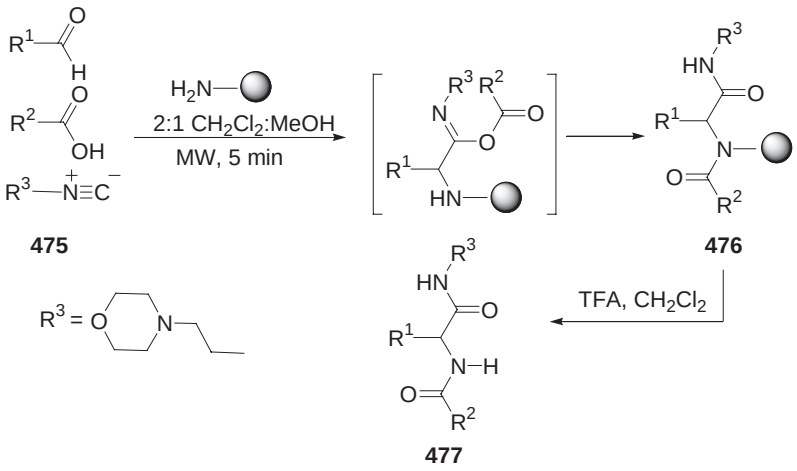
Scheme 92

α-acylamino amide derivatives **476**. Subsequent cleavage from the resin gave **477** in high purity and in 24–95% yields after 5 min (Scheme 93) (99TL3941).

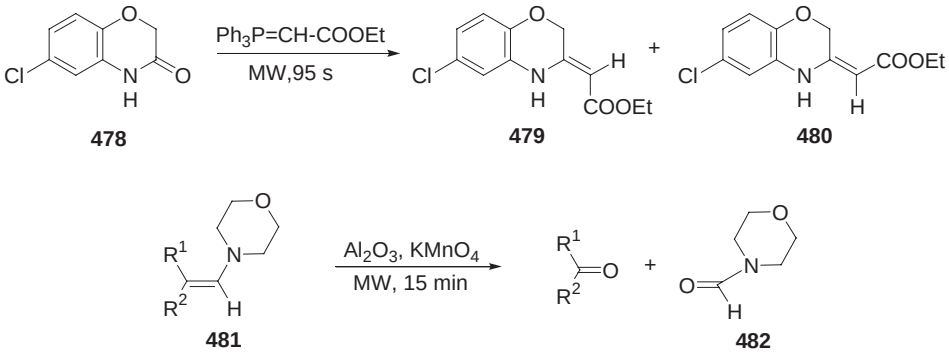
Wittig olefination of **478** with the two carbon stable ylide ethoxycarbonylmethylene (triphenyl)phosphorane under MWI gave **479** and **480** in a total yield of 76% within 95 s (Scheme 97). The *E*/*Z* ratio was 15/85 (99TL165).

The oxidative cleavage of *β*,*β*-disubstituted enamines **481** in a homogeneous medium with $K_2Cr_2O_7$, CrO_3, MnO_2, or $NaIO_4$ over montmorillonite K_{10} under MWI led to the hydrolysis of the enamine. Also, with MnO_2 over bentonite, hydrolysis was the main reaction, but small yields of ketones were formed. However, oxidative cleavage over $KMnO_4$ supported on alumina without a solvent, under MW heating for 15 min, led to ketones and formamide **482** (Scheme 94). Homogeneous irradiation in a focused MW oven gave better yields of ketones than heterogeneous irradiation in a domestic oven, but the yield of **482** was not reported (98TL541).

A general method for preparing phenothiazines **484** by ring closure of the corresponding diphenylamines **483** using sulfur as a reagent and iodine as a catalyst was sometimes tedious and often accompanied by degradation reactions. Adsorbing the reagents on an inorganic solid support, namely, alumina and using MWI for 7–10 min, phenothiazines **484** were obtained in 58–80% yield. On the other hand, the thionation of diphenylamines with sulfur was faster (0.8–3 min) and the yields were better (69–90%), without the support (alumina), since on alumina irreversible



Scheme 93

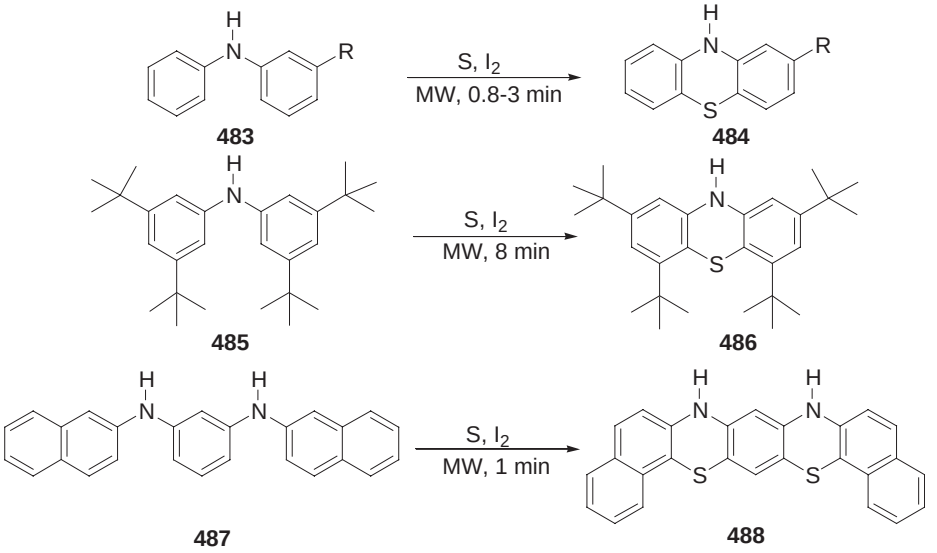


Scheme 94

adsorption of the product after MW treatment probably took place (Scheme 95). Similarly, on the solid support (alumina), compounds **486** and **488** were obtained from **485** and **487**, respectively, within 20 and 10 min in 5% and 70% yield, respectively, while without alumina support they were formed in 50% and 89% yield within 8 and 1 min, respectively (Scheme 95) (98SC337). Conventional conditions required longer times (30–285 min) to produce comparable yields.

B. Pyridazines

Reaction of hydrazide **489** with chloroacetic acid, dichloroacetic acid, and chloroacetyl chloride in the presence of aqueous NaOH afforded the pyridazinediones **490**, **491**, and **492** in 81%, 77%, and 84% yields, respectively (Scheme 96). The reactions required MWI for 1–2 min (97G263).



Scheme 95

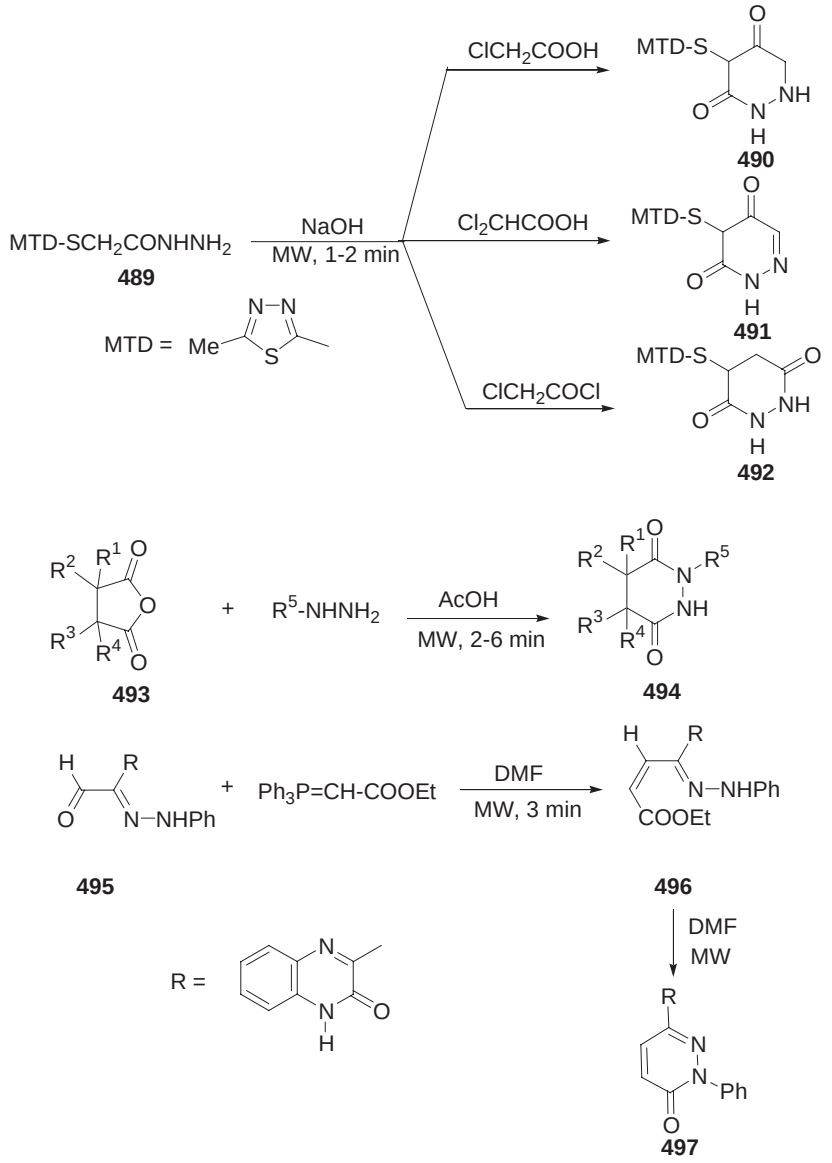
The conditions for the condensation of cyclic anhydrides **493** with hydrazines in acetic acid to give the substituted pyridazinediones **494** were varied, depending on both the reactants, from 1 h by stirring at room temperature to 24 h at solvent reflux. The yields were 45–85% and in some cases no products were obtained. However, under MWI the reaction times can be reduced to 2–6 min leading to the expected derivatives in good to excellent yields (72–88%) (Scheme 96) (96TL4145).

Olefination of hydrazone **495** with ethoxycarbonylmethylene (triphenyl)phosphorane in DMF gave product **496** in 88% yield after MWI for 3 min; conventional conditions required 4 h to give a 76% yield. Further, MWI of compound **496** afforded the pyridazinone **497** while 4 h were needed under heating in DMF to give a 62% yield (Scheme 96) (05UP4).

Glyoxal monophenylhydrazone **498** reacted with methyl acetoacetate under MWI at 70 °C in the presence of piperidine to give the corresponding pyridazinone **499** in 78% yield within 3 min (Scheme 97) (96T5819).

Reaction of **500** and **501** with 2-amino-1-propene-1,1,3-tricarbonitrile (**502**) under reflux for 3 h in the presence of a few drops of piperidine gave compounds **503** and **504**, respectively. When the same reactants were irradiated by MW for 5–10 min, **503** and **504** were obtained in 30% and 40% yields, respectively (Scheme 97) (03MI3).

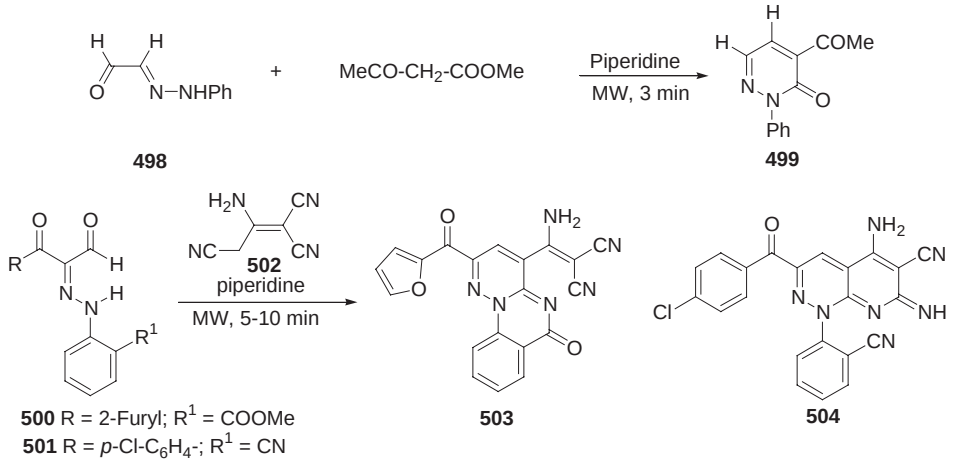
MW played an important role in producing regioselective isomers from Suzuki coupling of 4,5-dichloropyridazinone (**505**) with phenylboronic acid in the presence of Pd catalyst. An extensive MW-assisted screen led to the identification of $Pd(PEt_3)Cl_2$ as an ideal catalyst with superior rate and selectivity. Thus, a mixture of **505** and phenylboronic acid in aqueous acetonitrile was heated under MW for 10 min in the presence of Na_2CO_3 and $Pd(PEt_3)Cl_2$. The catalyst offered excellent selectivity for **505**, whereby 100% conversion occurred to give pyridazinones **506**, **507**, and **508**



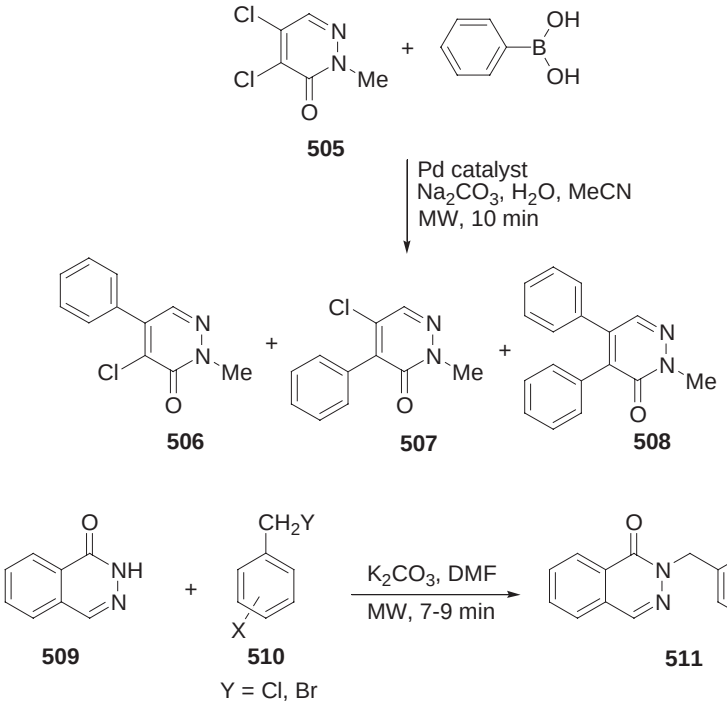
Scheme 96

in 7.7:1.4:1 ratio, respectively. The reaction required 5–8 h at room temperature or 1–6 h at 90 °C to get 100% conversion to **506**, **507**, and **508**. The ratio shows that **506** was the major isomer and **507** or **508** was the minor one (Scheme 98) (04H851).

Benzylation of 1(2*H*)-phthalazinone (**509)** with benzyl halides **510** in the presence of K_2CO_3 in dry DMF took place by MWI to afford 2-benzyl-1(2*H*)-phthalazinones **511** in moderate yields (33–69%) within 7–9 min (Scheme 98) (99JHC1095).



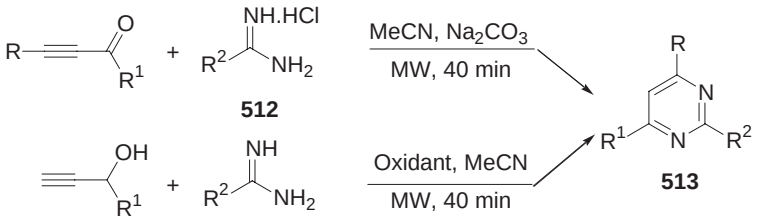
Scheme 97



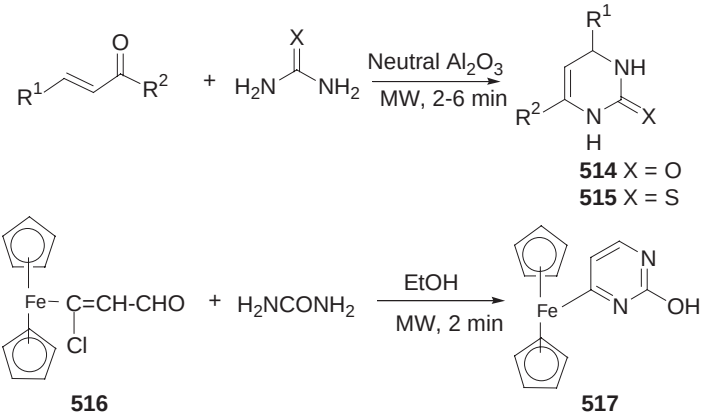
Scheme 98

C. Pyrimidines

Various biodynamic heterocycles such as pyrimidines have been prepared by MWI methodology. Thus, alkynones were reacted with either benzamidine, acetamidine,



Scheme 99



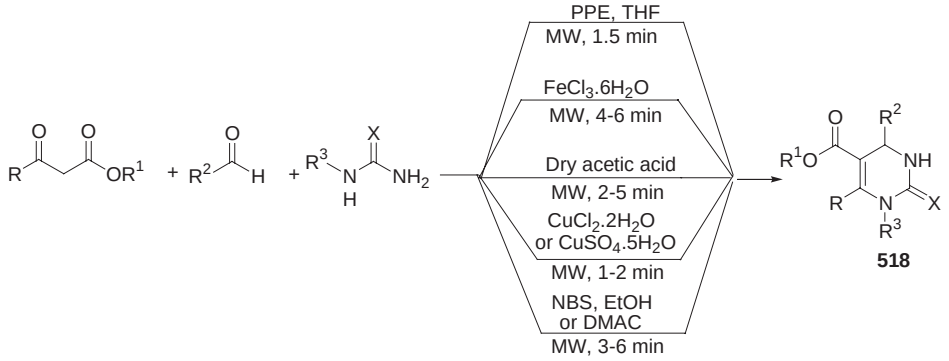
Scheme 100

or guanidine hydrochloride **512** in acetonitrile and in the presence of Na_2CO_3 by irradiation for 40 min to give pyrimidines **513** in nearly quantitative yields (Scheme 99), often without further purification. Under traditional heating, the reaction took place within 2 h to give lower yields (60–98%) that usually required further purification (03SL259).

In a one-pot oxidation-heteroannulation process, pyrimidines **513** were synthesized from propargylic alcohols and benzamidine or acetamidines in the presence of *o*-iodoxybenzoic acid (IBX) or MnO_2 under MWI conditions within 40 min (Scheme 99). The yields (61–84%) were higher than those (30–69%) after heating under reflux (03SL1443).

Chalcones are good precursors for the synthesis of various heterocycles such as pyrimidines. Thus, their treatment with urea supported on neutral alumina under dry conditions and MWI produced 4,6-diaryl-3,4-dihydropyrimidin-2(1*H*)-ones **514**, while on treatment with thiourea produced the corresponding 4,6-diaryl-3,4-dihydropyrimidine-2(1*H*)-thiones **515** (Scheme 100). Shorter times (2–6 min instead of 4–5 h) and better yields (69–85% instead of 59–72%) of products were achieved compared to conventional heating (99SC3237).

Reaction of 3-chloro-3-ferrocenylacrylaldehyde (**516**) with urea gave 49% of 2-hydroxy-4-ferrocenylpyrimidine (**517**) after 2 min of irradiation in an MW oven



Scheme 101

(Scheme 100). However, the same reaction with thiourea afforded a polar green-blue solid that could not be characterized (94CCC175).

Under conventional conditions, a mixture of polyphosphate ester (PPE) in THF served as a better reaction mediator in the three-component Biginelli reaction than the traditional protic solvent/mineral acid media (e.g., EtOH/HCl) (98SL718). Under MWI, a neat mixture of β-keto ester, aryl aldehyde, (thio)urea derivatives, and PPE gave Biginelli products **518** in 65–95% yields within 1.5 min (Scheme 101). The method eliminated the use of solvent and reflux conditions (24 h) and produced higher yields compared to the conventional heating (15–79%) (99S1799).

Biginelli products **518** were obtained by irradiation of thiourea, ethyl acetoacetate, and aldehydes over acidic alumina under MWI to give appreciable yields (80–85%) within 8.5–10.5 min (02JCS(P1)1845). When the reaction was carried out without using a solid support, solvent, or acid, the equimolar amounts of neat reactants gave **518** in better yields (82–90%) within a shorter reaction time (1.5–6.5 min) (02JCS(P1)1845) (Scheme 101).

Racemic monastrol **518** (R = Me, R^1 = Et, R^2 = *m*-OHC_6H_4, R^3 = H) was prepared in 60% yield by MW-promoted condensation of ethyl acetoacetate, 3-hydroxybenzaldehyde, and thiourea in a solvent-free variation of the classical Biginelli synthesis using PPE (00T1859). The racemic mixture was resolved by enantioselective HPLC and the absolute configuration of the (*S*)-(+) enantiomer was established by CD spectroscopy.

Some dihydropyrimidines **518** were prepared in high yields (82–97%) under MWI within 2–5 min by a one-pot cyclocondensation of aldehydes, ethyl acetoacetate, and urea using dry acetic acid. Although the same cyclocondensation gave good yields under conventional conditions, it required much more time (6–15 h) (00JCR(S)345). When the same reaction mixture was catalyzed by ferric chloride hexahydrate under MWI, the synthesis of ethyl 4-aryl-6-methyl-1,2,3,4-tetrahydropyrimidin-2-one-5-carboxylates **518** in 87–95% yields was completed in 4–6 min (Scheme 101) (02SC147).

The reaction was also catalyzed by $CuCl_2 \cdot 2H_2O$ or $CuSO_4 \cdot 5H_2O$ in the absence of a solvent to yield **518** in 80–99% yields within 1–2 min (Scheme 101) (04SL235).

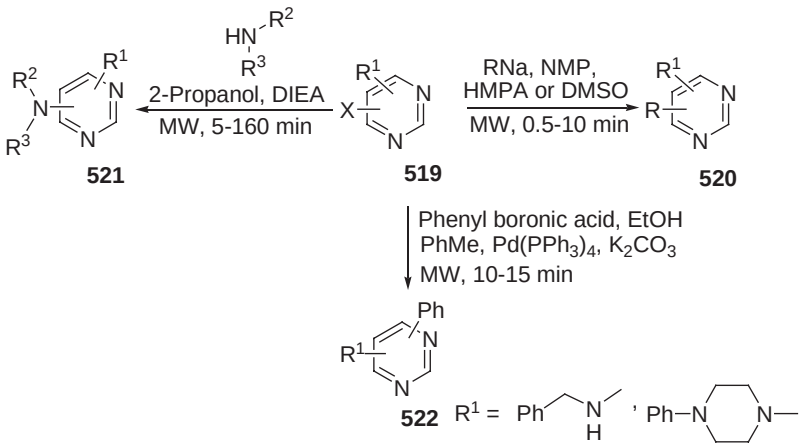
The reaction took place in much longer times (60–112 min) by conventional heating with lower yields (20–50%) (98JOC3454).

A wide variety of dihydropyrimidinones **518** was prepared by MWI using NBS as a mild, efficient, and almost neutral catalyst, whereby aromatic aldehydes containing either electron-withdrawing or electron-donating groups were reacted with urea or thiourea and ethyl acetoacetate in ethanol or DMAC to afford dihydropyrimidines **518** in high yields (80–92%) within 3–6 min (Scheme 101). The role of NBS was said to be a source of "Br^+" ions, which activate aldehydes for further reaction with ethyl acetoacetate (04S1239).

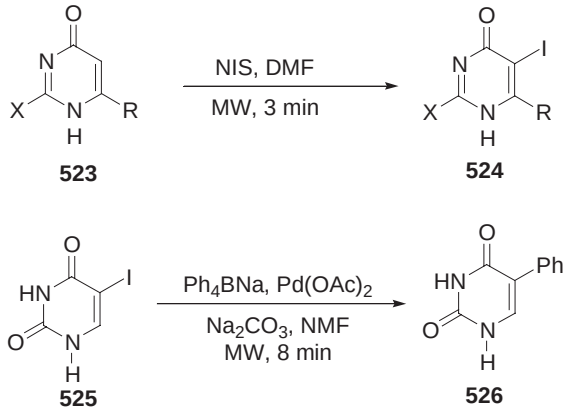
When a polyethylene glycol (PEG) 4000-linked acetoacetate, urea, and aldehyde were subjected to MWI and then the product was cleaved from PEG, pyrimidin-2(1*H*)-one-5-carboxylate derivatives **518** were obtained within very short reaction times (1.5–2.5 min) and in comparable yields (71–85%) to that from a PEG-supported liquid-phase reaction using HCl/NeCN, which required 18 h under reflux (Scheme 101) (03S262).

Nucleophilic substitutions of pyrimidyl halides **519** with MeSNa, PhSNa, PhONa, MeONa, or EtONa as nucleophiles under irradiation in a monomode MW reactor in the presence of NMP, HMPA, or DMSO gave 69–97% yields of **520** within 0.5–10 min (Scheme 102). On conventional heating in the presence of NMP, 5-bromopyrimidine reacted with PhSNa to give only a 7% yield of 5-phenylthiopyrimidine when compared to 96% yield under MWI (02T887).

A series of aminopyrimidines **521** were prepared by nucleophilic substitution of **519** with amines under MWI in 2-propanol as solvent and in the presence of diisopropylethyl amine (DIEA) to give 29–97% yields of **521** within 5–160 min (Scheme 102); conventional heating required 2 h. Arylation of compounds **519** by a Suzuki coupling gave under MWI and in the presence of phenyl boronic acid *C*-arylpyrimidines **522** in 79–92% yields within 10–15 min, but under conventional heating it took many hours to days (02TL5739).



Scheme 102



Scheme 103

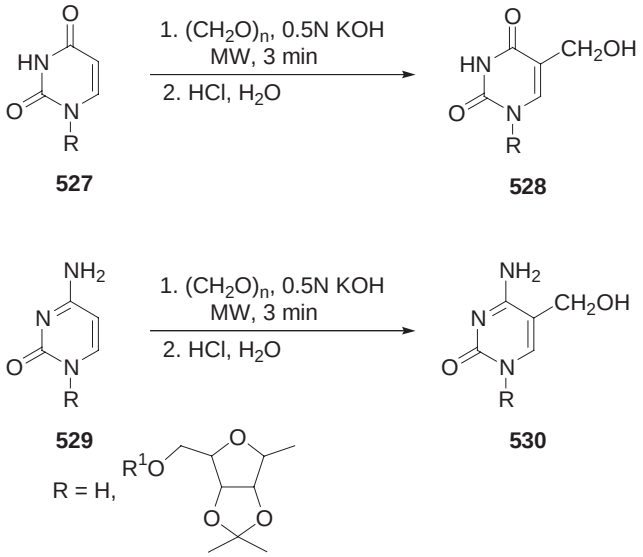
Iodination under MWI of pyrimidinones and their nucleosides **523** with *N*-iodosuccinimide (NIS) gave the 5-iodo derivatives **524** in 65–98% yields after 3 min, useful intermediates in the formation of new carbon–carbon or carbon–heteroatom bonds *via* replacement of the iodine atom with electrophiles. The reaction required 1–6 h to give 50–60% yields (Scheme 103) (03S1039).

A rapid and efficient palladium-catalyzed phenylation of 5-iodouracil **525** with sodium tetraphenylborate in NMF under focused MWI within 8 min gave 5-phenyluracil **526** in 70% yield (Scheme 103) (01TL635).

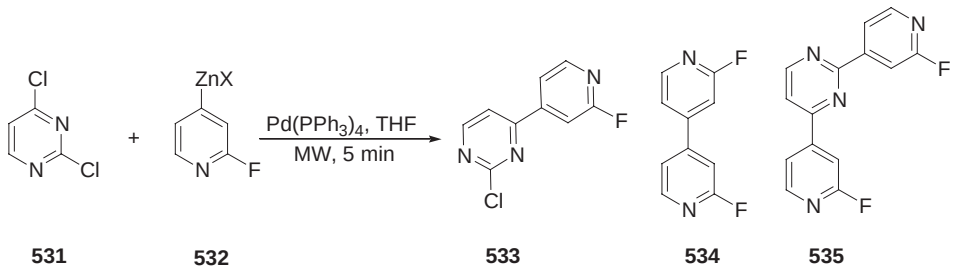
An efficient method for the hydroxymethylation of **527** and **529** was carried out using paraformaldehyde in 0.5 N KOH under MWI, followed by acidification to give 5-hydroxymethyl derivatives **528** and **630** in 93–99% yields (Scheme 104) (02SL2043). The reaction required 1–3 days under conventional conditions (59JA2521, 66CB3884, 79JCR(S)226, 67T2315).

Pyridinyl-pyrimidines can be synthesized through the Negishi cross-coupling reaction under either classical or MW-assisted conditions. The coupling of 2,4-dichloropyrimidine (**531**) with organozinc reagent **532** in dry THF and $Pd(PPh_3)_4$ catalyst gave pyridinyl-pyrimidine **533** in excellent yield (90%) within 4 h and traces (5%) of the dipyridine derivative **534**. Switching to MW as an energy source, compound **533** was obtained as a major product (54–90%) accompanied by minor quantities of homocoupling product **534** (3–36%) in addition to the *bis*-coupled product **535** (4–15%) within 5 min at 100 °C (Scheme 105). Formation of **535** was not observed under thermal conditions. However, compound **535** was isolated as the major product (84%) when the reaction was conducted under MWI at 130 °C for 5 min (03SL1862).

The reaction of aromatic aldehydes with thiobarbituric acid **67** (X = S, R = H) was carried out in water by heating at 95–100 °C for 45 min to give 5-arylidenethiobarbituric acids **536** in 50–95% yields. When this reaction was carried out under MWI in the absence of water, it gave better yields (76–96%) within shorter reaction times (2–12 min) (Scheme 106) (04H583).



Scheme 104

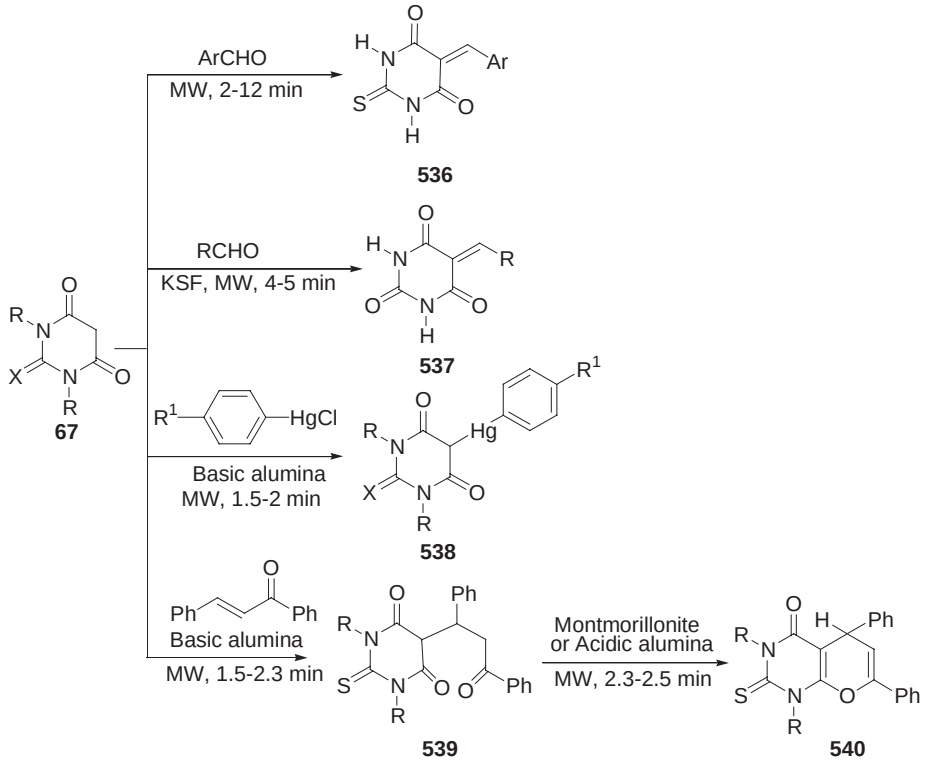


Scheme 105

MWI also allowed fast and efficient dry condensation of barbituric acid **67** (X = O, R = H) with aldehydes in the presence of acidic montmorillonite KSF to give 5-(arylmethylene)-2,4,6-(1*H*,3*H*,5*H*)pyrimidinetriones **537** in 68–98% yields within 4–5 min (Scheme 106), instead of the slow reaction at room temperature (90SC3333).

Organomercury compounds **538** have been synthesized by the reaction of barbituric acid or thiobarbituric acid derivatives **67** (X = O, R = H; X = S, R = Ph) with aryl mercuric chloride under MWI using basic alumina as a solid support; less time (1.5–2 min) and better yields (90–96%) (Scheme 106) were found as compared to the conventional method (99POL2641).

Michael addition of chalcone to thiobarbituric acid (R = H, aryl) **67** supported on basic alumina under MWI for 1.5–2.3 min gave the adduct **539** in 83–87% yields. Cyclization of **539** on montmorillonite or acidic alumina under MWI gave pyrano[2,3-*d*]pyrimidines **540** in 80–89% yields within 2.3–2.5 min (Scheme 106). A



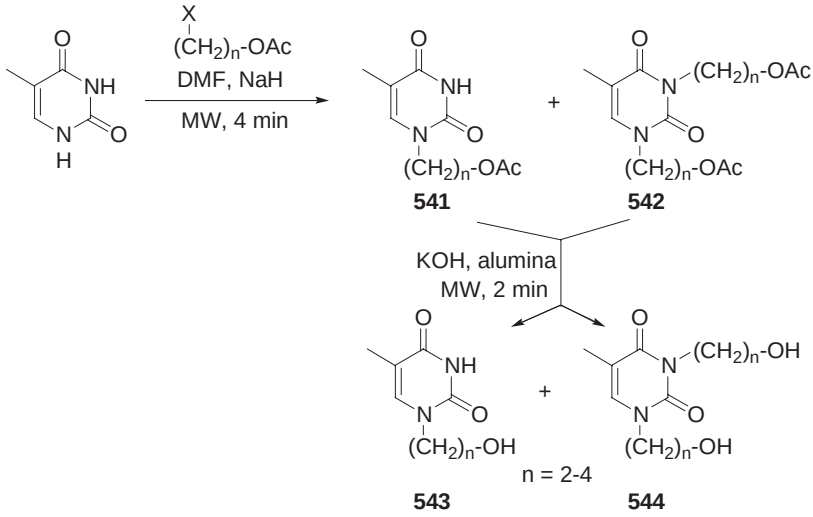
Scheme 106

longer irradiation of **67** with the chalcone gave **540** directly in 90–93% yields within 3.2–3.5 min. They were obtained in about 50% yield after 5–6 h of conventional heating in the presence of montmorillonite, and in 60–70% yields after heating for 4 h with basic alumina (02SC2161).

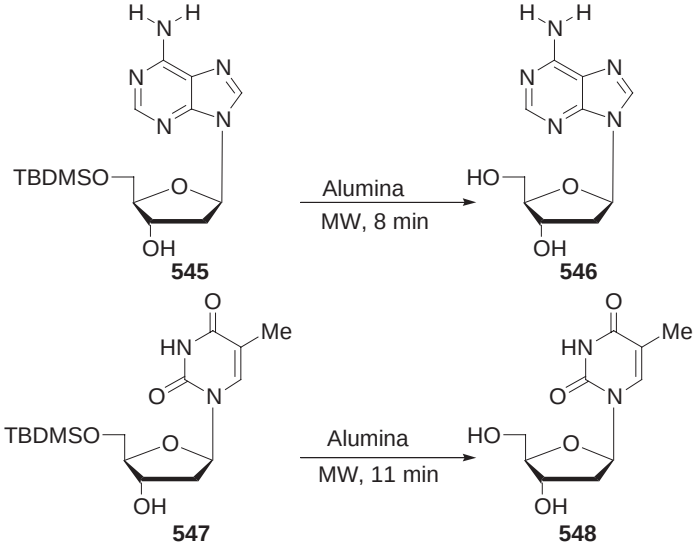
Alkylation of thymine with haloalkyl acetates in DMF, in the presence of NaH, for 4 min in an MW oven afforded the N-1 monoalkylthymines **541** and dialkylthymine **542** in 17–38% yields (Scheme 107); conventional heating required 48 h to give 21–55% yields. Saponification of compounds **541** and **542** was achieved under MWI in dry media in the presence of excess KOH adsorbed onto alumina to give deacetylated products **543** and **544** within 2 min in nearly quantitative yield (96%) (04MI1).

The *t*-butyldimethylsilyl (TBDMS) group, a widely used protecting group, can be cleaved simply from their TBDMS ethers **545** and **547** under MWI. This occurred on an alumina surface under mild and solvent-free conditions for 8 and 11 min to give **546** and **548** in 68% and 75% yields, respectively (Scheme 108) (93TL3029).

Alkylation of 6-amino-2thiouracil **549** with alkyl halides in DMF under MWI gave selectively the corresponding alkylated aminothiouracil derivatives **550** in good yields (83–84%) within 9–11 min. When the alkylation of **549** was carried out in the



Scheme 107

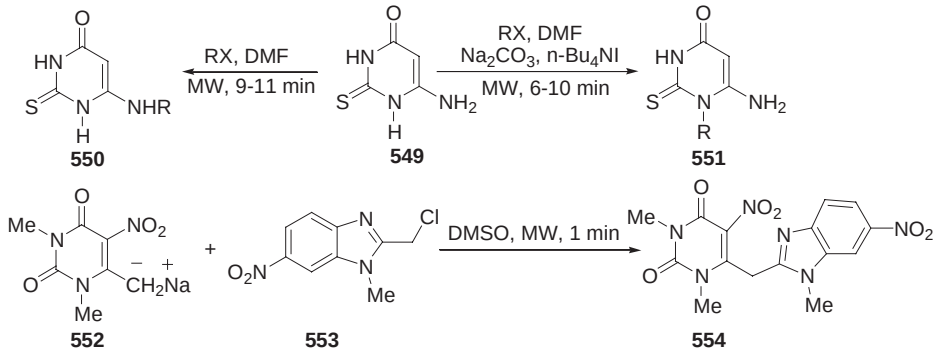


Scheme 108

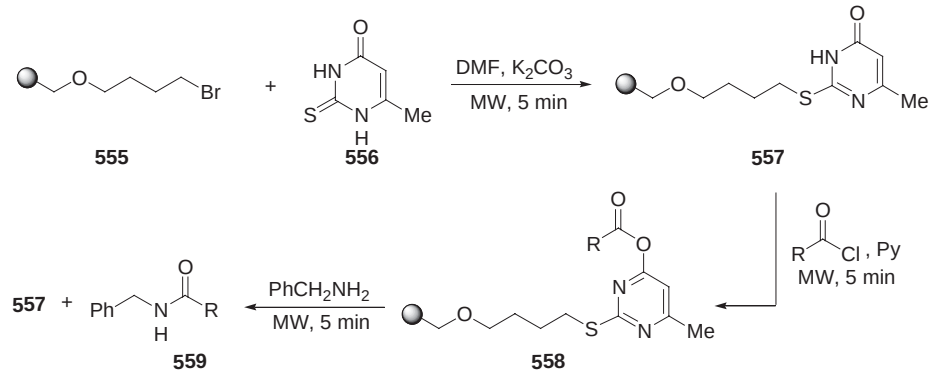
presence of a base using MWI under PTC conditions, it led to *N*-1-alkylthiouracil derivatives **551** in excellent yields (87–95%) (Scheme 109). The selective alkylation at the 6-amino group of the neutral 6-amino-2-thiouracil and at position-1 of its anion was justified by considering a theoretical approach taking into account the orbital coefficients on the nitrogen atoms (01H291).

2-Chloromethyl-1-methyl-6-nitro-1*H*-benzimidazole (**553**) reacted with the sodium salt of 1,3,6-trimethyl-5-nitro-1*H*-pyrimidine-2,4-dione (**552**) under MWI to give the C-alkylated product **554** in 83% yield (Scheme 109) (02H1423).

Solid-supported reagents were used to assist the synthesis of 4-*O*-acylated pyrimidines **558**; they are useful reagents for the selective acylation of amines. Thus, nucleophilic substitution of **555** with 6-methyl-2-thiouracil **556** in DMF and in the presence of K_2CO_3 was carried out under MWI within 5 min to give **557**. When **557** reacted with acyl halides under MWI, it gave polymer-bound 4-acyloxypyrimidines **558** within 5 min rather than a few days under standard conditions. Pyrimidines **558** were used for the selective acylation of benzylamine to give amides **559** under MWI for 5 min in 40–100% yields (Scheme 110). The most effective were those with R = *p*-BrC_6H_4 or *p*-ClC_6H_4, to give the corresponding amides **559** in 100% and 85% yields, respectively, while that with R = *o*-BrC_6H_4 (yield 40%) was the least effective, owing to steric hindrance exerted by the *o*-bromo substituent (04JOC7880).



Scheme 109



Scheme 110

D. Quinazolines

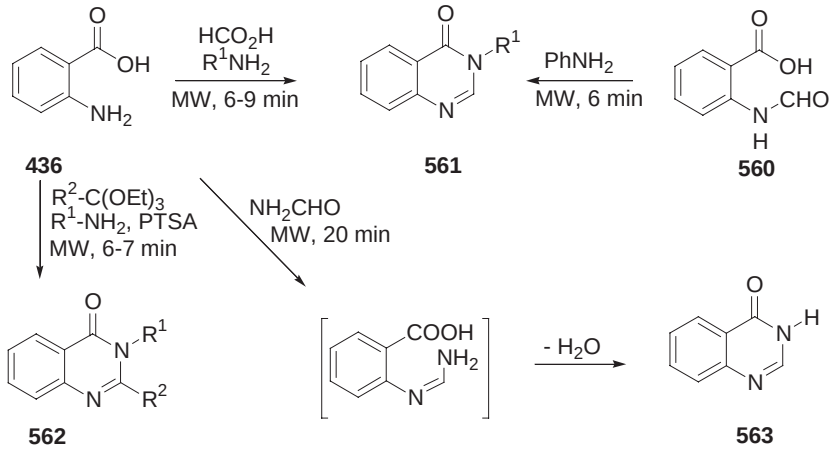
Quinazolin-4(3*H*)-ones **561** were efficiently prepared in 68–87% yields by irradiating a mixture of anthranilic acid **436**, formic acid, and an amine in an MW oven for 6–9 min in the absence of solvent and any dehydrating agents. Alternatively, MWI of a mixture of 2-formamidobenzoic acid (**560**) and aniline gave **561** (R^1 = Ph) in 71% yield (Scheme 111). Using orthoesters with a catalytic amount of PTSA instead of formic acid led to the formation of 2,3-disubstituted quinazolin-4(3*H*)-ones **562** in 79–89% yields (98JCR(S)702).

The synthesis of quinazoline **563** in 59% yield by heating **436** with formamide at 150 °C for 6 h (1895JPR564) was improved by applying MWI to give a 90% yield within 20 min. The method was used to prepare a series of quinazolines in 70–87% yields after MWI for 15–40 min (Scheme 111) (02TL3911).

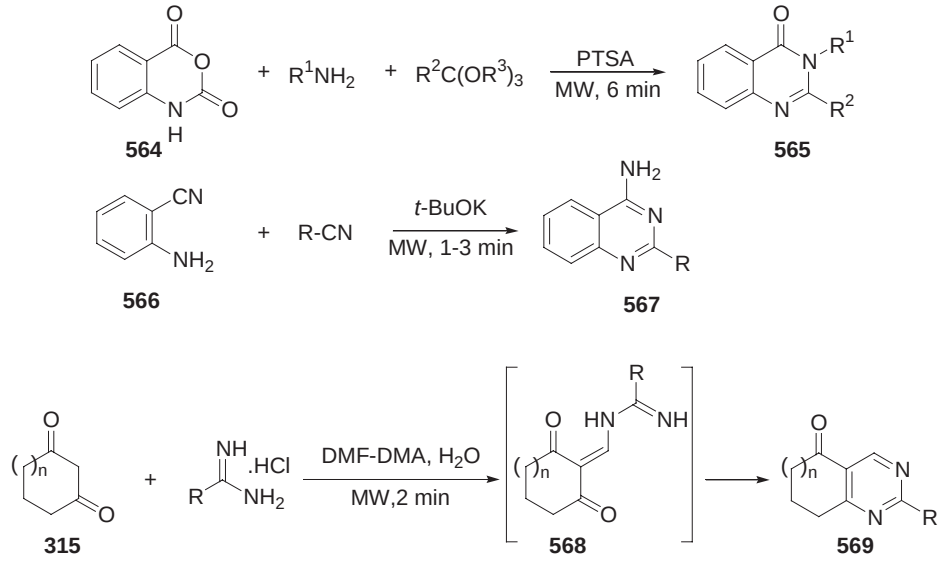
Condensation of isatoic anhydride **564**, amines, and orthoesters under MWI in the presence of catalytic amounts of PTSA gave quinazolines **565** in 74–96% yields within 6 min (Scheme 112). The condensation required 5 h in refluxing ethanol to give 65–82% yields (04H1417).

Anthranilonitrile (**566**) reacted with aromatic nitriles in the presence of *t*-BuOK in an MW oven to afford the corresponding 4-aminoquinazolines **567** in 73–93% yields after irradiation for 1–3 min (Scheme 112) (00TL2215).

Conversion of 1,3-diketones **315** into 2-substituted 7,8-dihydroquinazolin-5(6*H*)-ones **569** by a reaction with substituted amidine hydrochloride and dimethylformamide dimethyl acetal (DMF-DMA) was achieved under MWI and in aqueous media. The aqueous conditions led to an environmentally friendly work-up. Compounds **569** were obtained in 21–68% yields within 2 min (Scheme 112). The reaction is a tandem addition–elimination/cyclodehydration that took place *via* a Michael addition of the terminal amino group of the substituted amidine to form intermediate **568**, followed by an intramolecular cyclodehydration to give dihydroquinazolinone derivatives **569** (02S1669).



Scheme 111



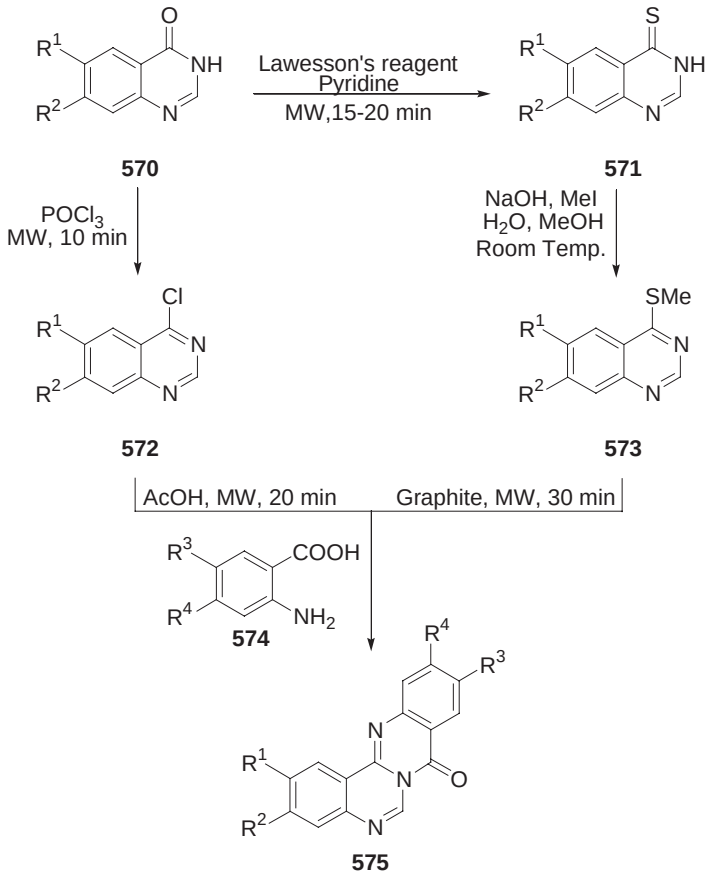
Scheme 112

E. Fused Heterocycles Incorporating Pyrimidine and Quinazoline Rings

Thionation of quinazolinones **570** was performed under MWI using Lawesson's reagent in the presence of pyridine to give 4(3*H*)-quinazolinethiones **571** in 84–93% yields within 15–20 min instead of 18 h using classical heating. S-Methylation of **571** gave 4-(methylthio)quinazoline **273**, whose reaction with anthranilic acids **574** adsorbed on graphite under MWI gave 8*H*-quinazolino[4,3-*b*]quinazolin-8-ones **575** in 21–79% yields and in a shorter time (30 min) (Scheme 113) than the thermal procedures; the yields were in accordance with the reactivity of anthranilic acids.

Short exposure (10 min) of a mixture of quinazolinones **570** with phosphoryl chloride to MW led to 4-chloroquinazolines **572** in good yields (70–90%); several hours were needed by conventional heating. Irradiation of **572** with **574** in acetic acid gave **575** within 20 min instead of 1 h of classical heating (Scheme 113). When the reaction was carried out at atmospheric pressure under solvent-free conditions with graphite as solid support, decomposition of the starting material occurred (03T1413).

The reaction of *N*-arylimino-1,2,3-dithiazoles **576** with alcohols gave the corresponding 4-alkoxyquinazoline-2-carbonitriles **577** in 0–60% yields after heating for 5 days; the time was reduced to 40 h and the yields were improved to 12–82% in the presence of sodium hydride or potassium fluoride (96JCS(P1)2857). Further reduction of time to 35–120 min and an increase in yields (31–80%) were achieved when the reactants were subjected to MWI (Scheme 114) (96JCS(P1)2857, 98T6475). Addition of the alkoxide ion to the cyano group in **576** promoted the cyclization, and loss of sulfur and HCl to give **577** was the proposed mechanism. Similarly, the first

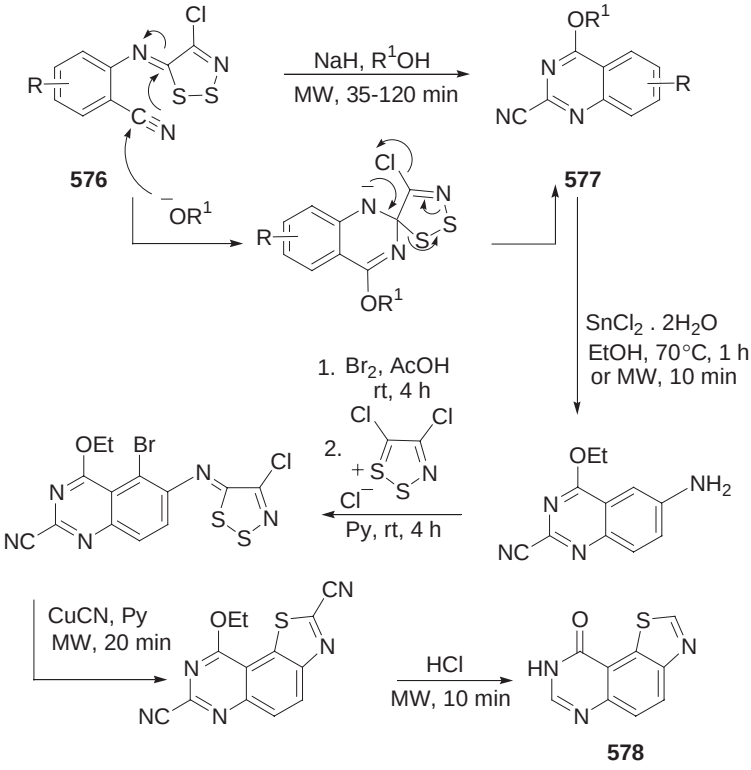


Scheme 113

step in the synthesis of thiazolo[5,4-*f*]quinazoline **578** from **577** (R = 6-NO_2, R^1 = Et) was performed under focused MWI (Scheme 114), followed by the sequence shown in the scheme to give the desired compounds in comparable and sometimes better yields than those obtained by conventional heating (00TL1027).

A regioselective ring opening of isatoic anhydride **564** with isatin-3-imines **579**, in the presence of a catalytic amount of KF-Al_2O_3 under MWI gave 6-arylimino-*6H*-indolo[2,1-*b*]quinazolin-12-ones **580** in 70–83% within 4 min. A small amount of *N*,*N*-dimethylacetamide (DMAC) increased the energy input in a shorter time and provided uniform heating since it is an excellent energy-transfer solvent with a high dielectric constant. When this condensation was promoted with K_2CO_3 under MWI products, **580** were obtained in lower yields (24–50%) within 5 min (Scheme 115) (04H791).

The self-polymerization reaction of isatoic anhydride **564** doped over montmorillonite under MWI yielded dibenzo[3,4:7,8][1,5]diazocinodiquinazolin-10,21-dione (**582**) in 46% yield but in a very short time (7 min) (Scheme 115) (02S2168).



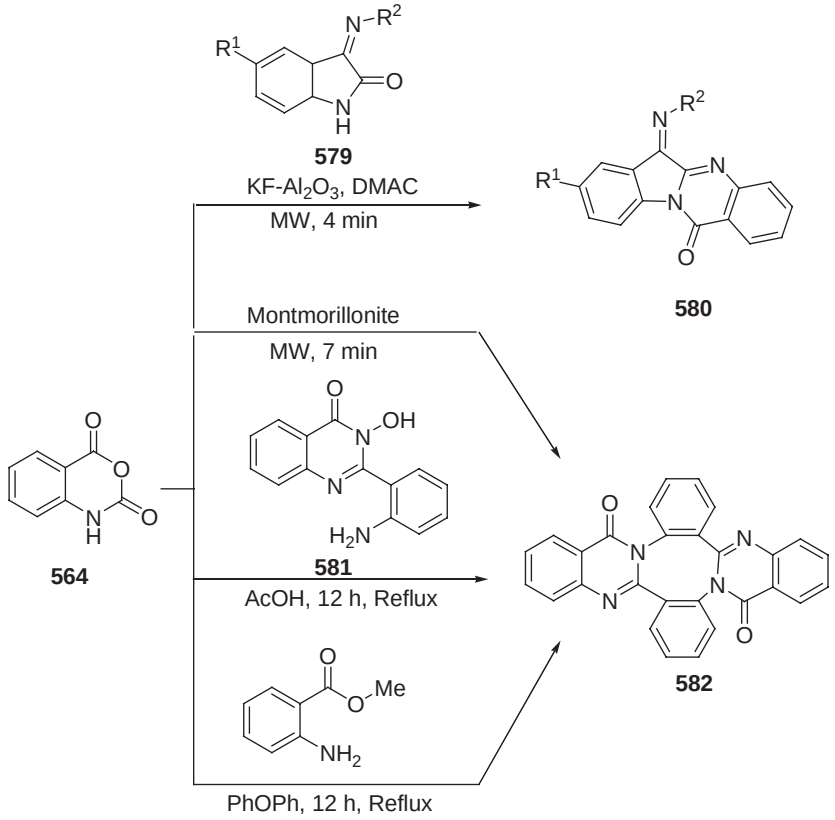
Scheme 114

Conventionally, **582** was obtained in 62% and 60% yields from **564** with quinazolinone derivative **581** or methyl anthranilate, respectively (54JCS3429, 02S2168).

The benzimidazo[1,2-*c*]quinazolines and indolo[1,2-*c*]quinazolines are considered as synthetic analogs of the natural alkaloid hinckdentine A and have a close structural analogy with other cytotoxic agents with potential pharmaceutical value. Heterocyclization of *N*-[2-(1*H*-benzimidazol-2-yl)phenyl]benzamides **583** under MWI and solvent-free conditions using a solid inorganic support (a 95:5 mixture of silica gel/MnO_2) gave 6-phenylbenzimidazo[1,2-*c*]quinazolines **584** in moderate yields (37–56%) within 30–45 min (Scheme 116). Thermal conditions (reflux in dry *m*-xylene over 15 h) afforded a mixture of starting materials and products (04S436).

Syntheses of indolo[1,2-*c*]quinazolines and benzimidazo[1,2-*c*]quinazolines **587** have been achieved in 53–77% yields by the condensation of the 2-cyanobenzothiazoles or benzoxazoles **585** with 2-(2-aminophenyl)benzimidazole or 2-(2-aminophenyl)indole **586** under MWI in the presence of graphite for 10–240 min (Scheme 116). Conventional heating required lengthy and tedious conditions to give very low yields (<35%) and various impurities were detected in the final mixture (03T773).

MWI promoted the synthesis of fused quinazolines with bridge-head nitrogen by cyclocondensation of 2-(2-aminophenyl)benzimidazole (**586**) with orthoesters to give 6-substituted benzimidazo[1,2-*c*]quinazolines **588** in 85–94% yields after irradiation



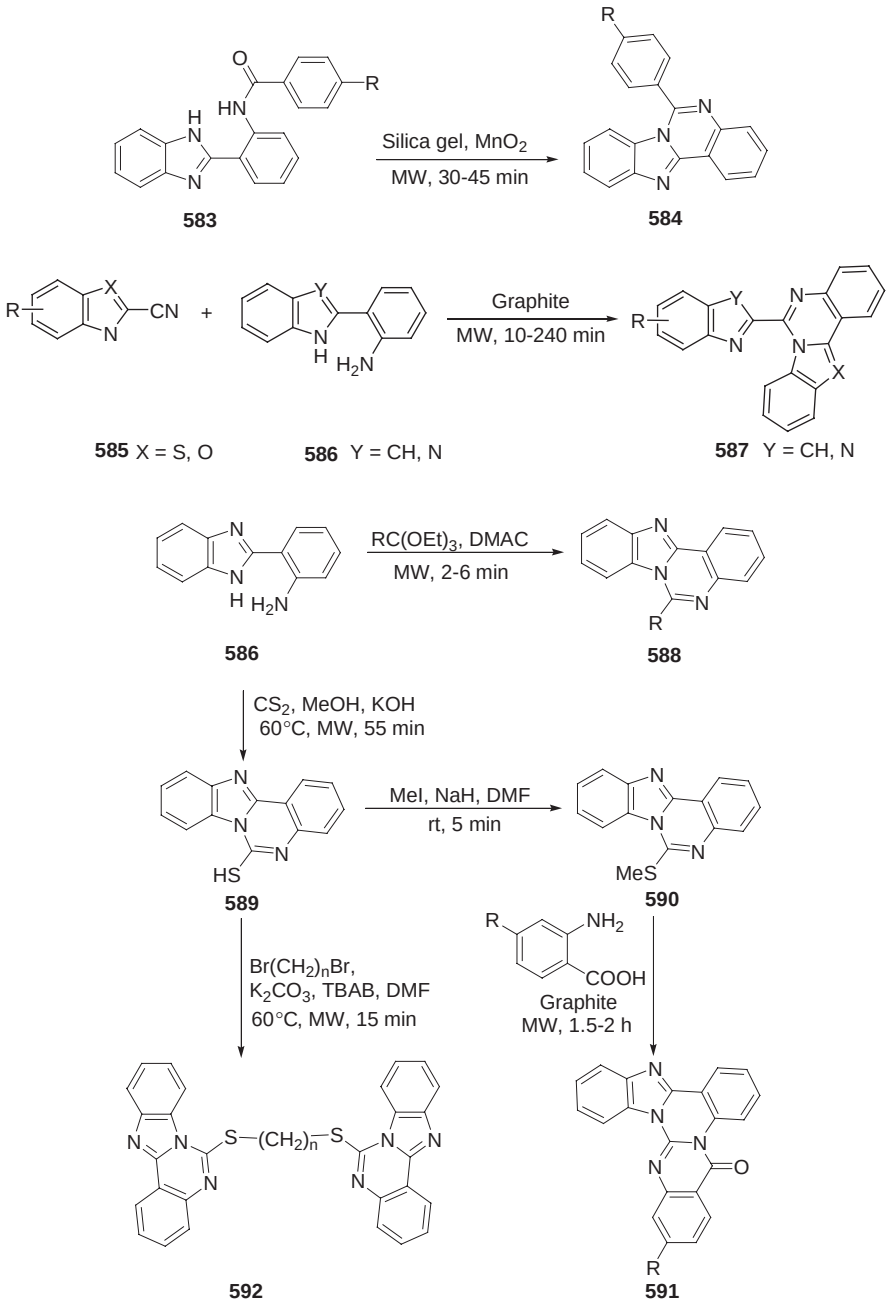
Scheme 115

for 2–6 min in the presence of DMAC solvent and MW energy transfer; no products were obtained in the absence of DMAC (Scheme 116) (99SC2617).

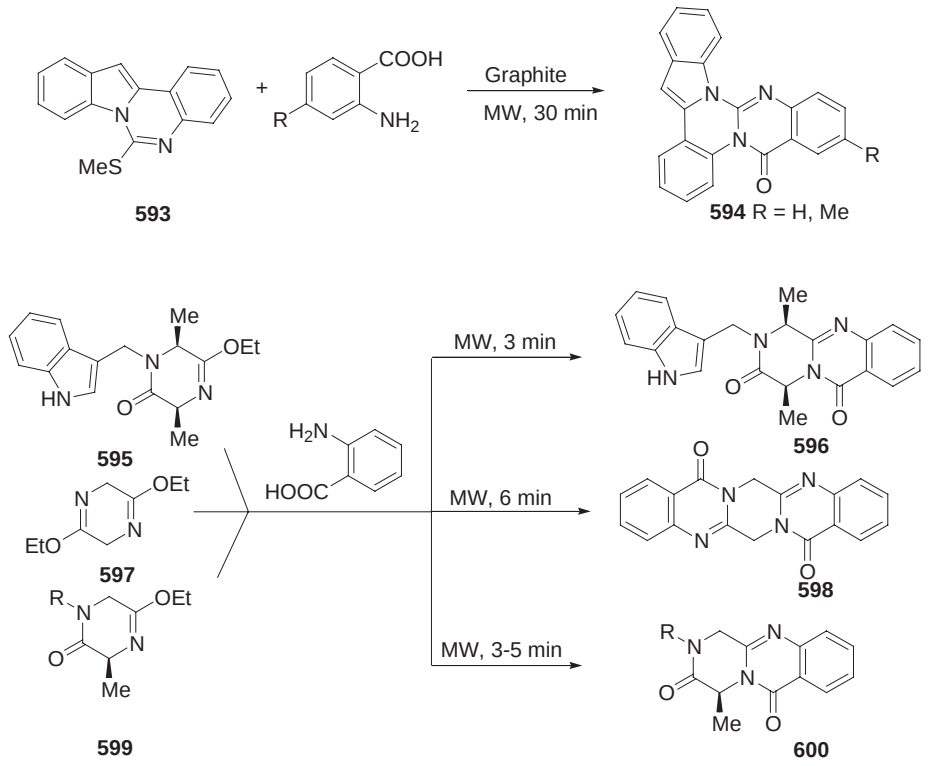
Similarly, the synthesis of 6-mercaptobenzimidazo[1,2-*c*]quinazoline (**589**) was accomplished (95%) under MWI in 55 min by the reaction of **586** with carbon disulfide in the presence of methanolic potassium hydroxide. Methylation of **589** with an excess of MeI in DMF in the presence of NaH gave 6-methylmercaptobenzimidazo[1,2-*c*]quinazoline (**590**) in 95% yield. Thermal heating of **590** with anthranilic acid derivatives at 120 °C or in boiling butanol for 48 h did not give more than 50% of **591**, but under MWI conditions the time was reduced to 6 h with no improvement in yield (Scheme 116). However, irradiation of the reactants adsorbed on graphite led to **591** in 75–95% yields and in a shorter time (1.5–2 h).

The reaction of **589** with dibromomethane and dibromoethane in the presence of K_2CO_3 and TBAB needed long heating (12 h) to provide the dimers **592** in good yields. But, under MWI, the reaction times were reduced to 15 min, and similar yields of **592** (86–81%) were obtained (Scheme 116) (00TL5857).

A mixture of indoloquinazoline **593** and excess of anthranilic acids adsorbed on graphite led to the cyclized compound **594** in 80–90% yields within 30 min. Under


Silica gel, MnO2
MW, 30-45 min
583
584
Graphite
MW, 10-240 min
585 X = S, O
586 Y = CH, N
587 Y = CH, N
RC(OEt)3, DMAC
MW, 2-6 min
586
588
CS2, MeOH, KOH
60°C, MW, 55 min
MeI, NaH, DMF
rt, 5 min
589
590
Br(CH2)nBr,
K2CO3, TBAB, DMF
60°C, MW, 15 min
Graphite
MW, 1.5-2 h
592
591

Scheme 116



Scheme 117

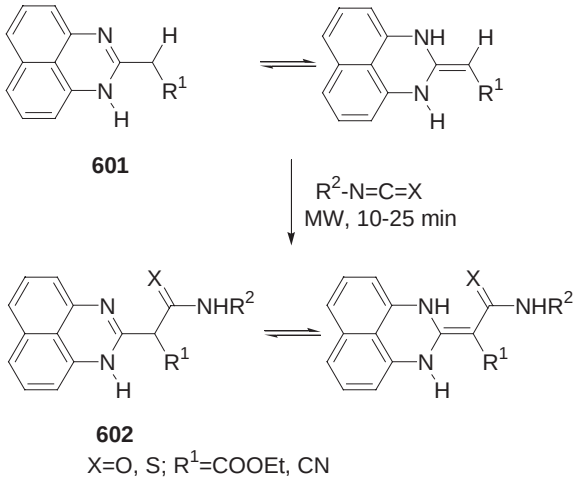
MWI no by-products were detected and reactions were cleaner than those from conventional heating after 24 h (Scheme 117) (01TL6671).

Transformation of imino-ether **595** into 1,4-disubstituted pyrazino[2,1-*b*]quinazoline-3,6-dione **596** in 48% yield resulted by reaction with anthranilic acid under MWI for 3 min, compared to a 16% yield produced by conventional heating for 2 h. Also, the double condensation of the *bis*-lactim ether **597** required 6 min to give **598** in 89% yield (Scheme 117) (04SL803), compared to a 54% yield by classical heating for 1 h (83AGE717).

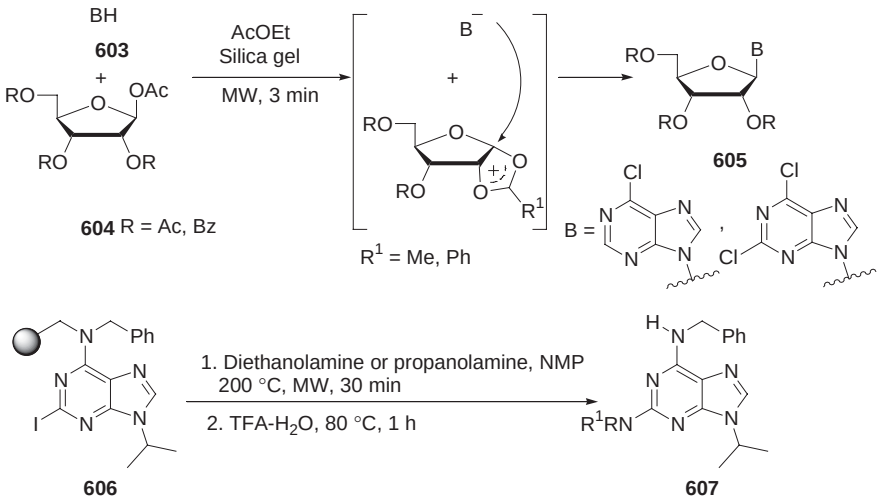
Irradiation of anthranilic acid with imino-ethers **599** for 3–5 min in an MW oven gave **600** in 56–63% yields, instead of 2 h at 120–140 °C to give lower yields (30–46%) (Scheme 117) (04SL803).

Regioselective C-electrophilic addition of isocyanates and isothiocyanates to 2-substituted 1*H*-perimidines **601** were carried out by refluxing in anhydrous acetonitrile for a long time (15–163 h) to afford **602** in 66–94% yields. When the addition was carried out under solvent-free conditions using either MWI or an oil bath, the yields were increased to 99% and the times were reduced to 10–25 min (Scheme 118) (96BSF587).

Reaction of 6-chloropurine and 2,6-dichloropurine **603** with 1,2,3,5-tetra-*O*-acetyl-β-D-ribofuranose or 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose (**604**) under MWI gave purine nucleosides **605** (Scheme 119) (02MI4).



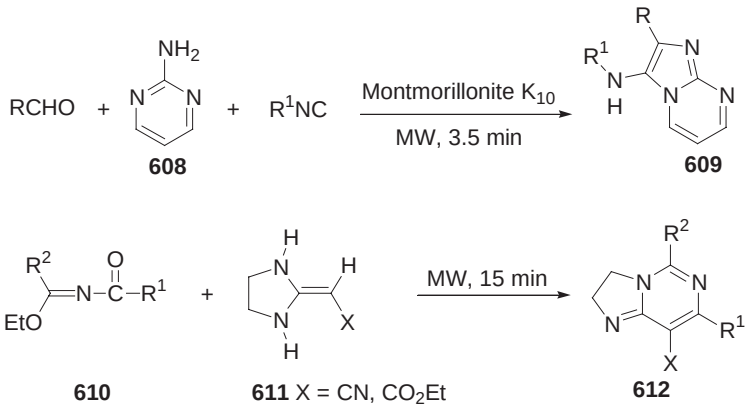
Scheme 118



Scheme 119

The synthesis of 2,6,9-trisubstituted purines **607** through nucleophilic displacement of iodine at C-2 of resin-bound purine **606** by amines was carried out under MWI. The displacement was accomplished in 30 min with either diethanolamine or propanolamine; subsequent cleavage of the polymer gave 30–80% yields (Scheme 119), conventional heating required 8 h (02TL6169).

A one-pot reaction of aldehydes, 2-aminopyrimidine **608**, and alkyl isocyanide afforded, without a solvent, under MWI in the presence of montmorillonite K_{10} imidazo[1,2-*a*]pyrimidines **609** in 56–58% yields within 3.5 min (Scheme 120) (99JHC1565).



Scheme 120

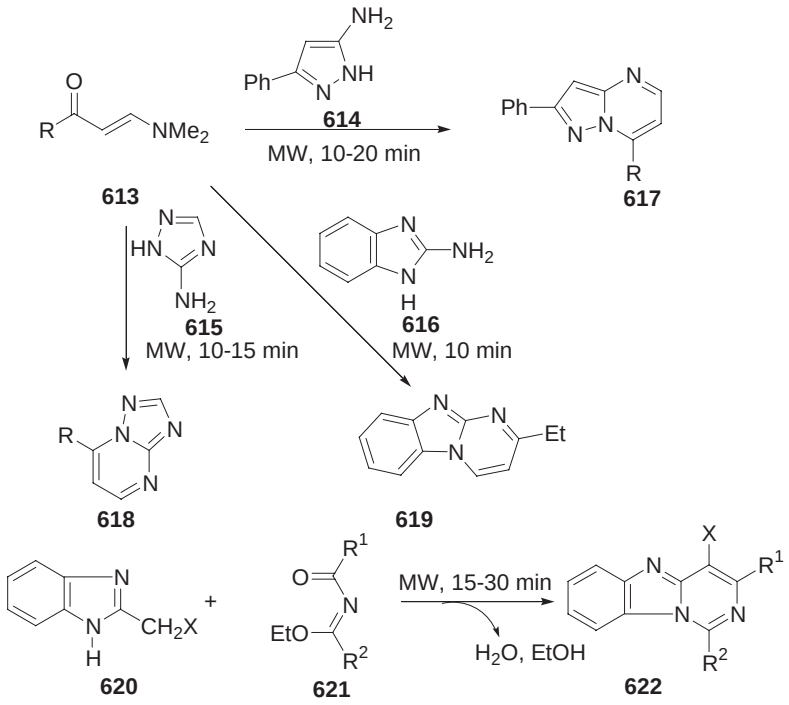
A route to 2,3-dihydro imidazo[1,2-*c*]pyrimidines was described by a reaction of *N*-acyl imidates **610** with imidazolidine ketene aminals **611** in a focused MW oven without a solvent to give **612** in good yields (60–92%) after 15 min. When X = CN, R^1 = Me, and R^2 = Et, two attacks were observed and the reaction gave a mixture of two regioisomers **612** (R^1 = Me, R^2 = Et, and R^1 = Et, R^2 = Me) in a ratio 3:1, respectively (Scheme 120). The attack on the carbonyl group was favored with respect to the attack on the imino group (96SC453).

The pyrimidine ring was fused to a number of heterocycles with a bridge-head nitrogen when mixtures of enaminones **613** and heterocyclic amines **614**, **615**, or **616** were subjected to MWI for 10–20 min. Thus, pyrazolo[1,5-*a*]pyrimidines **617**, triazolo[1,5-*a*]pyrimidines **618**, or pyrimido[1,2-*a*]benzimidazole **619** were obtained in 88–95% yields (Scheme 121). Those products required 0.5–6 h heating at reflux in absolute ethanol to give 70–80% yields (04JCR(S)174).

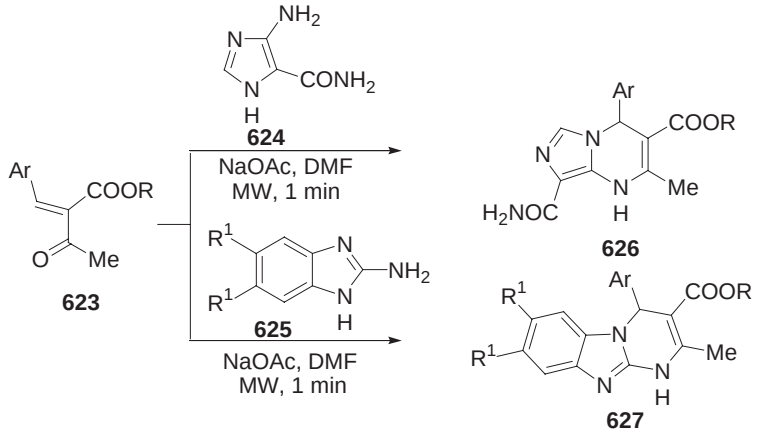
The ring closure of 2-benzimidazoles **620** with *N*-acyl imidates **621** as *β*-dielectrophiles without a solvent in open vessels under MWI for 15–30 min led to pyrimido[1,6-*a*]benzimidazoles **622** in 38–86% yields (Scheme 121). In contrast, no ring closure occurred when compounds **620** (X = COOMe) and **621** (R^1 = R^2 = Me) were heated in toluene with continuous azeotropic elimination of water for 48 h; 95% of **620** was recovered unchanged (94TL4563).

Reaction between arylmethylene acetoacetate **623** and aminoheterocycles **624** or **625** in DMF at 65 °C for 24–48 h led to the imidazo[1,5-*a*]pyrimidine derivatives **626** and benzo[4,5]imidazo[1,2-*a*]pyrimidine derivatives **627** in 74–80% and 68–78% yields, respectively. These compounds showed promising activity as calcium channel blockers (Scheme 122) (94MI1). When the reactions were exposed to MWI, the times were reduced to 1 min with comparable yields (95S389).

Condensation of 3-amino-4,6-disubstituted-1*H*-pyrazolo[3,4-*b*]pyridines **628** with 1,1,1-trifluoro-3-isobutoxymethylene-2-propenones **629** in xylene under MWI took 12–24 min to afford pyrido[2′,3′:3,4]pyrazolo[1,5-*a*]pyrimidines **630** in 62–82% yields (Scheme 123), higher than that obtained (~20%) under conventional heating (97JFC127).



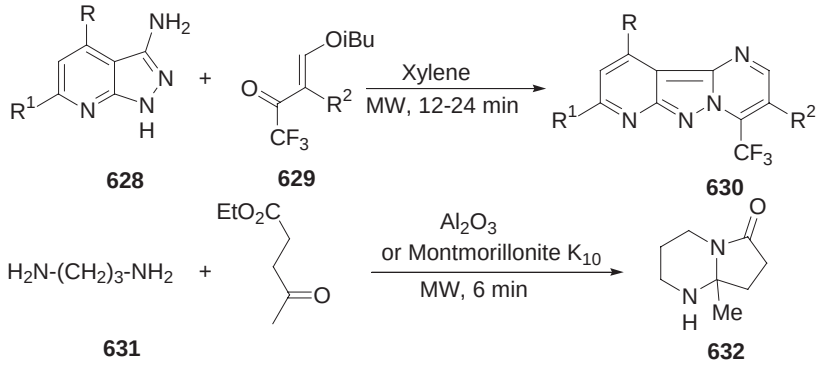
Scheme 121



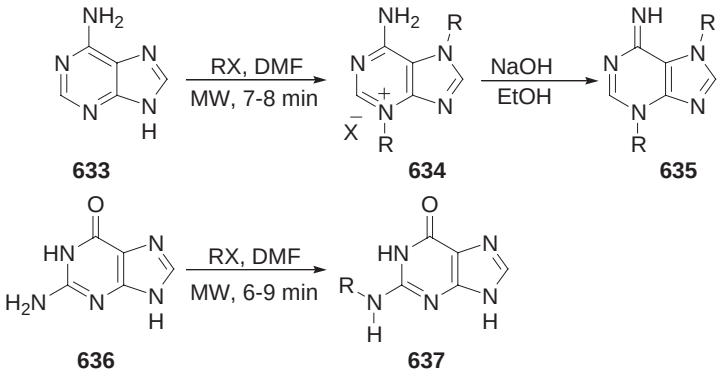
Scheme 122

1,3-Propylenediamine (**631**) adsorbed over alumina or montmorillonite K_{10} reacted with ethyl levulinate under MWI for 6 min to give pyrrolo[1,2-*a*]pyrimidine **632** in 86% yield (Scheme 123) (92SL219).

Alkylation of adenine **633** with several alkylating agents using MW assistance was performed in the presence of small amounts of DMF to give the dialkylated salt **634**,



Scheme 123

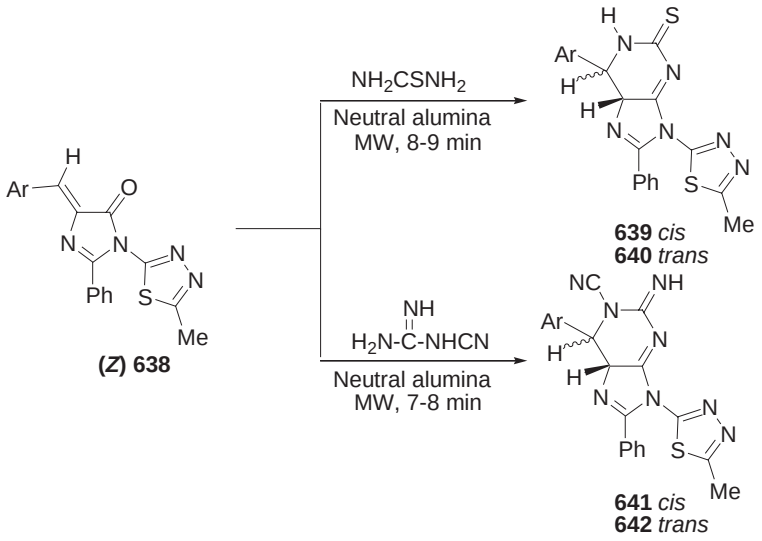


Scheme 124

which was subsequently extracted with ethanol and treated with NaOH to obtain the 3,7-disubstituted adenine **635** in 72–82% yields. The N-alkylation of guanine **636** occurred on the *C*-2-amino group leading to **637** in moderate yields (21–70%) (Scheme 124). The regioselectivity of alkylation of adenine occurring on N-3 and N-7 atoms and on the exocyclic nitrogen atom of guanine were consistent with a consideration of atomic charges on the relevant atoms as deduced from *ab initio* calculations (01H291).

Cyclization of imidazolones **638** with thiourea under dry conditions using MWI for 8–9 min, gave the *cis*- and *trans*-isomers of thioxopyrimido[4,5-*d*]imidazolines **639** and **640** in 76–80% and 10–18% yields, respectively. Also, the cyclization with cyanoguanidine under MWI for 7–8 min produced the isomeric *cis* **641** (75–80%) and *trans* **642** (13–15%) of iminoxypyrimido[4,5-*d*]imidazolines (Scheme 125). The cyclization under conventional heating required 3–5 h to give the *cis*- and *trans*-isomers in 50–58% and 11–22% yields, respectively (01S1509).

Thio and dithioxanthines, biologically active compounds, were prepared by the usual approach involving transformation of oxo-group into a thio-analog with P_2S_5/



Scheme 125

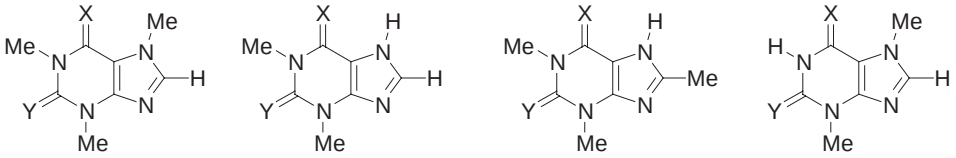
pyridine or Lawesson's reagent. These conventional approaches took place with excess reagent, long reaction times, drastic conditions, and the use of dry solvents, affording unwanted by-products in modest yields. Under MWI in solvent-free conditions, the xanthine bases caffeine **643a**, theophyline **644a**, methyltheophyline **645a**, and theobromine **646a** were converted into their corresponding 6-thio **643b**–**646b** and 2,6-dithio derivatives **643c**–**646c** by using 0.5 and 1.1 equivalents of Lawesson's reagent. The 6-thio and 2,6-dithioxanthines were obtained in 90–99% yields within 5–10 min (Scheme 126) (00H2275).

Cyclization of **647** with phosphorous oxychloride adsorbed on silica gel into imidazo[1,2-*c*]thieno[3,2-*e*]pyrimidines **648** in 81–89% yields was carried out under MWI within 1 min (Scheme 126) (01S2119).

When compound **649** was irradiated with MW for 7–20 min in the presence of a few drops of acetic acid, it gave the fused pyrimidine **650** in 30% yield. Similarly, boiling **649** in acetic acid for 2 h gave a 25% yield (Scheme 126) (03MI3).

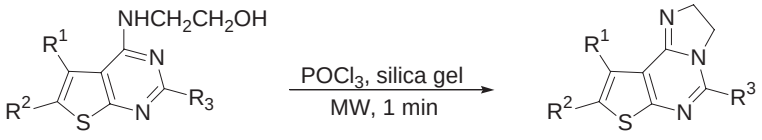
Azole Schiff bases **652** were reacted with glycine and acetic anhydride under solvent-free conditions and MWI for 5–7 min to produce 6-acetamido-6,7-dihydro-5*H*-1,3,4-oxa(thia)diazolo[3,2-*a*]pyrimidin-5-ones **654** and **655** in 79–88% yields (Scheme 127). Mechanistically, conjugate addition of oxazolone **651**, generated *in situ*, to Schiff bases **652** gave adducts **653**, which underwent intramolecular nucleophilic attack of the N-3 of the 1,3,4-oxa(thia)diazole ring at C-5 carbonyl of the oxazolone nucleus to yield **654** (**655**). This one-pot annulation of a pyrimidine ring into azoles was not complete (45%) even after 14 h of conventional heating (03S63).

The tautomeric form of 4-hydroxycoumarin (**103**), acting as a cyclic β-keto ester, was condensed with aldehydes and urea or thiourea in the presence of basic alumina by heating for 4–6 h at 110–120 °C to give benzopyrano[4,3-*d*]pyrimidines **656** and

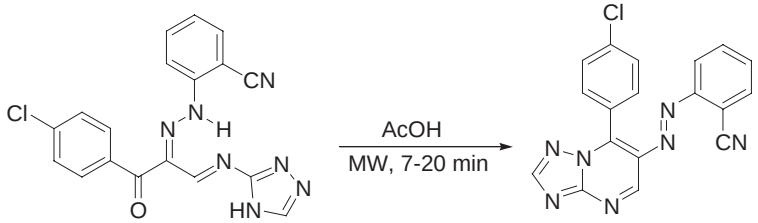


643 **644** **645** **646**

a. X = Y = O
b. X = S, Y = O
c. X = Y = S

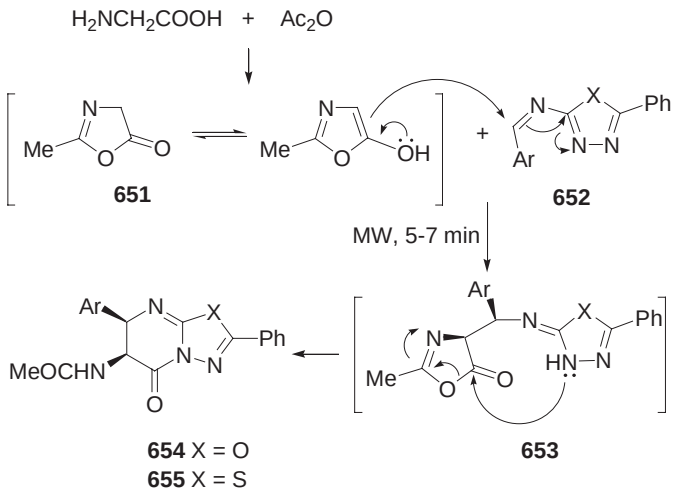


647 **648**



649 **650**

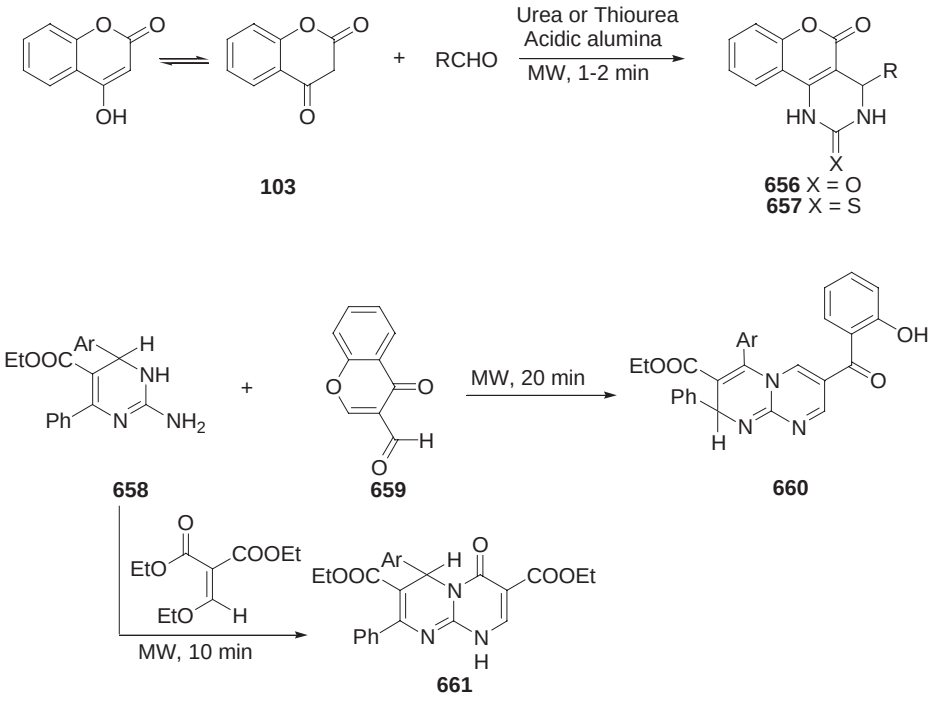
Scheme 126



651 **652** **653**

654 X = O
655 X = S

Scheme 127



Scheme 128

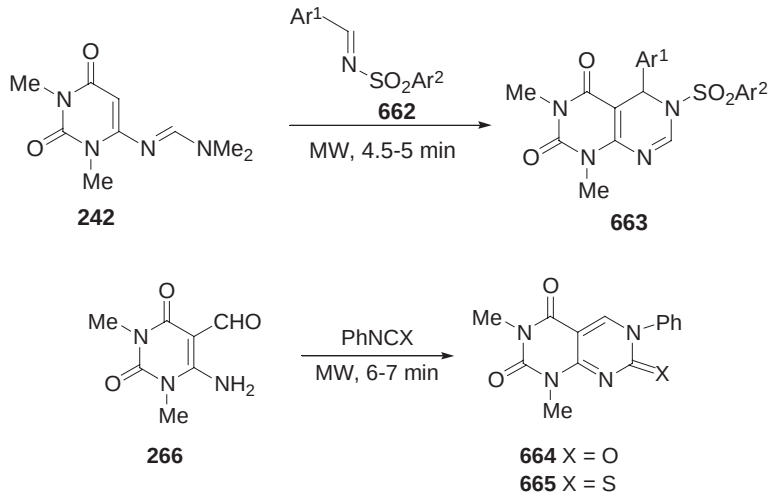
657 in 39–60% yields. Under MWI using silica gel montmorillonite or acidic alumina, it required 1–2 min to give 75–95% yields (Scheme 128) (02SC1639).

Under MWI, pyrimidine derivatives **658** and 3-formylchromone (**659**) were reacted to give pyrimido[1,2-*a*]pyrimidines **660** in >95% yields within 20 min. Under conventional heating in ethanol for 4 h, compounds **660** were obtained in 60–80% yields. Similarly, **658** were reacted with diethyl ethoxymethylenemalonate under MWI within 10 min to give **661** in yields exceeding 95%, compared to 40–60% produced after 8 h reflux in ethanol (Scheme 128) (01T1785).

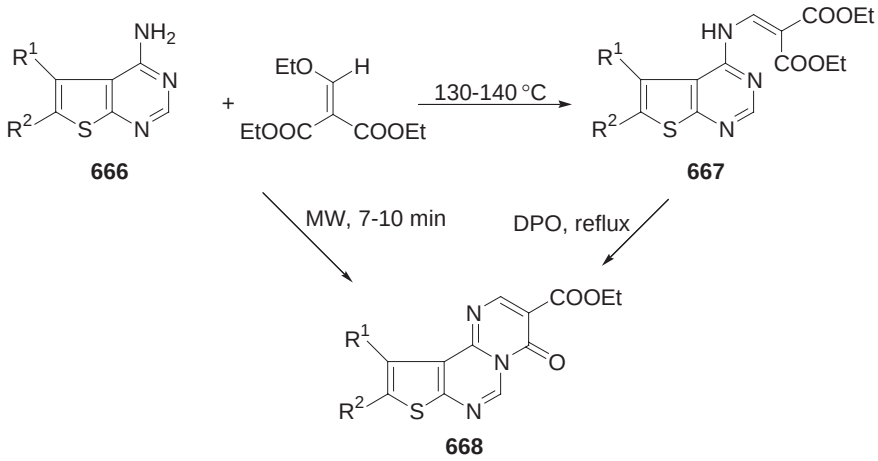
Treatment of 6-[(dimethylamino)]methylene]amino-1,3-dimethyluracil **242** with **662** under MWI for 5–45 min in an MW reactor gave pyrimido[4,5-*d*]pyrimidines **663** in 90–98% yields (Scheme 129). Thermal heating in dry DMF required 3.5–4 h to give 70–75% yields (04SL1179).

Reaction of the functionalized pyrimidine **266** with phenyl iso(thio)cyanate afforded pyrimido[4,5-*d*]pyrimidines **664** and **665** in 84% and 80% yields, respectively (Scheme 129) (04TL2405).

MWI-assisted reaction of 4-aminothieno[2,3-*d*]pyrimidines **666** with diethyl (ethoxymethylene)malonate without a solvent provided 8,9-disubstituted thieno[3,2-*e*]pyrimido[1,2-*c*]pyrimidines **668** in 80–83% yields in a single step within 7–10 min (99H1819) (Scheme 130). The reaction required 3.5–4 h at 130–140 °C to give **667**, which upon thermal cyclization in boiling diphenyl oxide (DPO) at 250 °C for 1.5–2 h provided **668** in 42–61% yields (99H1819).



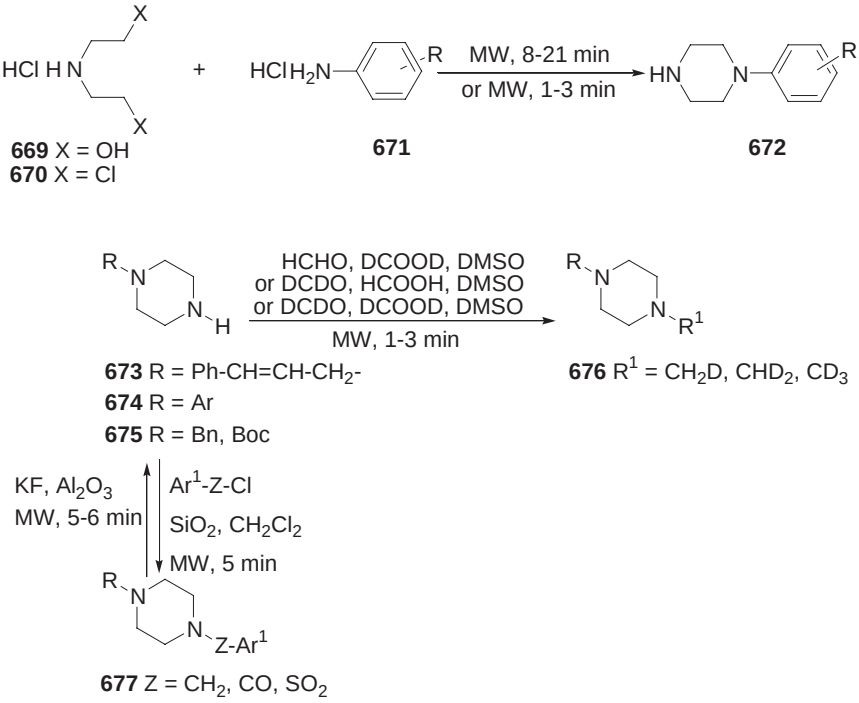
Scheme 129



Scheme 130

F. Pyrazines

1-Arylpiperazine derivatives **672** have wide applications as pharmaceuticals. Their conventional syntheses were achieved by heating the hydrochlorides of diethanolamine **669** and aniline derivatives **671** at about 240 °C for 8 h. The reaction was considered a good candidate for MW assistance as the reactants could couple effectively with MWI owing to their polarity. Sublimation and polymerization were controlled by adjusting the time for MWI. The time was reduced drastically to



Scheme 131

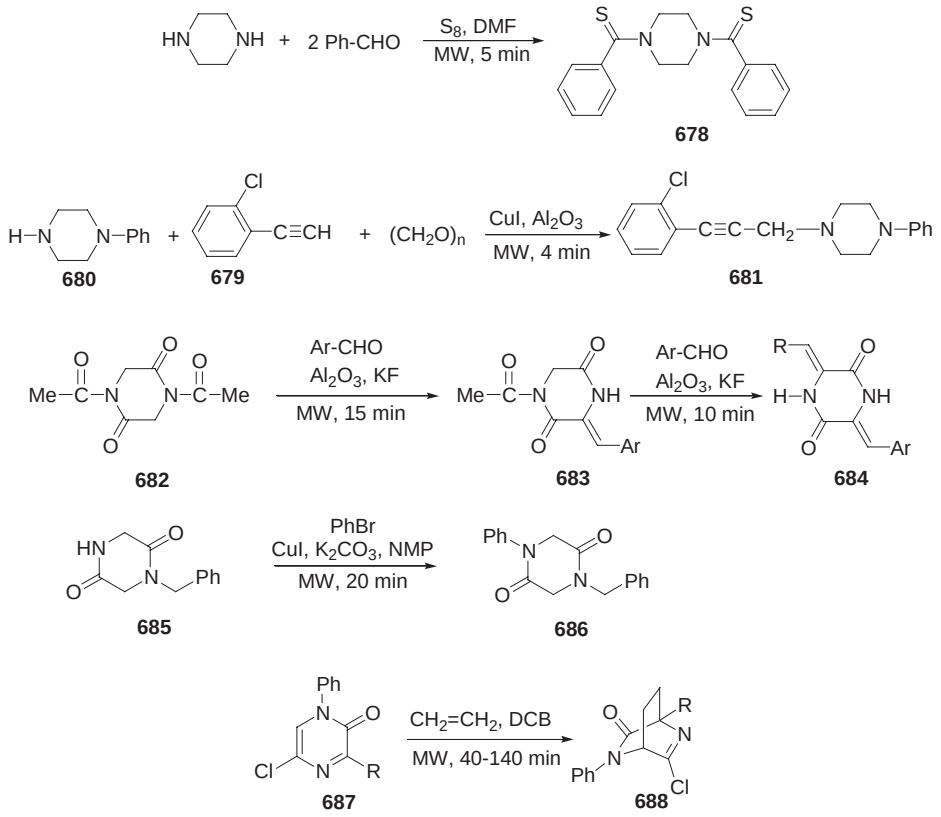
8–21 min and the yields of products **672** (18–50%) were comparable with those obtained by the conventional method (Scheme 131) (98SC1175). Alternatively, 1-arylpiperazines **672** were synthesized in 53–73% yields from *bis*(2-chloroethyl)amine hydrochloride **670** and substituted anilines under MWI without a solvent within 1–3 min (97TL6875).

Deuteromethylation of 1-substituted piperazine **673** represented the first application of the MW-enhanced reaction in the labeling area. It was achieved by selecting the reagents, HCHO/DCOOD, DCDO/HCOOH, or DCDO/DCOOD to give **676** under MWI (Scheme 131). The reaction was usually complete within 1–3 min instead of 24 h under thermal conditions (02TL9487).

The synthesis of 1-substituted arylpiperazines **677** in 72–99% yields from arylpiperazines **674** or **675** was done with benzyl, benzoyl, and arylsulfonyl chlorides adsorbed onto the silica gel under MWI for 5 min (Scheme 131) (00MI5). An efficient method for the cleavage of sulfonamides **677** has been achieved under MWI using KF–Al_2O_3 to give **673** or **674** in 76–80% yields within 5–6 min (99SL1745).

1,4-Dithiocarbonyl piperazine (**678**) was synthesized in 85% yield within 5 min under MWI in the presence of DMF solvent by a reaction of benzaldehyde with piperazine and sulfur. On thermal heating in xylene, the reaction also required 5 min, and the yield was lower (48%) (Scheme 132) (01SC53).

Mannich condensation was enhanced under MWI on CuI-doped alumina under solvent-free conditions where 1-phenylpiperazine (**680**) reacted with terminal



Scheme 132

alkynes **679** and paraformaldehyde to afford Mannich adduct **681**. The condensation required 4 min to produce the adduct in high yield (81%) (Scheme 132) (01SL676).

When equivalent amounts of 1,4-diacetylpiperazine-2,5-dione (**682**) and aldehydes were adsorbed on KF/alumina and irradiated by MW, the *Z*-isomer of the monoarylidene products **683** were obtained in 83–100% yield (Scheme 132). The reaction also took place at room temperature in DMF, but the yield was poorer. Further condensation with another aldehyde gave the mixed double condensation products **684** in 70–91% yield (90SC3325).

4-Benzylpiperazine-2,5-dione (**685**) reacted with bromobenzene under MWI to give 4-benzyl-1-phenylpiperazine-2,5-dione (**686**) in 51% yield within 20 min (Scheme 132); the reaction proceeded slowly (20 h) under thermal conditions at 200 °C (02TL1101).

Diels–Alder cycloaddition of pyrazinone **687** with ethene in the presence of 1,2-dichlorobenzene (DCB) under MWI gave the bicyclic cycloadducts **688** in 86–89% yields within 40–140 min (Scheme 132). Under conventional heating, these reactions were carried out in an autoclave for 12 h (02JOC7904).

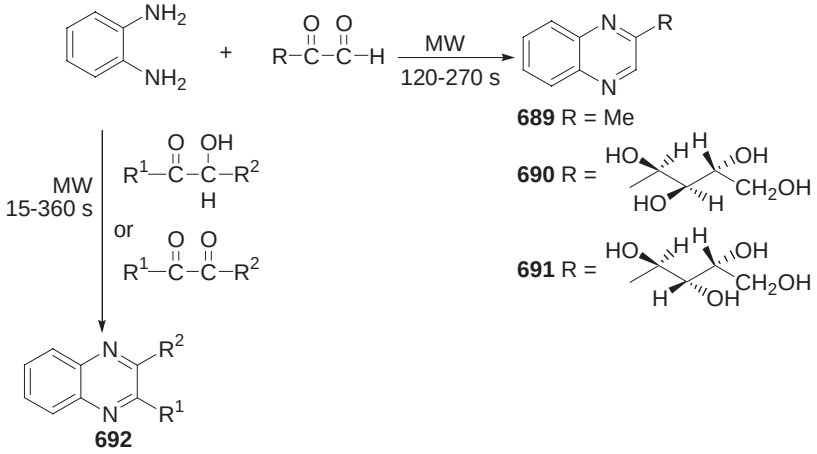
G. Quinoxalines

Quinoxalines are an important class of nitrogen heterocyclic compounds, existing in pharmaceuticals and natural products. MW-assisted condensation of *o*-phenylenediamine with methylglyoxal or aldohexoses without addition of sodium bisulfite or hydrazine hydrate gave **689** in 95% yield within 120 s and sugar derivatives **690** and **691** in 60% yield within 270 s (Scheme 133) (02TL8371).

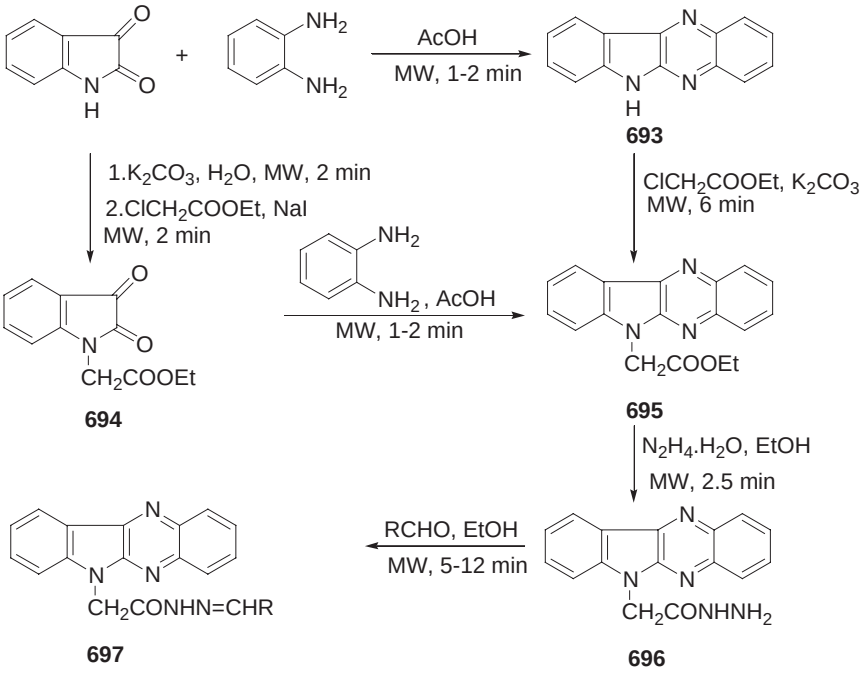
A convenient synthetic method for 2,3-disubstituted quinoxalines **692** was described by heating aryl or alkyl acyloins with *o*-phenylenediamine in dry media under MWI for 3–6 min; the products were obtained in 20–94% yields (Scheme 133) (98SC193). The condensation of the α-dicarbonyl compounds with *o*-phenylenediamine was catalyzed by PTSA without a solvent under focused MWI. Thus, camphorquinone, 1,2,3-triketo-hydrindane hydrate, *o*-quinones, phenanthrenequinone, and acenaphthenequinone gave easily the corresponding quinoxalines within 15 s to 4 min (95SC2319).

Indoloquinoxaline **693** was obtained in 83–90% yield by irradiating a mixture of isatin with *o*-phenylenediamine in acetic acid in an MW oven in either an open flask or closed Teflon vessel for 1–2 min. Carbethoxymethylation of isatin with ethyl chloroacetate in the presence of K_2CO_3 and NaI was carried out under MWI to give compound **694** in 70% yield within 4 min. It could be converted into **695** by reaction with *o*-phenylenediamine in acetic acid in either an open flask (2 min) or closed Teflon vessel (1 min) (Scheme 134). Alternatively, carbethoxymethylation of **693** under MWI for 6 min afforded a 53% yield of **695**. Reaction of **695** with hydrazine hydrate in ethanol under MWI gave the hydrazide **696** in 84% yield. MWI has been also used to condense **696** with aromatic aldehydes and monosaccharides to yield the hydrazone derivatives **697** in 58–99% yields (Scheme 134) (05JCR(S)299).

Pyrazine derivatives have also served as precursors for quinoxalines in acceptable yields under MWI in solvent-free conditions through the reaction of pyrazine *o*-quinodimethane intermediates with electron-rich dienophiles. Thus, 2,3-*bis*



Scheme 133

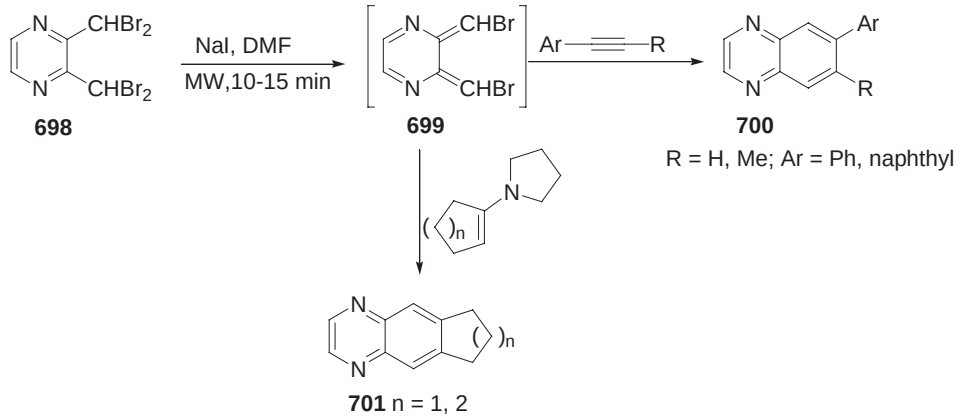


Scheme 134

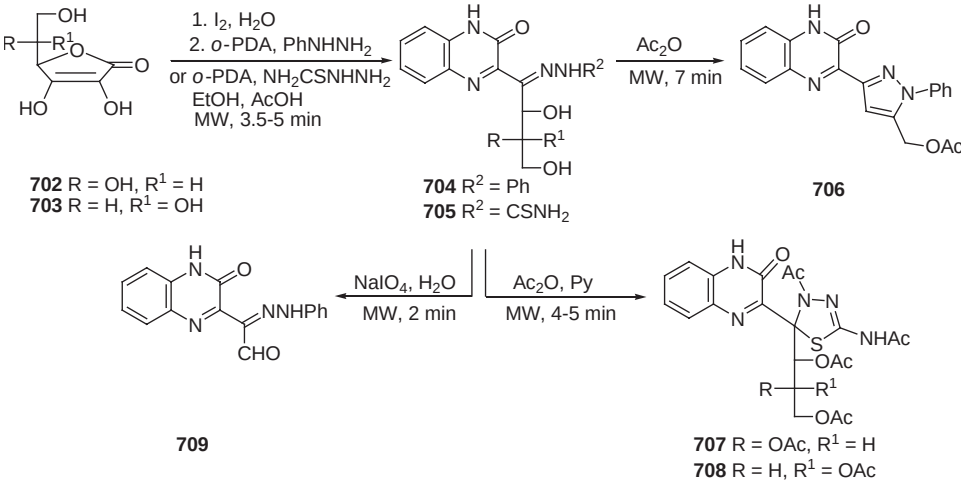
(dibromomethyl)pyrazine (**698**) was irradiated in the presence of NaI and small amount of DMF to dissolve the formed salt under MWI for 10–15 min to give pyrazine *o*-quinodimethane intermediate **699**. Subsequent Diels–Alder reaction with dienophiles such as alkynes or enamines in solvent-free conditions gave the corresponding cycloadducts **700** and **701** in 33–43% yields within 10–15 min (Scheme 135). Classical heating using an oil bath afforded traces of cycloadducts (3%) (02SL2037).

MWI of dehydro-L-ascorbic acid or -D-isoascorbic acid generated by oxidation of **702** or **703** with iodine, *o*-phenylenediamine, and phenylhydrazine in ethanol and in the presence of acetic acid for 3.5 min gave quinoxalinones **704** in 80–86% yields. Similarly, thiosemicarbazones **705** were obtained within 5 min in 69–79% yields by using thiosemicarbazide instead of phenylhydrazine (Scheme 136). Cyclization of **704** to the pyrazolyl-quinoxalinone **706** (88–95%) was also achieved by MWI for 7 min by using acetic anhydride, and bentonite as a support MWI of **705** with acetic anhydride in pyridine for 4–5 min afforded the L-threo and D-erythro thiadiazolyl-quinoxalinones **707** and **708** in 80% and 79% yields from the two epimers of **705**, respectively. Periodate oxidation of **704** under MWI gave **709** in 90–92% yields (Scheme 136) (05UP4).

The combination of soluble polymer-supported synthesis with MW technology provided a highly versatile platform for the generation of chiral quinoxalin-2-one libraries. A simple work-up and cleaner products were achieved compared with



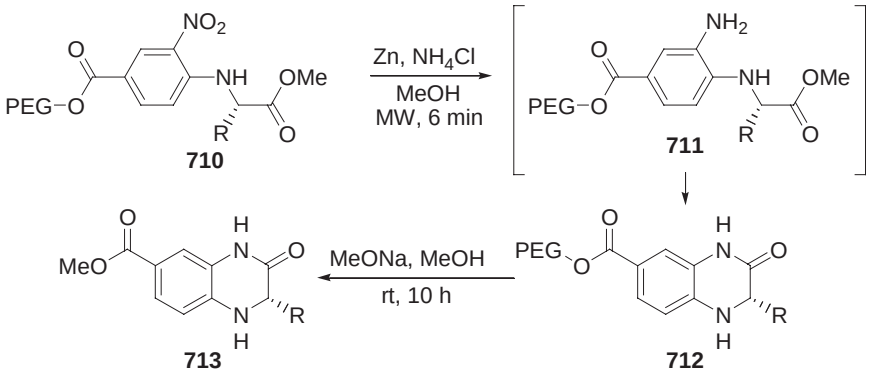
Scheme 135



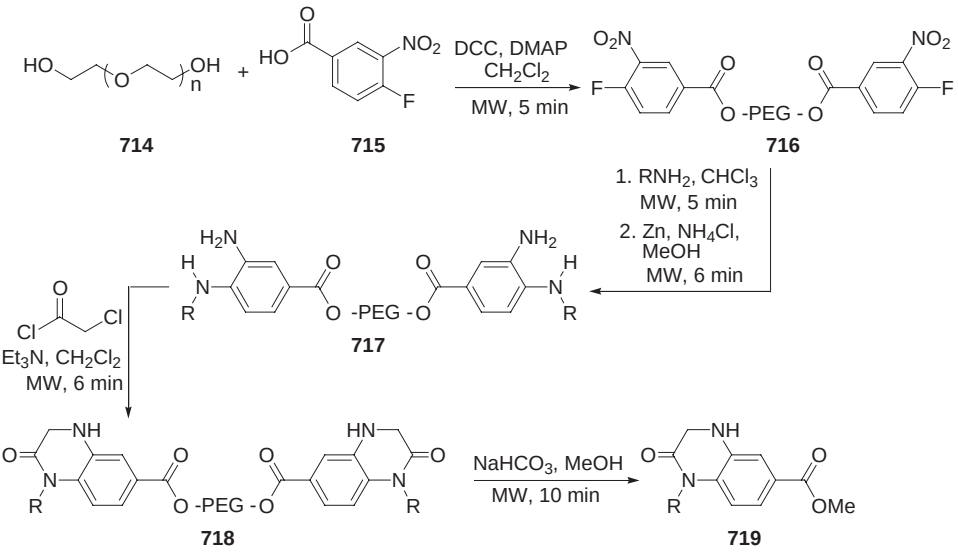
Scheme 136

conventional thermal heating. Moreover, the polymer-supported intermediates and the polymer support itself remained stable under MW exposure. Polymer-immobilized *o*-nitrophenylamino ester **710** was reduced with Zn/NH_4Cl in methanol for 6 min in an MW cavity to give **711**, followed by synchronous intramolecular cyclization to give 1,2,3,4-tetrahydroquinoxalinones **712**, which then were cleaved to **713** in 73–97% yields (Scheme 137). The use of Zn/NH_4Cl was more convenient than tin(II) chloride dihydrate, which has been extensively used to reduce nitro groups (04TL1159).

The advantages of MW technology combined with liquid-phase combinatorial chemistry were also successfully applied to a rapid synthesis of quinoxalin-2-ones. PEG bound *o*-fluoronitrobenzene **716** was synthesized by coupling of 4-fluoro-3-nitrobenzoic acid (**715**) with PEG **714**, in the presence of DCC and a catalytic



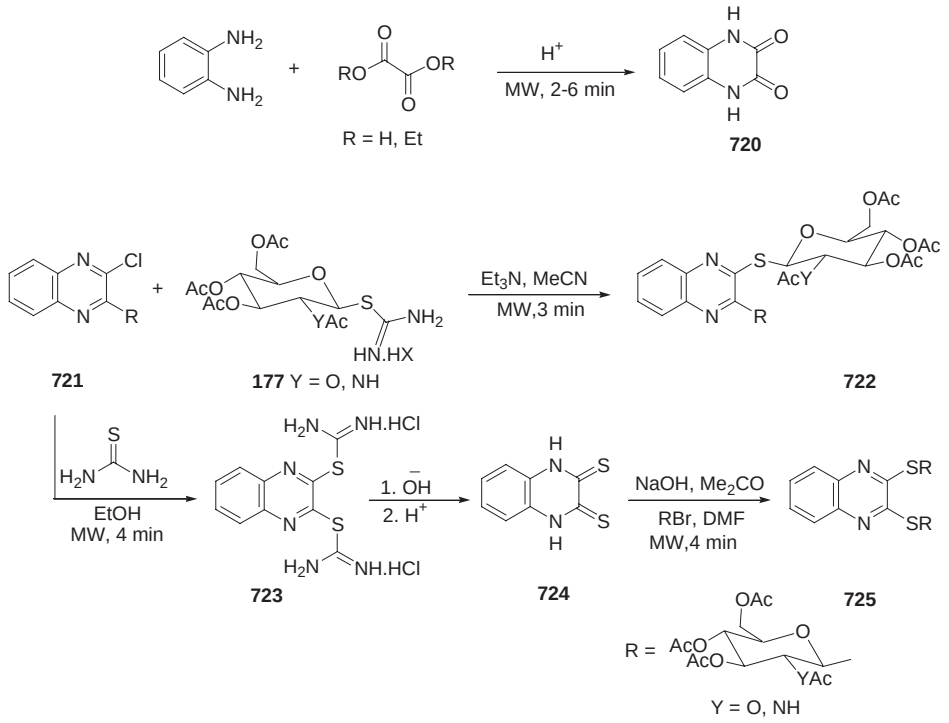
Scheme 137



Scheme 138

amount of DMAP in dichloromethane under MWI for 5 min. The fluorine atom was displaced by various amines and the nitro group was then reduced to give diamines **717**, whose reaction with chloroacetyl chloride under MWI for 6 min gave the polymer bound 1,2,3,4-tetrahdroquinoxalin-2-one **718** and subsequent cleavage under MWI for 10 min gave **719** in 76–99% yields (Scheme 138). Compared to conventional thermal heating, MWI decreased the reaction time from several days to several minutes and improved the yields (03SL1688).

A monomodal MW heating (94MI2) technique under solvent-free conditions in the presence of acidic media was used to accelerate the cyclocondensation of diethyl oxalate with *o*-phenylenediamine to give quinoxaline-2,3-dione **720** in good to high



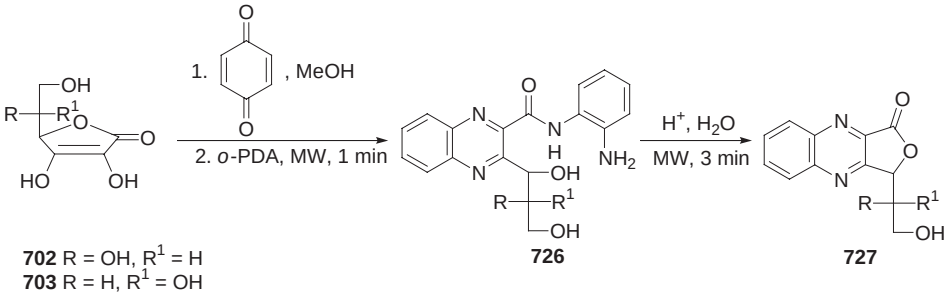
Scheme 139

yields after 2–6 min. When the reactions were attempted using solid supports with solvents that couple well with MW (H_2O, MeCN, and DMSO), only trace amounts of **720** were obtained (<2%) (Scheme 139). However, in the absence of solvents, comparable yields were obtained by using Dowex 50 × 8 and KSF. Moreover, the use of PTSA nearly doubled the yields over those obtained with the solid supports (01H109). Typically the cyclization proceeded slowly in refluxing solvents in the presence of mineral acids (62JCS1170).

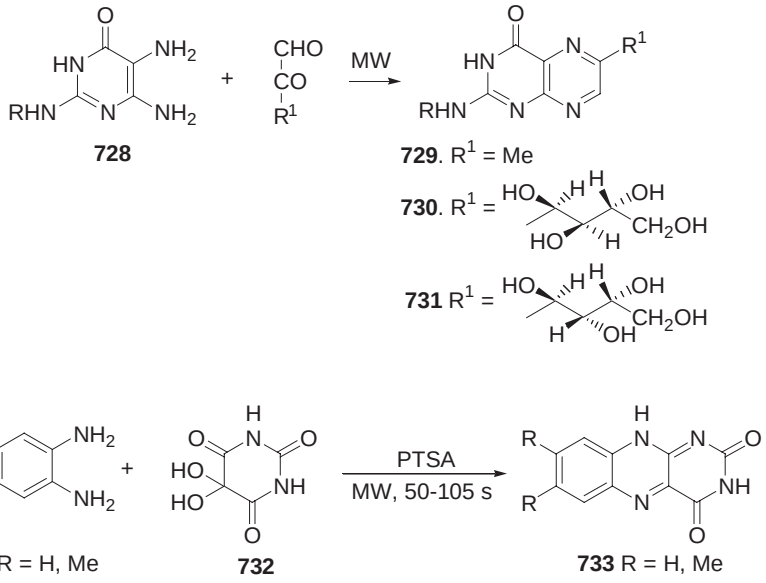
Cyclocondensation of oxalic acid with *o*-phenylenediamine in an acidic medium gave **720** in 93% yield after MWI for 2 min (Scheme 139), while a lower yield (75%) was obtained under conventional heating for 10 min (05UP4).

Under MWI isothiouronium salts **177** were coupled with 2-chloroquinoxalines **721** in acetonitrile containing Et_3N to give thioglycosides **722** in 60–66% yields within 3 min (Scheme 139). Under conventional conditions, **722** were obtained in 40–48% yields after 10 h (05UP1).

2,3-Dichloroquinoxaline (**721**, R = Cl) was prepared in 90% yield from quinoxaline-2,3-dione (**720**) with $POCl_3$ under MWI for 3 min. Reaction of **721** (R = Cl) with thiourea under MWI for 4 min gave 86% yield of a **723**, which upon treatment with alkali followed by neutralization afforded quinoxaline-2,3-dithione **724**. Reaction of **724** with acetobromoglucose or 2-amino-2-deoxy-2,3,4,6-tetra-*O*-acetyl α-D-glucopyranosyl bromide in DMF under MWI for 4 min gave **725** in 71% compared with a 69% yield after 3 h of conventional heating (Scheme 139) (05UP4).



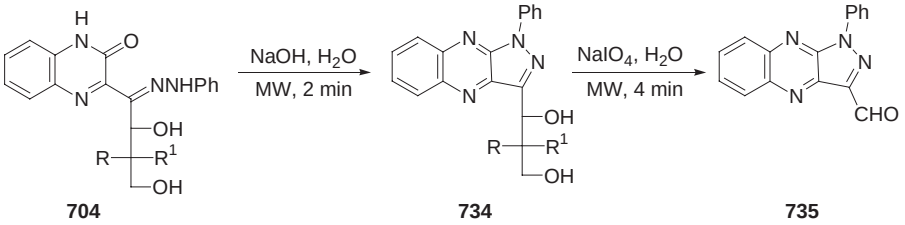
Scheme 140



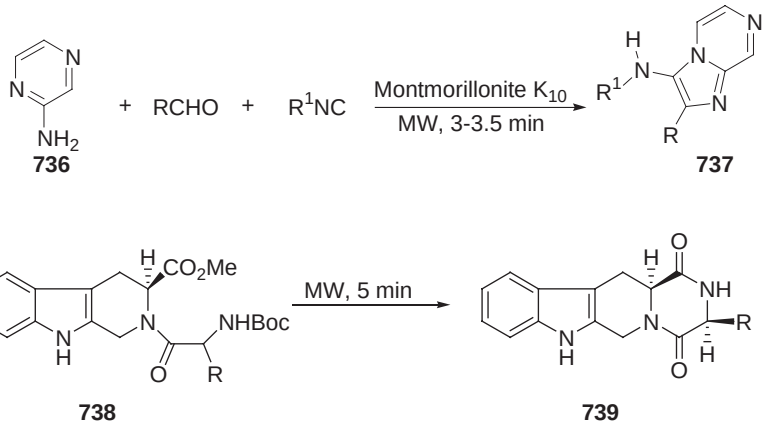
Scheme 141

Oxidation of L-ascorbic (**702**) or D-isoascorbic acid (**703**) with *p*-benzoquinone followed by MWI with two equivalents of *o*-phenylenediamine for 1 min gave 87–94% yields of quinoxaline **726**. Acid hydrolysis of **726** was also achieved under MWI for 3 min to give the corresponding quinoxaline lactone **727** in 48–53% yields (Scheme 140) (05UP4). The yields were higher with a shorter reaction time than conventional methods (92AHC233, 00MI6).

A regioselective synthesis of 6-substituted pterins **729**, **730**, and **731** was achieved using an MW-assisted direct Isay-type condensation of triamine **728** with methylglyoxal or aldohexoses to give under MWI, without addition of sodium bisulfate or hydrazine hydrate, **729** in 70% yield within 62 s and the sugar derivatives **730** and **731** in 40% and 38% yields, respectively, within 270 s (Scheme 141) (02TL8371).



Scheme 142



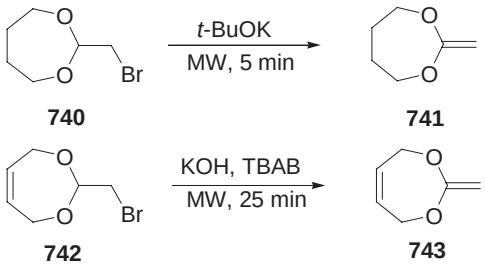
Scheme 143

Condensation of alloxan monohydrate **732** with 1,2-diaminobenzene or 1,2-diamino-4,5-dimethylbenzene was catalyzed by PTSA without a solvent under MWI to give isoalloxazine **733** (R = H) and lumichrome **733** (R = Me), respectively, the heterocyclic part of riboflavine (vitamine B_2) (Scheme 141) (95SC2319).

Dehydrative cyclization of the L-threo and D-erythro quinoxalines **704** with aqueous NaOH under MWI for 2 min gave flavazoles **734** in 95% yield. Further cleavage to 3-formyl-1-phenylpyrazolo[3,4-*b*]quinoxaline (**735**) (60–76%) was also carried out under MWI within 4 min (Scheme 142) (05UP4).

Irradiating a mixture of aldehydes and 2-aminopyrazine **736** in the presence of montmorillonite K_{10} with MW generated iminium ion, then further irradiated with isocyanide to afford imidazolo[1,2-*a*]pyrazines **737** in 64–83% yields within 3–3.5 min (Scheme 143) (99JHC1565).

Cyclization of pyrido[3,4-*b*]indoles **738** under MWI in solvent-free conditions afforded (*S*)-3-substituted 2,3,6,7,12,12a-hexahydropyrazino[1′,2′:1,6]pyrido[3,4-*b*]indole-1,4-diones **739** in high yields (88-95%) within 5 min instead of 59-63% yields from a conventional method using trifluoroacetic acid in CH_2Cl_2 for 1-2 h (Scheme 143). The reaction occurred through the removal of Boc group *in situ* with intramolecular cyclization by the loss of one mole of methanol (01T4437).



Scheme 144

H. Dioxepines

Ketene *O*,*O*-acetals **741** and **743** were prepared in 97% and 82% yields, respectively, from the corresponding bromo derivatives **740** and **742** and strong base (*t*-BuOK) or milder base (KOH) and TBAB, respectively, under MWI and solvent-free conditions (Scheme 144). The phase-transfer agent TBAB was not necessary with *t*-BuOK, owing to the strength of this base, which promoted a β-elimination and gave an almost quantitative yield of product. The yields under MWI were better than those obtained by ultrasound or classical heating (96TL1695).

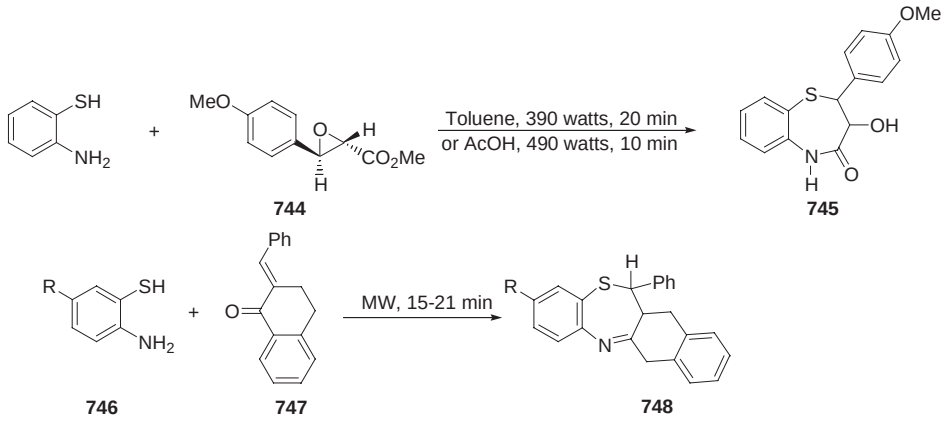
I. Benzothiazepines

A diastereoselective one-pot synthesis of the *trans*- and *cis*-3-hydroxy-2-(4-methoxyphenyl)-2,3-dihydro-1,5-benzothiazepin-4(5*H*)-one (**745**) was carried out under MWI. The variation of solvent and power output was found to direct the stereochemistry of ring opening of the oxirane ring in *trans*-3-(4-methoxyphenyl)glycidate ester **744** (96TL6413). Reaction of 2-aminothiophenol with **744** in toluene under MWI at 390 W gave benzothiazepinone **745** in 75% yield (*cis*/*trans* 9:1) within 20 min. Varying the polarity of the solvent by using acetic acid instead of toluene and changing the irradiation power from 390 to 490 W gave an 84% yield of **745** (*cis*/*trans* 1:9) after 10 min (Scheme 145) (96TL6413).

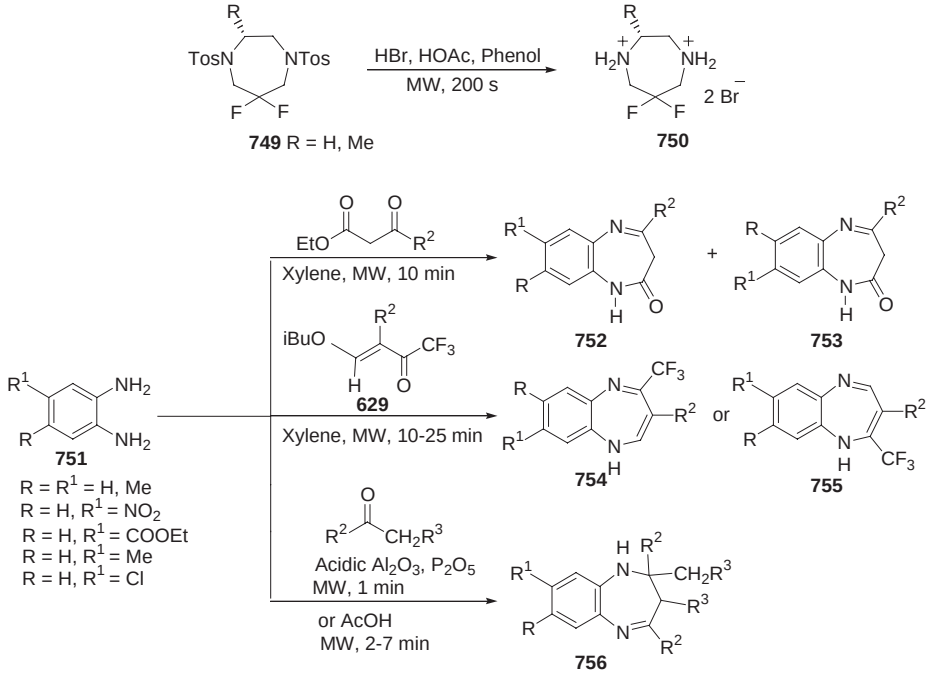
Condensation of substituted aminothiophenols **746** and 2-arylidene-1-tetralone **747** under MWI at 102–129 °C using montmorillonite KSF as a solid support in dry media gave substituted 1,4thiazepines **748** in high yields (69–81%) with high purity within a very short time 15–21 min (Scheme 145). Under conventional heating at reflux in ethanol in the presence of conc. HCl products, **748** were obtained in lower yields (58–67%) and longer times (280–480 min) (03H563).

J. Diazepines and their Fused Rings

The N-detosylation of 6,6-difluorohomopiperazine **749** by heating with 30% anhydrous hydrogen bromide in acetic acid and phenol gave traces of **750**. However, when this reaction was performed under MWI, compounds **750** were produced in



Scheme 145



Scheme 146

high yields (70–90%) within 200 s (Scheme 146) (02S223). Most of the publications on that ring system utilizing MW deal with their benzoanalogs.

An efficient synthesis of 1,5-benzodiazepin-2-ones **752** and **753** was carried out by the condensation of *o*-phenylenediamines with *β*-keto esters in xylene under MWI. The condensation occurred within 10 min and the products were obtained in 80–98%

yields, while under classical heating by-products were formed in considerable yield (94TL8373). When the condensation was done in DMAC under MWI, it gave 4-phenyl-1,3-dihydro-2*H*-1,5-benzodiazepin-2-ones **752** ($R^2 = Ph$) in 73–84% yields (Scheme 146) (96JCR(S)92).

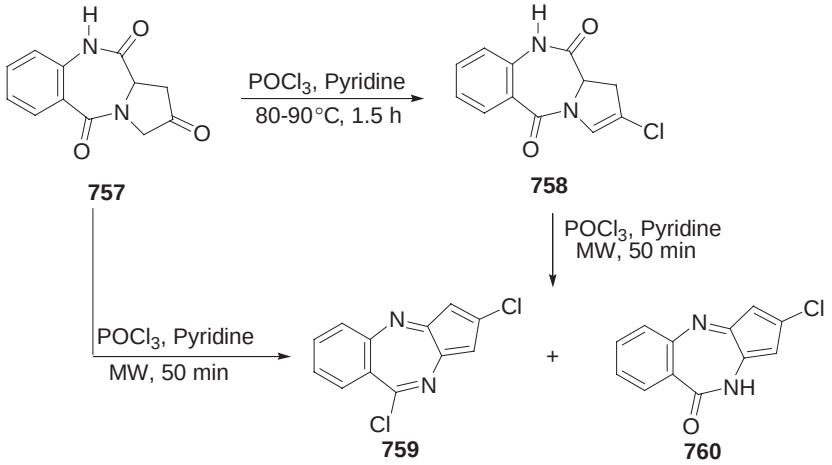
Condensation of *o*-phenylenediamines with 1,1,1-trifluoromethyl-3-(isobutoxymethylene)-2-propanones **629** in xylene under MWI produced single products **754** or **755** in 73–93% yields (Scheme 146) (97T5847, 96TL2845).

The synthesis of 2,3-dihydro-1*H*-1,5-benzodiazepines included the condensation of *o*-phenylenediamines with α,β-unsaturated carbonyl compounds, β-haloketones, or ketones in the presence of BF_3-etherate, $NaBH_4$, PPA, SiO_2, MgO, $POCl_3$, and $Yb(OTf)_3$ (74JCS(P1)2657, 86H135, 99SC1941, 01TL1127, 01TL3193). Many of these processes suffer from major or minor limitations, such as drastic reaction conditions, expensive reagents, low yields, tedious work-up procedures, and the occurrence of several side reactions. MW enhanced this synthetic route on irradiating a mixture of *o*-phenylenediamine with ketones under solvent-free conditions on acidic alumina/P_2O_5 to give **756** in 73–85% yields within 1 min (Scheme 146) (01H1443).

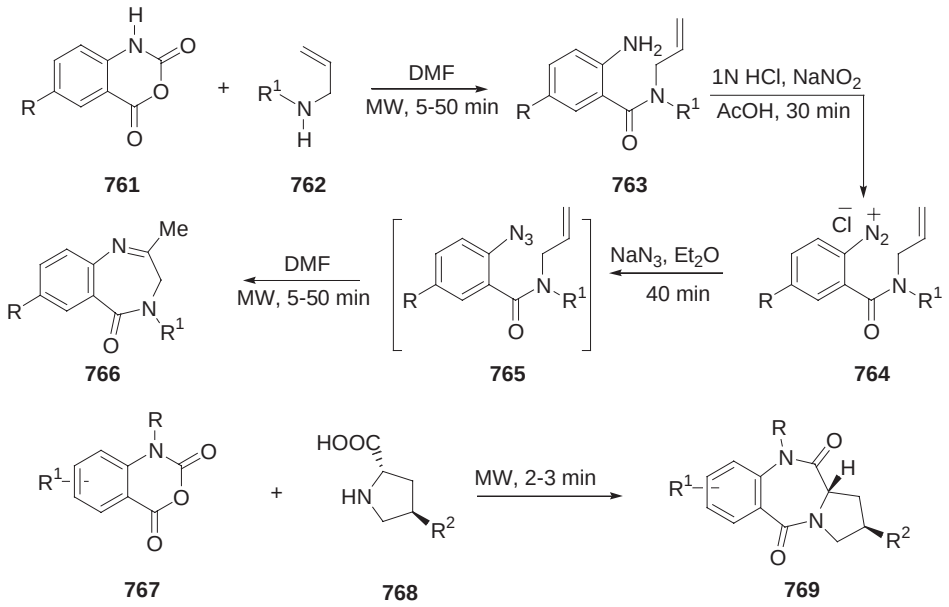
The synthesis of **756** can also be carried out by mixing *o*-phenylenediamines with ketones in the presence of a catalytic amount of acetic acid and then by irradiation in an MW oven for 2–7 min. The benzodiazepine derivatives were obtained in 90–99% yields (Scheme 146) (02TL1755).

When pyrrolo[2,1-*c*][1,4]benzodiazepine-2,5,11-trione (**757**) was heated with $POCl_3$ and a catalytic amount of pyridine for 1.5 h, compound **758** was obtained. When the reaction was subjected to MWI for 50 min, compound **757** rearranged and subsequently aromatized to 2,5-dichlorocyclopenta[*b*][1,4]benzodiazepine (**759**) as a major product and its lactam **760** in a ratio 85:15 in 47% yield (97TL2271). Treatment of **758** with $POCl_3$/pyridine under MWI also gave **759** and **760** (Scheme 147).

Reaction of 5-substituted isatoic anhydride **761** with allylamines **762** in DMF under MWI for 5–50 min gave 2-amino-5-substituted-*N*-alkyl-*N*-(2-propenyl)



Scheme 147



Scheme 148

benzamides **763** in 50–97% yields; 20–69% yields were obtained under conventional heating for 3 h. The intermediates **763** were subjected to diazotization to give **764**, whose subsequent nucleophilic substitution by sodium azide gave **765**, which were cyclized by a second exposure to MWI to give 2-methyl-1,4-benzodiazepin-5-ones **766** in better yields (55–69%) than those (27–45%) obtained by conventional heating in DMF for 1 h (Scheme 148) (01TL2397).

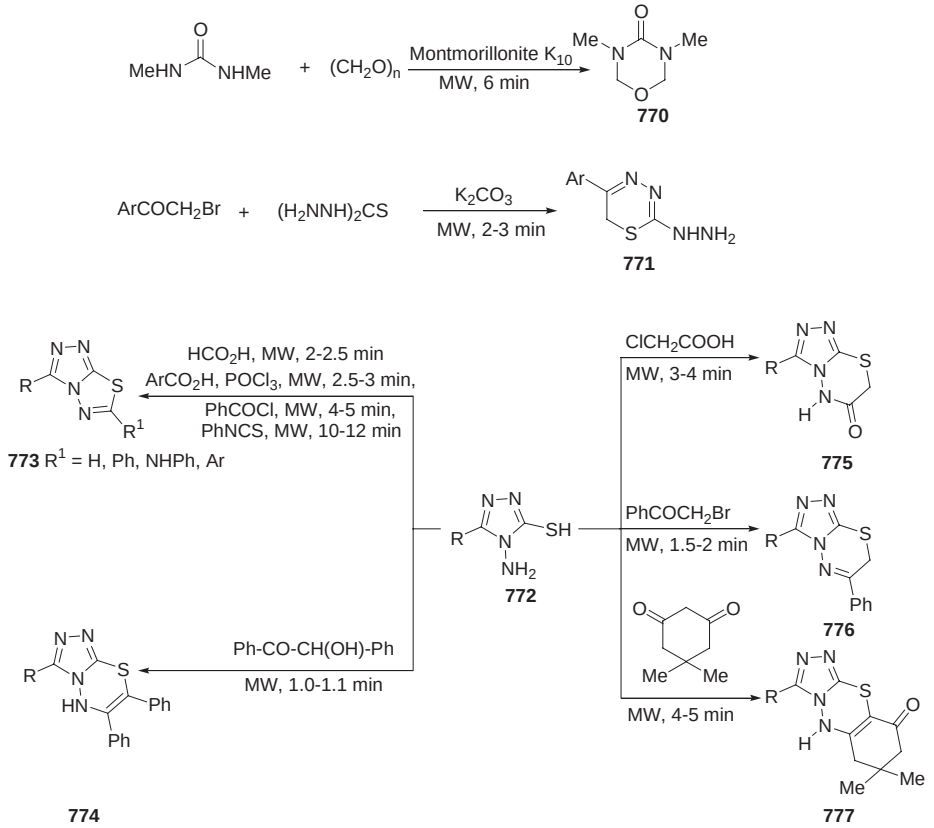
The noncovalent DNA-binding agents pyrrolo[2,1-*c*][1,4]benzodiazepine-5,11-diones **769** have been successfully synthesized in 80–92% yields from isatoic anhydride **767** with L-proline **768** under MWI for 2–3 min (Scheme 148) (99SL1251).

IV. Heterocycles with Three Heteroatoms

A. Oxa(thia)diazines

Condensation of dimethyl urea with paraformaldehyde supported on montmorillonite K_{10} using MWI in dry media gave 4-oxo-oxadiazinone **770** in 67% yield (Scheme 149). Formation of **770** may occur by the attack of the nucleophilic nitrogens of urea on formaldehyde (99JCR(S)392).

2-Hydrazinothiadiazines **771** were prepared in 86–95% yields from phenacyl bromides with thiocarbohydrazide in the presence of K_2CO_3 using MW heating for 2–3 min (Scheme 149) (02JHC1045).

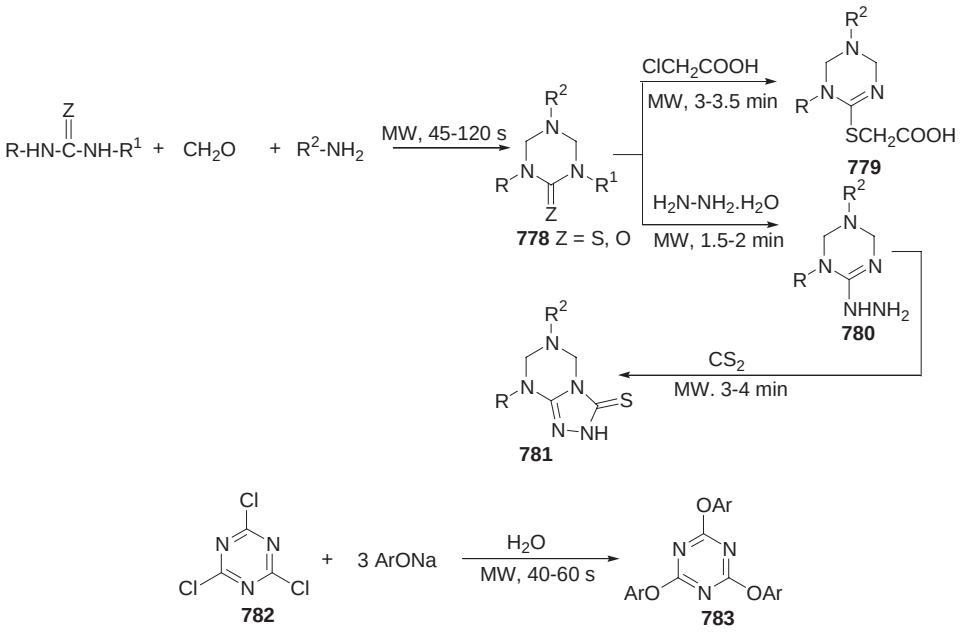


Scheme 149

1,2,4-Triazolo[3,4-*b*][1,3,4]thiadiazoles **773** were obtained in 70–94% yields by the condensation of 4-amino-5-substituted-4*H*-1,2,4-triazole-3thiols **772** with one-carbon cyclizing agents such as formic acid, acid chlorides, phenyl isothiocynate, and aromatic acids under MWI for 2–12 min. The classical approach required 2–20 h (96JCR(S)254, 97IJC(B)782). Similarly, triazolothiadiazines **774**, **775**, **776**, and **777** were prepared in 50–85% yields by MWI of **772** with benzoin, chloroacetic acid, phenacyl bromide, and dimedone, respectively (Scheme 149) (97IJC(B)782).

B. Triazines

Condensation of substituted aromatic or heterocyclic amines with formaldehyde and urea or phenylthioureas under MWI in an aqueous medium gave 2-(oxo)thioxo-hexahydro-1,3,5-triazines **778** in 92–98% yields within 45–120 s, but conventional heating gave 50–58% yields within 10–12 h. Triazines **778** further reacted with chloroacetic acid or hydrazine hydrate to give **779** and **780**, respectively. Compounds **780** were obtained in 86–90% yields within 1.5–2.0 min under MWI, but classically



Scheme 150

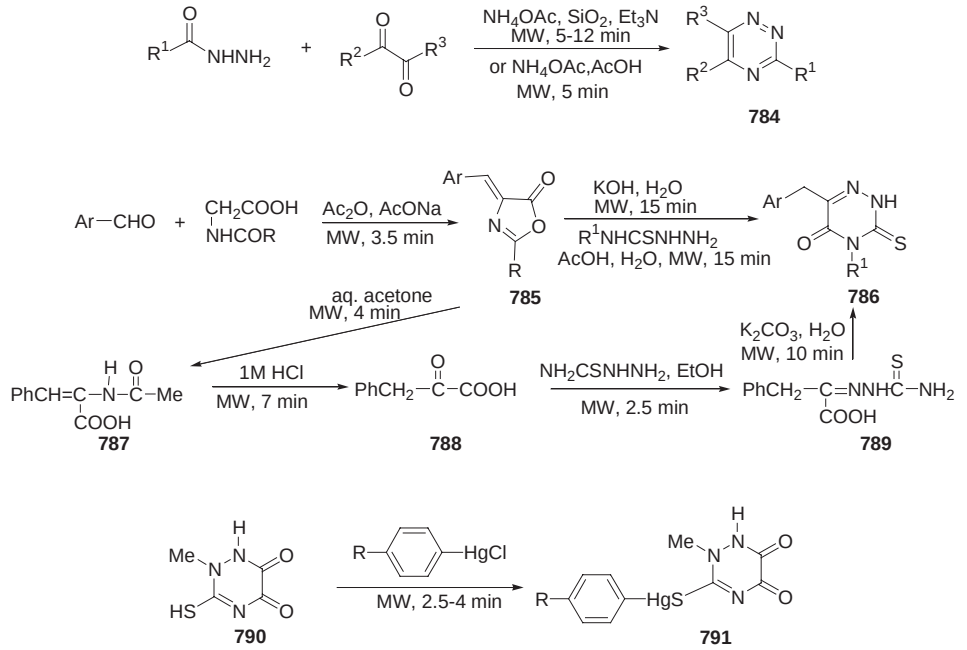
the reaction times were 7–10 h and the yields were 52–58%. Similarly, **779** were produced in 84–85% compared to 60–62% yields under classical heating for a long time. Further, triazolo[4,3-*a*]triazines **781** were obtained in 86–92% yields by a one-pot reaction of triazinyl hydrazine **780** with CS_2 under MWI for 3–4 min (Scheme 150). Conventional conditions required a 4 h reflux in the presence of anhydrous pyridine to give lower yields (52–60%) (04SC1141).

Condensation of dimethyl urea, paraformaldehyde, and primary amines supported on montmorillonite K_{10} under MWI in dry media gave triazinones **778** ($R = R^1 = Me$, $Z = O$) in 71–84% yields within 6 min (Scheme 150) (99JCR(S)392).

2,4,6-Triaryloxy-1,3,5-triazines **783** are important chemicals used in various fields such as polymers, dyes, and pharmaceuticals. In view of their potential applications, a rapid synthesis of **783** in excellent yields (85–90%) was reported by heating cyanuric chloride (**782**) with the sodium salt of phenolic compounds in water by using focused MW. Moreover, it was considered to be an environmental friendly procedure (Scheme 150) (00SC1719).

A one-pot condensation reaction of acid hydrazide, ammonium acetate, and α-dicarbonyl compounds on the surface of silica gel in the presence of triethylamine under MWI gave 1,2,4-triazines **784** in 61–93% yields within 5–12 min (Scheme 151) (02SC1899).

The traditional thermal conditions were applied to the reaction of heterocyclic acyl hydrazide with heterocycles containing a 1,2-diketone in a 1:1 ratio by using an excess of ammonium acetate in refluxing acetic acid for 10–24 h to give 3-heterocyclo-1,2,4-triazines **784** in less than 30% yield. On the other hand, when the



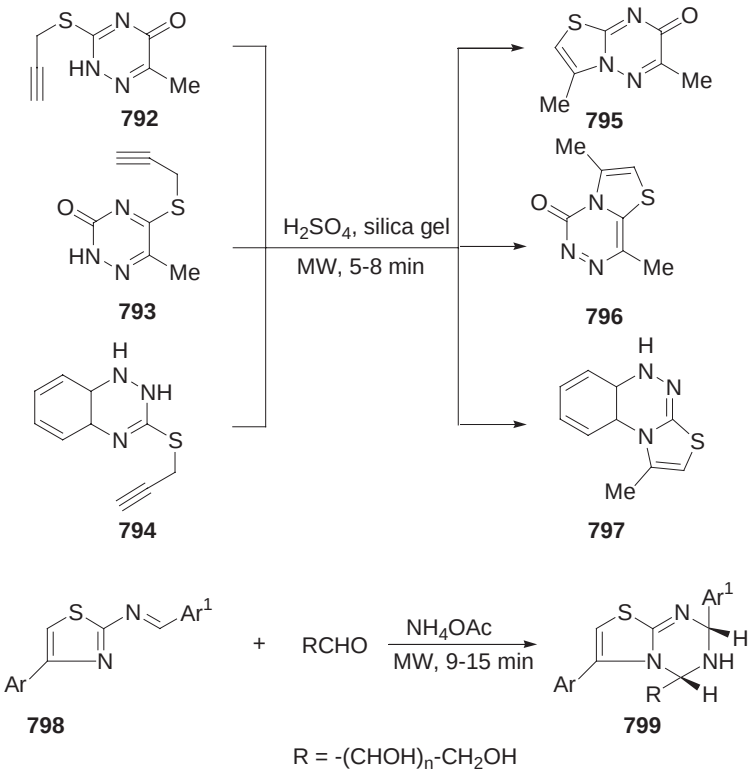
Scheme 151

reaction was conducted using MWI the yields increased to 62–92% within 5 min (Scheme 151) (03TL1123).

The synthesis of azlactones **785** has been carried out by irradiating in an MW oven for 3.5 min a mixture of the aromatic aldehyde, acyl glycine, acetic anhydride, and sodium acetate. The yield of **785** ranged between 78% and 90%, instead of 59–76% under classical heating. Irradiating a mixture of **785** and KOH in H_2O for 15 min followed by adding thiosemicarbazide or 4-phenyl-3thiosemicarbazide in AcOH–-H_2O and further irradiation for 15 min led to triazinones **786** in 59–76% yields. Hydrolysis of **785** (R = Me, Ar = Ph) with aqueous acetone was carried out under MWI for 4 min to give 2-acetamidocinnamic acid (**787**) in 74% yield. MWI of **787** in 1 M HCl in a closed Teflon vessel for 7 min gave phenylpyruvic acid (**788**) in 78% yield. Under MWI, the condensation of **788** with thiosemicarbazide gave thiosemicarbazone **789** (97%), which was cyclized with aqueous K_2CO_3 under MWI to give **786** (R^1 = H, Ar = Ph) in 56% yield (Scheme 151) (05MI1).

Organomercurials **791** have been synthesized in 68–73% yields from **790** with aryl mercuric chloride under MWI. The reaction time was reduced to 2.5–4.0 min instead of 7–9 h under conventional heating (Scheme 151) (97M1291).

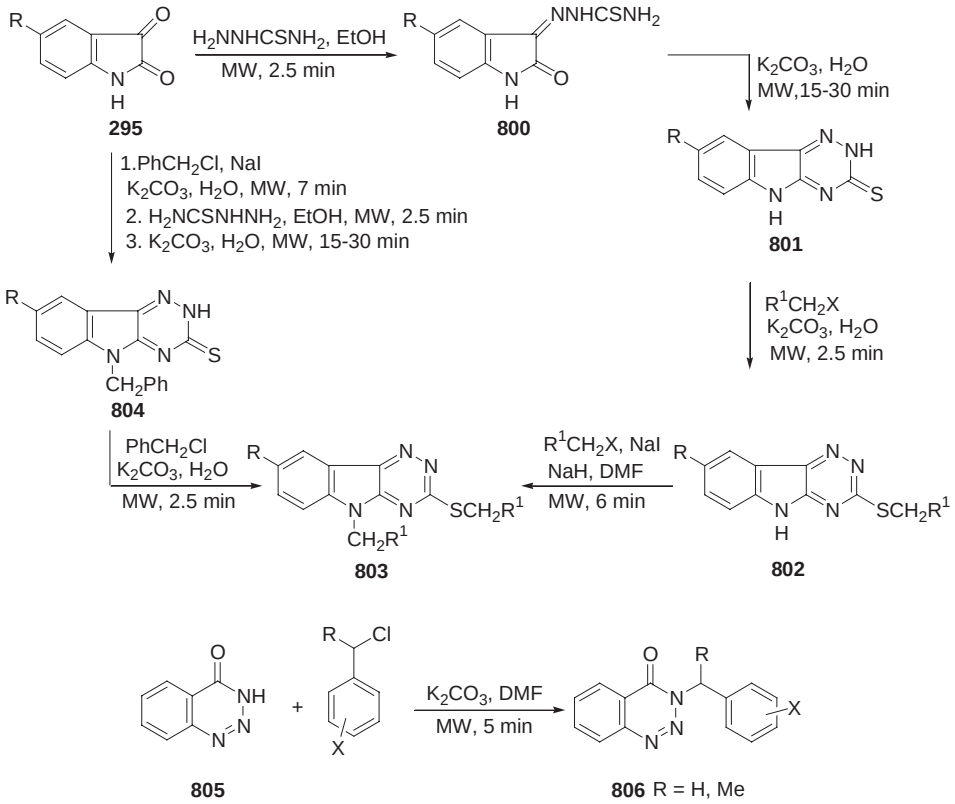
Regioselective cyclization and isomerization of propargylthio-1,2,4-triazinones **792**, **793**, and **794** were achieved rapidly under MWI by the catalytic action of sulfuric acid adsorbed on silica gel in 5–8 min to give the corresponding fused heterocycles **795**, **796**, and **797** in 75–80% yields. The cyclization did not occur in the absence of a catalyst on exposure to MWI (Scheme 152) (00JCR(S)464).



Scheme 152

Acyclic C-nucleosides **799** incorporating the thiadiazolo-1,3,5-triazine structure were synthesized through three-component one-pot reactions of thiazole Schiff's bases **798**, ammonium acetate, and an aldose under solvent-free MWI conditions to give thiazolotriazines **799** (*cis*/*trans*) in 76–88% overall yield within 9–15 min (Scheme 152). The formation of **799** was highly diastereoselective in favor of the *cis*-isomers; the diastereomeric ratio was >96:4 under MWI, while under conventional heating in an oil bath the (*cis*/*trans*) ratio was >56:<44 in a lower overall yield (20–31%) within the same time. The higher diastereoselectivity in favor of *cis*-isomers under MWI could be due to the higher polar character of the activated complex leading to the formation of *cis*- over the *trans*-isomer because MWI favors reactions occurring *via* more polar intermediates (03TL8951).

Conversion of isatins **295** to the their respective isatin 3thiosemicarbazones **800** has been carried out by a reaction with thiosemicarbazide in ethanol under MWI for 2.5 min. The cyclization of **800** in aqueous K_2CO_3 using MWI gave the corresponding 1,2,4-triazino[5,6-*b*]indole-3thiols **801** within 15–30 min in 83–87% yields. Alkylation of **801** with benzyl chloride or ethyl chloroacetate in K_2CO_3 under MWI for 2.5 min gave the S-alkylated derivatives **802** in 82–89% yields. Further alkylation of **802** with an alkyl halide in the presence of NaH and NaI in DMF under MWI



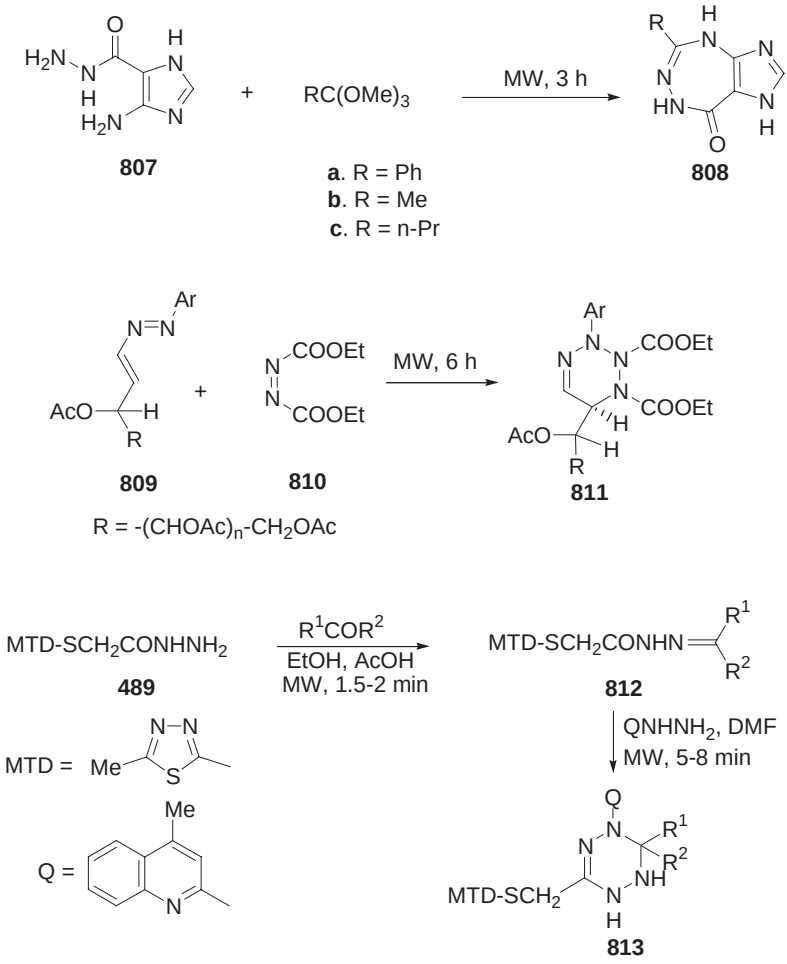
Scheme 153

afforded **803** within 6 min in 70–85% yields (Scheme 153). Also, N-benzylation of **295** could be achieved under MWI within 7 min in 72% yield by using benzyl chloride and K_2CO_3 in the presence of NaI. The product was then converted into **804**, further benzylated under MWI within 2.5 min to give **803** in 85% yield (Scheme 153) (04SL723).

Several 3-benzyl-1,2,3-benzotriazin-4(3*H*)-ones **806** were prepared in moderate yields (52–75%) by alkylating 1,2,3-benzotriazin-4(3*H*)-one (**805**) with benzyl halides in the presence of K_2CO_3 and DMF under MWI within 5 min (Scheme 153) (97JHC1391, 99JHC1095).

C. 1, 2, 4-Triazepines

The imidazotriazepines **808** were obtained on heating hydrazide **807** and an orthoester. Although the yield of **808** was 74% on reacting **807** with trimethyl *ortho*-benzoate in ethanol for 22 h (84JHC1817), the replacement of the phenyl group of the orthoester by a methyl or an *n*-propyl group led to a low yield of 12% and 8%, respectively. However, MWI improved the reaction leading to imidazotriazepines



Scheme 154

808 in a shorter time (3 h) and higher yields (38–47%) (Scheme 154). These poor yields were explained by the lower reactivity of alkyl orthoesters and the poor nucleophilicity of the NH_2 group that is delocalized with the imidazole ring (02SL519).

V. Heterocycles with Four Heteroatoms

A. Tetrazines

Hetero Diels–Alder reactions of chiral 1-aryl-1,2-diaza-1,3-butadienes **809**, derived from acyclic carbohydrates, with diethyl azodicarboxylate **810** in dry benzene

at room temperature gave the corresponding functionalized 1,2,3,6-tetrahydro-1,2,3,4-tetrazines **811** after ~30 days (99JOC6297). When the reactions were carried out without solvents under MWI in a focused MW reactor, the adducts were obtained within 6 h in excellent yields (80–96%) (Scheme 154) (99JOC6297).

Hydrazide **489** when treated with substituted benzaldehydes or acetophenones furnished the corresponding hydrazones **812** in a very short time (1.5–2.0 min) under MWI as compared with conventional heating (3–4 h). Condensation of **812** with 2-hydrazino-4-methyl quinoline under MWI using DMF as an energy-transfer agent afforded the tetrazine derivatives **813** in 51–64% yields in only 5–8 min (Scheme 154), but heating in ethanol under reflux gave 32–41% yields within 24–31 h (97G263).

VI. Spiroheterocycles

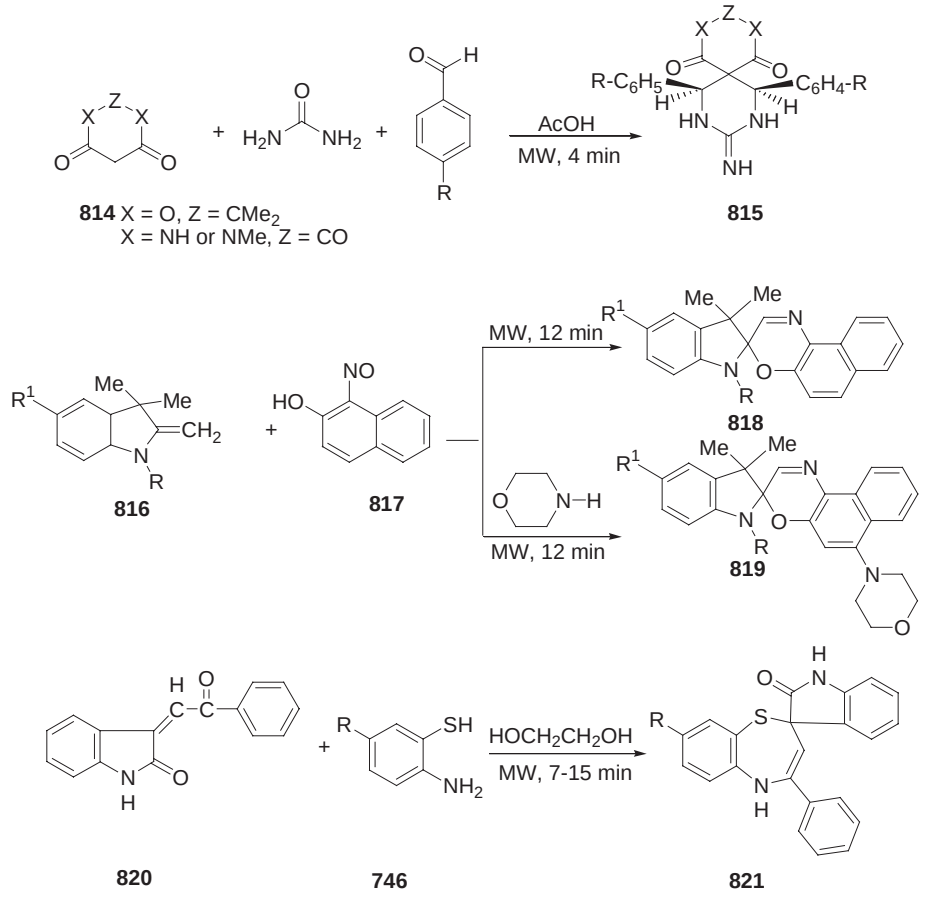
A solvent-free one-pot reaction of a mixture of Meldrum's acid or barbituric acid derivatives **814**, urea, and aldehyde under MWI in the presence of acetic acid gave, stereoselectively, heterobicyclic compounds **815** within 4 min in good yields (70–83%) (Scheme 155). The procedure also avoided problems connected with solvent use; times were reduced from several hours to few minutes (04TL2575).

Condensation of 2-methylene indoline derivatives **816** with 1-nitroso-2-naphthol (**817**) under MWI gave spiro indolinonaphth[2,1-*b*][1,4]oxazines **818** in 27–67% yields within 12 min. When the same reaction was carried out in the presence of morpholine, **819** were also formed in 19–34% yields (Scheme 155) (04SC315).

Reaction of 1,3-dihydro-3-(2-phenyl-2-oxoethylidene)indol-2(1*H*)-one (**820**) with 2-aminobenzenethiols (**746**) to give 8-substituted-2,5-dihydro-1,5-benzothiazepin-2-spiro-3′-3′*H*-indol-2′-(1′*H*)-ones **821** in 49–65% yields was induced under MWI conditions. Ethylene glycol was used as the energy-transfer medium and the reaction required 7–15 min (Scheme 155). However, conventional heating of **820** and **746** in ethanol saturated with hydrogen chloride for 4–6 h gave 51–52% yields (98JCR(S)752).

Isatin-3-imines **822** are versatile precursors for the synthesis of spiroheterocycles. They were prepared by grinding together an equimolar mixture of isatin and aromatic or heterocyclic amine. Subsequent treatment with mercaptoacetic acid using inorganic supports such as montmorillonite KSF, alumina, or silica gel in an open vessel upon MWI gave spiro compounds **823** within 5–7 min. The montmorillonite KSF is the best solid support, giving the best yields (92–97%) in the shortest time and easiest work-up (Scheme 156) (03OPP401).

Compounds **824** have also been prepared under MWI by condensing isatin, an aromatic amine, and mercaptoacetic acid in dry ethanol or DMAC without isolating the isatin-3-imines. Both thermal and MW methods gave good to excellent yields, but reaction times were reduced from several hours to few minutes on using MWI (Scheme 156) (00SC537). A one-step synthesis of spiro[indoline-3,2′-[1,3]thiazinane]-2,4′-diones **823** took place also under MWI in absolute ethanol within 11–18 min to give 62–84% yields, whereas conventional heating needed 14–20 h to give 14–74% yields (98JCR(S)360).

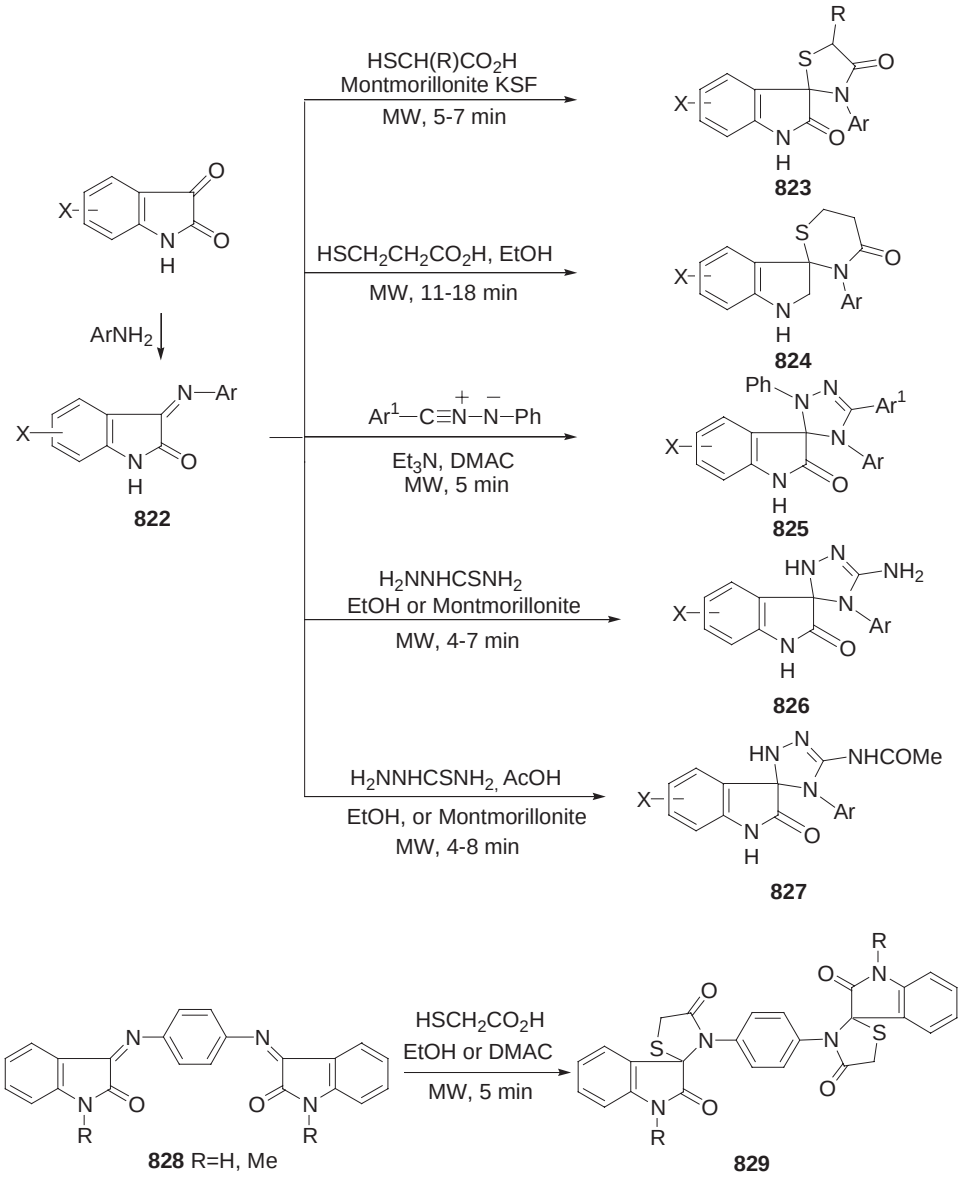


Scheme 155

Spiro[3*H*-indole-3,5′(4′*H*)-[1,2,4]triazoline]-2-ones **825** were obtained under MWI from imines **822** with nitrilimines, generated *in situ* from the hydrazonyl chlorides (Scheme 156). Yields were 85–95% and the reaction was completed in 5 min, compared to 20–30% yields under conventional heating for 6–10 h. On the other hand, when the reaction was carried out at ambient temperature, the products were obtained in excellent yields but after a very long time (30 h) (01SC1069).

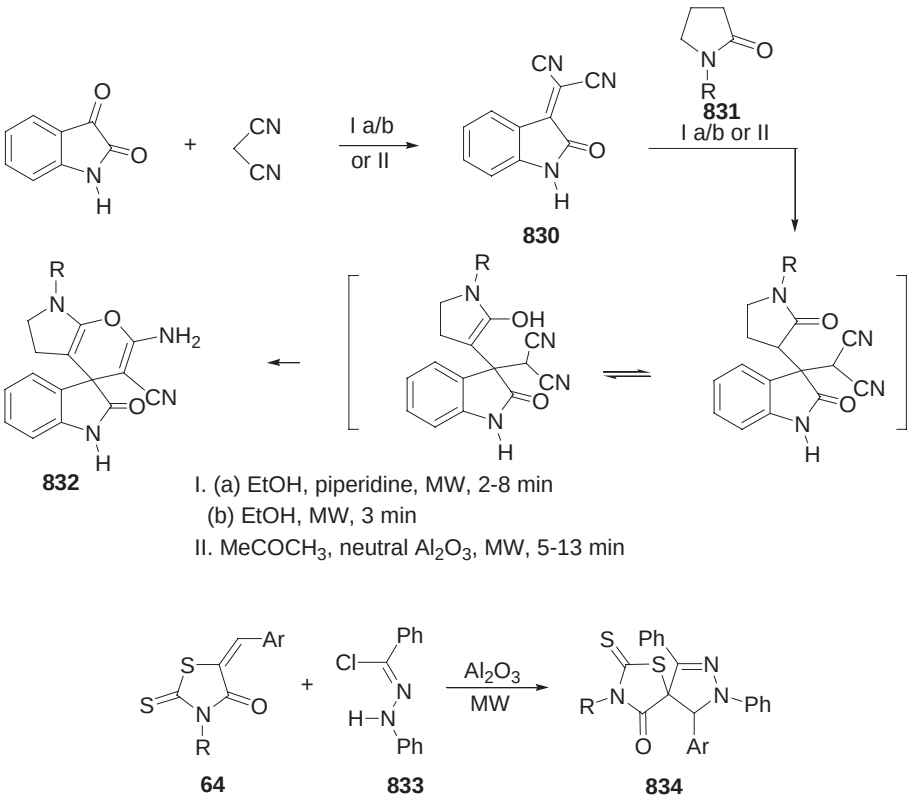
Spiro compounds **826** or their acetyl derivatives **827** were synthesized under MWI by the condensation of **822** with thiosemicarbazide in the absence or presence of acetic acid, respectively (Scheme 156). Montmorillonite efficiently catalyzed the reaction giving the maximium yield (94–98%) within a shorter period and easier work-up (00JCR(S)272).

Cyclocondensation of mercaptoacetic acid with diimines **828**, prepared from two equivalents of isatin or *N*-methylisatin with one equivalent *p*-phenylenediamine, was carried out under MWI to yield **829** in 74–78% yields (Scheme 156) (00SC537).



Scheme 156

1,3-Dihydrodicyanomethylene-2*H*-indol-2-one (**830**) (X = H) was synthesized in 70–94% yields under MWI from indole-2,3-dione and malononitrile in the presence of piperidine and a support such as acidic, basic, or neutral alumina and montmorillonite K_{10} or KSF. Neutral alumina gave the maximum yield. MWI accelerated the Michael condensation of **830** with 2-pyrrolidones **831** adsorbed on neutral



Scheme 157

alumina in dry media or using absolute ethanol as energy-transfer medium to afford spiro **832** in 30–78% yields (Scheme 157) (99SC2323).

The 1,3-dipolar addition of diphenylnitrilimine **833** to some 5-arylidenerhodanines **64** on solid inorganic supports in dry media under MWI gave the spiro-rhodanine-pyrazolines **834** in 75–90% yields (Scheme 157) (98MI1).

References

1884MI1 A. Bernthsen, *Justus Liebigs Ann. Chem.*, **1**, 224 (1884).

1893CB1903 A. Bischler and B. Napieralski, *Chem. Ber.*, **26**, 1903 (1893).

1895JPR564 S. Von Niementowski, *J. Prakt. Chem.*, **51**, 564 (1895).

46JOC257 E. Graef, J. M. Fredericksen, and A. Burger, *J. Org. Chem.*, **11**, 257 (1946).

49JA4003 A. P. Phillips, *J. Am. Chem. Soc.*, **71**, 4003 (1949).

54JCS3429 F. C. Cooper and M. W. Partridge, *J. Chem. Soc.*, 3429 (1954).

58JA992 A. G. Anderson Jr. and G. J. Berkelhammer, *J. Am. Chem. Soc.*, **80**, 992 (1958).

59JA2521 R. E. Cline, R. M. Fink, and K. Fink, *J. Am. Chem. Soc.*, **81**, 2521 (1959).

62JCS1170 G. W. H. Cheeseman, *J. Chem. Soc.*, 1170 (1962).
64MI1 M. Furdik and A. Gvozdjakova, *Acta Fac. Rerum. Nat. Univ. Comeniane, Chemica*, **8**, 581 (1964).
66CB3884 K. H. Scheit, *Chem. Ber.*, **99**, 3884 (1966).
67T2315 H. P. M. Fromageot, B. E. Grieffin, C. B. Reese, and J. E. Sulston, *Tetrahedron*, **23**, 2315 (1967).
74JCS(P1)2657 J. A. L. Herbert and H. Suschitzky, *J. Chem. Soc., Perkin Trans. 1*, 2657 (1974).
76MI1 H. Meyer, F. Bossert, and H. Horstmann, *Justus Liebigs Ann. Chem.*, 1762 (1976).
78S702 G. A. Olah and Y. A. Vankar, *Synthesis*, 702 (1978).
79JCR(S)226 J.-L. Fourrey, G. Henry, and P. Jouin, *J. Chem. Res. (S)*, 226 (1979).
80S659 G. A. Olah, S. C. Narang, and A. Garcia-Luna, *Synthesis*, 659 (1980).
80TL5011 G. Bram and G. Decodts, *Tetrahedron Lett.*, **21**, 5011 (1980).
82T993 S. Scheibye, R. Shabana, S. -O. Lawesson, and C. Roemming, *Tetrahedron*, **38**, 993 (1982).
83AGE717 R. Gompper and W. Breitschaft, *Angew. Chem., Int. Ed. Engl.*, **22**, 717 (1983).
83JOC4214 J. A. Zoltewicz and G. A. Locko, *J. Org. Chem.*, **48**, 4214 (1983).
84CPB3926 Y. Kanaoka, A. Kobayashi, E. Sato, H. Nakayama, T. Ueno, D. Muno, and T. Sekine, *Chem. Pharm. Bull.*, **32**, 3926 (1984).
84JHC1817 P. Scheiner, L. Frank, I. Giusti, S. Arwin, S. A. Pearson, F. Excellent, and A. P. Harper, *J. Heterocycl. Chem.*, **21**, 1817 (1984).
85BSB849 A. Maquestiau, J. J. Vanden Eynde, and P. Papleux, *Bull. Soc. Chim. Belg.*, **94**, 849 (1985).
86H135 H. R. Morales, A. Bulbarela, and R. Contreras, *Heterocycles*, **24**, 135 (1986).
86TL279 R. N. Gedye, F. E. Smith, K. C. Westway, H. Ali, L. Baldisera, L. Labergi, and J. Rousell, *Tetrahedron Lett.*, **27**, 279 (1986).
86TL4945 R. J. Giguere, T. L. Bray, S. M. Duncan, and G. Majtich, *Tetrahedron Lett.*, **27**, 4945 (1986).
87JOC4130 M. M. Abelman, T. Oh, and L. E. Overman, *J. Org. Chem.*, **52**, 4130 (1987).
88JHC857 T. Kappe, A. S. Karem, and W. Stadbauer, *J. Heterocycl. Chem.*, **25**, 857 (1988).
88TL773 D. L. Comins and D. H. La Munyon, *Tetrahedron Lett.*, **29**, 773 (1988).
90SC3325 D. Villemin and A. Ben Alloum, *Synth. Commun.*, **20**, 3325 (1990).
90SC3333 D. Villemin and B. Labiad, *Synth. Commun.*, **20**, 3333 (1990).
91H1947 A. Loupy, N. Philippon, P. Pigeon, and H. Galons, *Heterocycles*, **32**, 1947 (1991).
91JOC6968 A. K. Bose, M. S. Manhas, M. Ghosh, M. Shah, V. S. Raju, S. S. Bari, S. N. Newaz, B. K. Banik, A. G. Chaudhary, and K. J. Barakat, *J. Org. Chem.*, **56**, 6968 (1991).
91OPP683 R. A. Abramovitch, *Org. Prep. Proc. Int.*, **23**, 683 (1991).
91SC2137 F. Delgado, C. Alvarez, O. Garcia, G. Penieres, and C. Marquez, *Synth. Commun.*, **21**, 2137 (1991).
91TL1723 A. Stambouli, M. Chastrette, and M. Soufiaoui, *Tetrahedron Lett.*, **32**, 1723 (1991).
91TL3839 A. Maquestiau, A. Mayence, and J. -J. V. Eynde, *Tetrahedron Lett.*, **32**, 3839 (1991).
91TL5251 R. A. Abramovitch, D. A. Abramovitch, K. Iyanar, and K. Tamareselvy, *Tetrahedron Lett.*, **32**, 5251 (1991).
92AHC233 E. S. H. El Ashry, A. Mousaad, and N. Rashed, *Adv. Heterocycl. Chem.*, **53**, 233 (1992).

92S943 H. M. Meshram, *Synthesis,* 943 (1992).
92SL219 J. F. Pilard, B. Klein, F. Texier-Boullet, and J. Hamelin, *Synlett.,* 219 (1992).
92SL795 R. A. Abramovitch, and A. Bulman, *Synlett.,* 795 (1992).
92T9111 K. Afrinkia, V. Vinader, T. D. Nelson, and G. H. Posner, *Tetrahedron*, **48**, 9111 (1992).
93JOC2186 B. Lei and A. G. Fallis, *J. Org. Chem.*, **58**, 2186 (1993).
93SC419 D. Villemin, B. Labiad, and A. Loupy, *Synth. Commun.*, **23**, 419 (1993).
93TL623 O. Garcia, F. Delgado, A. C. Cano, and C. Alvarez, *Tetrahedron Lett.*, **34**, 623 (1993).
93TL2673 A. Molina, J. J. Vaquero, J. L. Garcia-Navio, and J. Alvarez-Builla, *Tetrahedron Lett.*, **34**, 2673 (1993).
93TL3029 R. S. Varma, J. B. Lamture, and M. Varma, *Tetrahedron Lett.*, **34**, 3029 (1993).
93TL8407 L. H. B. Baptistella, A. Z. Neto, H. Onaga, and E. A. M. Godoi, *Tetrahedron Lett.*, **34**, 8407 (1993).
94CCC175 M. Puciova, P. Ertl, and S. Toma, *Collect. Czech. Chem. Commun.*, 175 (1994).
94CL2443 T. Matumura-Inoue, M. Tanabe, T. Minami, and T. Ohashi, *Chem. Lett.*, 2443 (1994).
94H785 A. Diaz-Ortiz, E. Diez-Barra, A. de la Hoz, A. Loupy, A. Petit, and L. Sanchez, *Heterocycles*, **38**, 785 (1994).
94MI1 R. Alajarin, J. J. Vaquero, J. Alvarez-Builla, C. Sunkel, M. Fan de Casa-Juana, J. Priego, P. Gomez-Sal, and R. Torres, *Biomed. Chem.*, **2**, 323 (1994).
94MI2 S. Stone-Elander, N. Elander, J. -O. Thorell, G. Solas, and J. Svennebrink, *J. Lab. Comp. Radiopharm.*, **34**, 949 (1994).
94OPP383 S. P. Rajendran, M. Manonmani, and S. Vijayalakshni, *Org. Prep. Proc. Int.*, **26**, 383 (1994).
94SC2097 S. Sowmya and K. K. Balasubramanian, *Synth. Commun.*, **24**, 2097 (1994).
94TL4563 M. Rahmouni, A. Derdour, J. P. Bazureau, and J. Hamelin, *Tetrahedron Lett.*, **35**, 4563 (1994).
94TL8373 K. Bougrin, A. K. Bennani, S. F. Tetouani, and M. Soufiaoui, *Tetrahedron Lett.*, **35**, 8373 (1994).
95AJC1665 C. R. Strauss and R. W. Trainor, *Aust. J. Chem.*, **48**, 1665 (1995).
95JCS(CC)1101 A. Laurent, P. Jacquault, J. L. Di Martino, and J. Hamelin, *J. Chem. Soc., Chem. Commun.*, 1101 (1995).
95JOC5995 M. D. Bomann, I. C. Guch, and M. DiMare, *J. Org. Chem.*, **60**, 5995 (1995).
95S389 R. Alajarin, P. Jordan, J. J. Vaquero, and J. Alvarez-Builla, *Synthesis*, 389 (1995).
95SC857 Y. -W. Zhang, Z. -X. Shen, B. Pan, X. -H. Lu, and M. -H. Chen, *Synth. Commun.*, **25**, 857 (1995).
95SC2319 D. Villemin and B. Martin, *Synth. Commun.*, **25**, 2319 (1995).
95T6511 J. J. Vanden Eynde, F. Delfosse, A. Mayence, and Y. Van Haverbeke, *Tetrahedron*, **51**, 6511 (1995).
95T10403 S. Caddick, *Tetrahedron*, **51**, 10403 (1995).
95TL6673 S. Rault, A. C. Gillard, M. P. Foloppe, and M. Robba, *Tetrahedron Lett.*, **36**, 6673 (1995).
96BSF587 F. Cado, J. L. Di-Martino, P. Jacquault, J. P. Bazureau, and J. Hamelin, *Bull. Soc. Chim. Fr.*, **133**, 587 (1996).
96CL333 I. Almena, A. Diaz-Ortiz, E. Diez-Barra, A. de la Hoz, and A. Loupy, *Chem. Lett.*, 333 (1996).

96JCR(S)92 M. S. Khajavi, M. Hjihadi, and R. Naderi, *J. Chem. Res.(S)*, 92 (1996).
96JCR(S)254 M. Kidwai and P. Kumar, *J. Chem. Res. (S)*, 254 (1996).
96JCR(S)338 F. M. Moghaddam, A. Sharifi, and M. R. Saidi, *J. Chem. Res. (S)*, 338 (1996).
96JCS(P1)2857 T. Besson and C. W. Rees, *J. Chem. Soc., Perkin Trans. 1*, 2857 (1996).
96LA743 B. Garrigues, R. Laurent, C. Laporte, A. Laporterie, and J. Dubac, *Liebigs Ann.*, 743 (1996).
96SC453 M. Rahmouni, A. Derdour, J. P. Bazureau, and J. Hamelin, *Synth. Commun.*, **26**, 453 (1996).
96SC887 V. Bansal, S. Kanodia, P. C. Thapliyal, and R. N. Khanna, *Synth. Commun.*, **26**, 887 (1996).
96SC4545 F. Juncai, L. Bin, L. Yang, and L. Changchuan, *Synth. Commun.*, **26**, 4545 (1996).
96T5819 S. Jolivet, L. Toupet, F. Texier-Boullet, and J. Hamelin, *Tetrahedron*, **52**, 5819 (1996).
96TL1695 A. Diaz-Ortiz, P. Prieto, A. Loupy, and D. Abenhaim, *Tetrahedron Lett.*, **37**, 1695 (1996).
96TL2845 A. C. S. Reddy, P. S. Rao, and R. V. Venkataratnam, *Tetrahedron Lett.*, **37**, 2845 (1996).
96TL4145 L. Bourel, A. Tartar, and P. Melnyk, *Tetrahedron Lett.*, **37**, 4145 (1996).
96TL6413 J. A. Vega, S. Cueto, A. Ramos, J. J. Vaquero, J. L. Garcia-Navio, and J. Alvarez-Builla, *Tetrahedron Lett.*, **37**, 6413 (1996).
97CSR233 S. A. Galema, *Chem. Soc. Rev.*, **26**, 233 (1997).
97G263 M. Kidwai and R. Kumar, *Gazz. Chim. Ital.*, **127**, 263 (1997).
97IJC(B)175 M. Kidwai, P. Kumar, Y. Goel, and K. Kumar, *Indian J. Chem., Sect. B*, **36B**, 175 (1997).
97IJC(B)782 M. Kidwai, Y. Goel, P. Kumar, and K. Kumar, *Indian J. Chem., Sect. B*, **36B**, 782 (1997).
97JCR(S)16 V. K. Ahluwalia, P. Sharma, and R. Aggarwal, *J. Chem. Res. (S)*, 16 (1997).
97JCR(S)178 M. Kidwai and P. Kumar, *J. Chem. Res. (S)*, 178 (1997).
97JCR(S)266 V. K. Ahluwalia, B. Goyal, and U. Das, *J. Chem. Res. (S)*, 266 (1997).
97JCR(S)286 M. S. Khajavi, N. Montazari, and S. S. S. Hosseini, *J. Chem. Res. (S)*, 286 (1997).
97JFC127 A. C. S. Reddy, B. Narsaiah, and R. V. Venkataratnam, *J. Fluorine Chem.*, **86**, 127 (1997).
97JHC1391 M. J. Kornet, *J. Heterocycl. Chem.*, **34**, 1391 (1997).
97JOC2098 I. A. Motorina, F. W. Fowler, and D. S. Grierson, *J. Org. Chem.*, **62**, 2098 (1997).
97M1291 M. Kidwai, K. R. Bhushan, and R. Kumar, *Monatsh. Chem.*, **128**, 1291 (1997).
97MI1 D. M. P. Mingos and A. Whittaker, in *"Microwave Dielectric Heating Effects in Chemical Synthesis in Chemistry under Extreme or Non Classical Conditions"* (R. V. Eldik and C. D. Hubbard, eds.), p. 479, Wiley, New York (1997).
97SC3683 J. J. Van Eynde, N. Labuche, and Y. Van Haverbeke, *Synth. Commun.*, **27**, 3683 (1997).
97SL857 R. S. Varma and R. K. Saini, *Synlett*, 857 (1997).
97T5847 A. C. S. Reddy, P. S. Rao, and R. V. Venkataratnam, *Tetrahedron*, **53**, 5847 (1997).

97T12621 K. Subburaj, R. Katoch, M. G. Murugesh, and G. K. Trivedi, *Tetrahedron*, **53**, 12621 (1997).

97TL2271 A. C. Gillard, F. Fabis, S. Jolivet-Fouchet, and S. Rault, *Tetrahedron Lett.*, **38**, 2271 (1997).

97TL2623 R. S. Varma and R. K. Saini, *Tetrahedron Lett.*, **38**, 2623 (1997).

97TL6875 H. G. Jaisinghani and B. M. Khadilkar, *Tetrahedron Lett.*, **38**, 6875 (1997).

98CJC525 R. N. Gedye and J. B. Wei, *Can. J. Chem.*, **76**, 525 (1998).

98CSR213 C. Gabriel, S. Gabriel, E. H. Grant, B. S. J. Halstead, and D. M. P. Mingos, *Chem. Soc. Rev.*, **27**, 213 (1998).

98H639 B. K. Banik, V. S. Raju, M. S. Manhas, and A. K. Bose, *Heterocycles*, **47**, 639 (1998).

98IJC(B)174 M. Kidwai, Y. Goel, and R. Kumar, *Indian J. Chem., Sect. B*, **37B**, 174 (1998).

98JCR(S)280 J. Singh, J. Kaur, S. Nayyar, and G. L. Kad, *J. Chem. Res. (S)*, 280 (1998).

98JCR(S)330 S. Paul, R. Gupta, and A. Loupy, *J. Chem. Res. (S)*, 330 (1998).

98JCR(S)348 R. S. Varma, R. K. Saini, and D. Kumar, *J. Chem. Res. (S)*, 348 (1998).

98JCR(S)360 A. Dandia, M. Saha, and B. Rani, *J. Chem. Res. (S)*, 360 (1998).

98JCR(S)468 D. Bogdal, *J. Chem. Res. (S)*, 468 (1998).

98JCR(S)586 M. Kidwai, S. Kohli, and P. Kumar, *J. Chem. Res. (S)*, 586 (1998).

98JCR(S)702 K. Rad-Moghadam and M. S. Khajavi, *J. Chem. Res. (S)*, 702 (1998).

98JCR(S)752 A. Dandia, M. Upreti, B. Rani, and U. C. Pant, *J. Chem. Res. (S)*, 752 (1998).

98JCR(S)800 M. R. Saidi and K. Bigdeli, *J. Chem. Res. (S)*, 800 (1998).

98JOC3454 E. H. Hu, D. R. Sidler, and U. H. Dolling, *J. Org. Chem.*, **63**, 3454 (1998).

98JOC8038 R. S. Varma and R. Dahiya, *J. Org. Chem.*, **63**, 8038 (1998).

98M961 M. Kidwai, P. Misra, R. Kumar, R. K. Saxena, R. Gupta, and S. Bradoo, *Monatsh. Chem.*, **129**, 961 (1998).

98MI1 A. Ben-Alloum, S. Bakkas, K. Bougrin, and M. Soufiaoui, *New J. Chem.*, 809 (1998).

98S1213 A. Loupy, A. Petit, A. Hamelin, J. Texier-Boullet, F. Jacquault, and P. Mathe, *Synthesis*, 1213 (1998).

98SC193 F. Juncai, L. Yang, M. Qinghua, and L. Bin, *Synth. Commun.*, **28**, 193 (1998).

98SC337 S. V. Filip, I. A. Silberg, E. Surducan, M. Vlassa, and V. Surducan, *Synth. Commun.*, **28**, 337 (1998).

98SC1175 H. G. Jaisinghani, B. R. Chowdhury, and B. M. Khadilkar, *Synth. Commun.*, **28**, 1175 (1998).

98SC2407 J.-X. Wang (C.-H. Wang), M. Zhang, and Y. Hu, *Synth. Commun.*, 28 (1998) 2407.

98SC3195 D. Villemin, B. Martin, and M. Khalid, *Synth. Commun.*, **28**, 3195 (1998).

98SC4087 R. S. Varma and R. Dahiya, *Synth. Commun.*, **28**, 4087 (1998).

98SL718 C. O. Kappe and F. S. Falsone, *Synlett*, 718 (1998).

98SL1069 A. Diaz-Ortiz, J. R. Carrillo, M. J. Gomez-Escalonilla, A. de la Hoz, A. Moreno, and P. Prieto, *Synlett*, 1069 (1998).

98T6475 T. Besson, M. J. Dozias, J. Guillard, P. Jacquault, M. D. Legoy, and C. W. Rees, *Tetrahedron*, **54**, 6475 (1998).

98T10789 F. Fabis, S. Jolivet-Fouchet, M. Robba, H. Landelle, and S. Rault, *Tetrahedron*, **54**, 10789 (1998).

98TL431 B. Das, P. Madhusudhan, and A. Kashinatham, *Tetrahedron Lett.*, **39**, 431 (1998).
98TL541 H. Benhaliliba, A. Derdour, J. P. Bazureau, F. Texier-Boullet, and J. Hamelin, *Tetrahedron Lett.*, **39**, 541 (1998).
98TL1117 I. C. Cotterill, A. Ya. Usyatinsky, J. M. Arnold, D. S. Clark, J. S. Dordick, P. C. Michels, and Y. L. Khmelnitsky, *Tetrahedron Lett.*, **39**, 1117 (1998).
98TL2471 G. V. Salmoria, E. Dall'Oglio, and C. Zucco, *Tetrahedron Lett.*, **39**, 2471 (1998).
98TL3379 Y. D. Gong and M. J. Kurth, *Tetrahedron Lett.*, **39**, 3379 (1998).
98TL8437 R. S. Varma, K. P. Naicker, and P. J. Liesen, *Tetrahedron Lett.*, **39**, 8437 (1998).
98TL9587 M. Adamczyk and S. Rege, *Tetrahedron Lett.*, **39**, 9587 (1998).
99AJC83 C. R. Strauss, *Aust. J. Chem.*, **52**, 83 (1999).
99BCJ259 K. Subburaj and G. K. Trivedi, *Bull. Chem. Soc. Jpn.*, **72**, 259 (1999).
99H21 M. Suarez, A. Loupy, E. Salfran, L. Moran, and E. Rolando, *Heterocycles*, **51**, 21 (1999).
99H1819 C. G. Dave and R. D. Shah, *Heterocycles*, **51**, 1819 (1999).
99JCR(S)392 S. Balalaie, M. S. Hashtroudi, and A. Sharifi, *J. Chem. Res. (S)*, 392 (1999).
99JCR(S)574 F. M. Moghaddam, M. Ghaffarzadeh, and S. H. Abdi-Oskoui, *J. Chem. Res. (S)*, 574 (1999).
99JCS(P1)1755 R. S. Varma and D. Kumar, *J. Chem Soc., Perkin Trans. 1*, 1755 (1999).
99JHC1095 M. J. Kornet and G. Shakleford, *J. Heterocycl. Chem.*, **36**, 1095 (1999).
99JHC1565 R. S. Varma, *J. Heterocycl. Chem.*, **36**, 1565 (1999).
99JOC1713 D. S. Bose and B. Jayalakshmi, *J. Org. Chem.*, **64**, 1713 (1999).
99JOC6297 M. Avalos, R. Babiano, P. Cintas, F. R. Clemente, J. L. Jimenez, J. C. Palacios, and J. B. Sanchez, *J. Org. Chem.*, **64**, 6297 (1999).
99MI1 R. S. Varma, *Green Chem.*, **1**, 43 (1999).
99MI2 R. S. Varma, *Clean Prod. Process.*, **1**, 132 (1999).
99MI3 A. V. El'tsov, N. B. Sokolova, N. M. Dmitrieva, A. D. Grigor'ev, and A. S. Ivanov, *Russian J. Gen. Chem.*, **69**, 1317 (1999).
99MI4 B. P. Bangdgar, L. S. Uppalla, and D. S. Kurule, *Green Chem.*, 243 (1999).
99OL697 R. S. Varma and D. Kumar, *Org. Lett.*, **1**, 697 (1999).
99POL2641 M. Kidwai, P. Misra, and K. R. Bhushan, *Polyhedron*, **18**, 2641 (1999).
99S326 P. Molina, P. M. Fresneda, and S. Delgado, *Synthesis*, 326 (1999).
99S1799 C. O. Kappe, D. Kumar, and R. S. Varma, *Synthesis*, 1799 (1999).
99SC1013 M. M. Heravi, D. Ajami, and M. Ghassemzadeh, *Synth. Commun.*, 29, 1013 (1999).
99SC1333 R. S. Varma and D. Kumar, *Synth. Commun.*, **29**, 1333 (1999).
99SC1941 D. I. Jung, T. W. Choi, Y. Y. Kim, I. S. Kim, Y. M. Park, Y. G. Lee, and D. H. Jung, *Synth. Commun.*, 1941 (1999).
99SC2323 A. Dandia, H. Taneja, R. Gupta, and S. Paul, *Synth. Commun.*, **29**, 2323 (1999).
99SC2617 M. S. Khajavi, K. Rad-Moghadam, and H. Hazarkhani, *Synth. Commun.*, **29**, 2617 (1999).
99SC3237 M. Kidwai and P. Misra, *Synth. Commun.*, **29**, 3237 (1999).
99SC4403 G. Sabitha, R. S. Babu, B. V. S. Reddy, and J. S. Yadav, *Synth. Commun.*, **29**, 4403 (1999).
99SL1251 A. Kamal, B. S. N. Reddy, and G. S. K. Reddy, *Synlett*, 1251 (1999).

99SL1745 G. Sabitha, S. Abraham, B. V. S. Reddy, and J. S. Yadav, *Synlett*, 1745 (1999).

99SL1747 D. Heber and E. V. Stoyanov, *Synlett*, 1747 (1999).

99T2317 J. A. Vega, J. J. Vaquero, J. Alvarez-Builla, J. Ezquerra, and C. Hamdouchi, *Tetrahedron*, **55**, 2317 (1999).

99T3209 G. P. Kalena, P. Pradhan, and A. Banerji, *Tetrahedron*, **55**, 3209 (1999).

99T10851 S. Deshayes, M. Liagre, A. Loupy, J. L. Luche, and A. Petit, *Tetrahedron*, **55**, 10851 (1999).

99TL165 G. Sabitha, M. M. Reddy, D. Srinivas, and J. S. Yadov, *Tetrahedron Lett.*, **40**, 165 (1999).

99TL3941 A. M. L. Hoel and J. Nielsen, *Tetrahedron Lett.*, **40**, 3941 (1999).

99TL7275 P. M. Fresneda, P. Molina, and S. Delgado, *Tetrahedron Lett.*, **40**, 7275 (1999).

99TL7549 M. Nooshabadi, K. Aghapoor, H. R. Darabi, and M. M. Mojtahedi, *Tetrahedron Lett.*, **40**, 7549 (1999).

99TL7665 R. S. Varma and D. Kumar, *Tetrahedron Lett.*, **40**, 7665 (1999).

00CSR239 N. Elander, J. R. Jones, S. Y. Lu, and S. S. Elander, *Chem. Soc. Rev.*, **29**, 239 (2000).

00H2275 R. Rico-Gomez, F. Najera, J. M. Lopez-Romero, and P. Canada-Runder, *Heterocycles*, **53**, 2275 (2000).

00JCR(S)272 A. Dandia, H. Sachdeva, and R. Devi, *J. Chem. Res. (S)*, 272 (2000).

00JCR(S)345 J. S. Yadav, B. V. S. Reddy, E. J. Reddy, and T. Ramalingam, *J. Chem. Res. (S)*, 345 (2000).

00JCR(S)464 M. M. Heravi, N. Montazeir, M. Rahimizadeh, M. Bakavolia, and M. Ghassemzadeh, *J. Chem. Res. (S)*, 464 (2000).

00JCR(S)586 M. Kidwai, R. Venkataramanan, R. K. Garg, and K. R. Bhushan, *J. Chem. Res. (S)*, 586 (2000).

00M85 M. Kidwai, P. Sapra, K. R. Buhshan, R. K. Saxena, R. Gupta, and M. Singh, *Monatsh. Chem.*, 85 (2000).

00M1207 M. Kidwai, P. Misra, B. Dave, K. R. Buhshan, R. K. Saxena, and M. Singh, *Monatsh. Chem.*, 1207 (2000).

00MI1 J. Cleophax, M. Liagre, A. Loupy, and A. Petit, *Org. Process. Res. Dev.*, **4**, 498 (2000).

00MI2 M. Kidwai, K. R. Bhushan, P. Sapra, R. K. Saxenab, and R. Gupta, *Bioorg. Med. Chem.*, **8**, 69 (2000).

00MI3 J. S. Yadav and B. V. S. Reddy, *Green Chem.*, **2**, 115 (2000).

00MI4 A. Danel, K. Chaczatrian, and P. Tomasik, *Arkivoc*, **1**, 51 (2000).

00MI5 L. Williams, *Chem. Commun.*, 435 (2000).

00MI6 E. S. H. El Ashry and N. Rashed, *Curr. Org. Chem.*, **6**, 609 (2000).

00SC69 M. M. Mojtahedi, A. Sharifi, F. Mohsenzadeh, and M. R. Saidi, *Synth. Commun.*, **30**, 69 (2000).

00SC537 J. Azizian, A. V. Morady, K. Jadidi, M. Mehrdad, and Y. Sarraffi, *Synth. Commun.*, **30**, 537 (2000).

00SC643 F. M. Moghaddam, M. Mohammadi, and A. Hosseinnia, *Synth. Commun.*, **30**, 643 (2000).

00SC829 J. Jin, Z. Wen, J. Long, Y. Wang, T. Matsuura, and J. Meng, *Synth. Commun.*, **30**, 829 (2000).

00SC1719 A. D. Sagar, D. S. Patil, and B. P. Bandgar, *Synth. Commun.*, **30**, 1719 (2000).

00SL1013 R. M. Dinica, I. I. Druta, and C. Pettinari, *Synlett*, 1013 (2000).

00T605 C. Buon, L. Chacun-Lefevre, R. Rabot, P. Bouyssou, and G. Coudert, *Tetrahedron*, **56**, 605 (2000).

00T1361 A. Hinschberger, A. C. Gillard, I. Bureau, and S. Rault, *Tetrahedron*, **56**, 1361 (2000).

00T1569 A. Diaz-Ortiz, J. R. Carrillo, F. P. Cossio, M. J. Gomez-Escalonilla, A. de la Hoz, A. Moreno, and P. Prieto, *Tetrahedron*, **56**, 1569 (2000).

00T1859 C. O. Kappe, O. V. Shishkin, G. Uray, and P. Verdino, *Tetrahedron*, **56**, 1859 (2000).

00TL531 B. C. Ranu, A. Hajra, and U. Jana, *Tetrahedron Lett.*, **41**, 531 (2000).

00TL1027 T. Besson, J. Guillard, and C. W. Rees, *Tetrahedron Lett.*, **41**, 1027 (2000).

00TL2215 J. A. Seijas, M. P. Vazquez-Tato, and M. M. Martinez, *Tetrahedron Lett.*, **41**, 2215 (2000).

00TL3493 U. Sharma, S. Ahmed, and R. C. Boruah, *Tetrahedron Lett.*, **41**, 3493 (2000).

00TL5857 M. Soukri, G. Guillaumet, T. Besson, D. Aziane, M. Aadil, E. M. Essassi, and M. Akssira, *Tetrahedron Lett.*, **41**, 5857 (2000).

01H109 E. Vazquez, A. de la Hoz, N. Elander, A. Moreno, and S. Stone-Elander, *Heterocycles*, **55**, 109 (2001).

01H291 H. Rodriguez, R. Perez, M. Suarez, A. Lam, N. Cabrales, and A. Loupy, *Heterocycles*, **55**, 291 (2001).

01H1443 B. Kaboudin and K. Navaee, *Heterocycles*, **55**, 1443 (2001).

01JCR(S)78 D. Barbry and P. Champagne, *J. Chem. Res. (S)*, 78 (2001).

01JCR(S)292 S. Torchy and D. Barbry, *J. Chem. Res. (S)*, 292 (2001).

01JOC1947 N. Deka and J. C. Sarma, *J. Org. Chem.*, **66**, 1947 (2001).

01MI1 C.O. Kappe, *Combinatorial Chem.*, 314 (2001).

01MI2 M. Larhed and A. Hallberg, *Drug Discov. Today*, **6**, 406 (2001).

01MI3 H. -F. Zhoui, *Hua Xue Yan Jiu Yu Ying Yong*, **13**, 712 (2001).

01MI4 H. -Z. Li, X. -Z. Yang, T. -S. Li, S. -X. Wang, and J. -T. Li, *He Bei Da Xue Bao*, **21**, 45 (2001).

01S55 A. K. Pleier, H. Glas, M. Grosche, P. Sirsch, and W. R. Thiel, *Synthesis*, 55 (2001).

01S1509 M. Kidwai, P. Sapra, K. R. Bhushan, and P. Misra, *Synthesis*, 1509 (2001).

01S2119 M. R. Prasad, A. R. R. Rao, P. S. Rao, and K. S. Rajan, *Synthesis*, 2119 (2001).

01SC53 M. Gupta, S. Paul, and R. Gupta, *Synth. Commun.*, **31**, 53 (2001).

01SC425 Y. S. Yadav, B. V. S. Reddy, and K. B. Reddy, *Synth. Commun.*, **31**, 425 (2001).

01SC1069 J. Azizian, S. Soozangarzadeh, and K. Jadidi, *Synth. Commun.*, **31**, 1069 (2001).

01SC2657 S. Tu, Q. Wei, H. Ma, D. Shi, Y. Gao, and G. Cui, *Synth. Commun.*, **31**, 2657 (2001).

01SL236 A. Diaz-Ortiz, A. de la Hoz, P. Prieto, J. R. Carrillo, A. Moreno, and H. Neunhoeffer, *Synlett*, 236 (2001).

01SL676 G. W. Kabalka, L. Wang, and R. M. Pagni, *Synlett*, 676 (2001).

01SL1296 L. Ohberg and J. Westman, *Synlett*, 1296 (2001).

01T1785 J. J. V. Eynde, N. Hecq, O. Kataeva, and C. O. Kappe, *Tetrahedron*, **57**, 1785 (2001).

01T4365 S. Chatti, M. Bortolussi, and A. Loupy, *Tetrahedron*, **57**, 4365 (2001).

01T4437 S. K. Pandey, K. K. Awasthi, and A. K. Saxena, *Tetrahedron*, **57**, 4437 (2001).

01T6197 P. M. Fresneda, P. Molina, and S. Delgado, *Tetrahedron*, **57**, 6197 (2001).

01T9199 L. Perrux and A. Loupy, *Tetrahedron*, **57**, 9199 (2001).

01T9225 P. Lidstrom, J. Tiernery, B. Wathey, and J. Westman, *Tetrahedron*, **57**, 9225 (2001).

01TL635 D. Villemin, M. J. Gomez-Escalonilla, and J. F. Saint-Clair, *Tetrahedron Lett.*, **42**, 635 (2001).

01TL1127 M. S. Balakrishna and B. Kaboudin, *Tetrahedron Lett.*, **42**, 1127 (2001).

01TL1367 J. H. M. Lange, P. C. Verveer, S. J. M. Osnabrug, and G. M. Visser, *Tetrahedron Lett.*, **42**, 1367 (2001).

01TL2397 V. Santagada, E. Perissutti, F. Fiorino, B. Vivenzio, and G. Caliendo, *Tetrahedron Lett.*, **42**, 2397 (2001).

01TL2791 S. Frere, V. Thiery, and T. Besson, *Tetrahedron Lett.*, **42**, 2791 (2001).

01TL3193 M. Curini, F. Epifano, M. C. Marcotullio, and O. Rosati, *Tetrahedron Lett.*, **42**, 3139 (2001).

01TL3827 S. Paul, M. Gupta, R. Gupta, and A. Loupy, *Tetrahedron Lett.*, **42**, 3827 (2001).

01TL4363 H. Loghmani-Khouzani, M. M. Sadeghi, J. Safari, and A. Minaeifar, *Tetrahedron Lett.*, **42**, 4363 (2001).

01TL5625 J. Quiroga, C. Cisneros, B. Insuasty, R. Abonia, M. Nogueras, and A. Sanchez, *Tetrahedron Lett.*, **42**, 5625 (2001).

01TL6671 L. Domon, C. Le Coeur, A. Grelard, V. Thiery, and T. Bessona, *Tetrahedron Lett.*, **42**, 667 (2001).

02ACR717 M. Larhed, C. Moberg, and A. Hallberg, *Acc. Chem. Res.*, **35**, 717 (2002).

02H1299 H. Koshima and K. Kutsunai, *Heterocycles*, **57**, 1299 (2002).

02H1423 Y. Njoya, N. Boufatah, A. Gellis, P. Rathelot, M. P. Crozet, and P. Vanelle, *Heterocycles*, **57**, 1423 (2002).

02H1881 M. M. Blanco, G. J. Levin, and I. A. Perillo, *Heterocycles*, **57**, 1881 (2002).

02JCR(S)40 B. P. Bandgar, L. S. Uppalla, and V. S. Sadavarte, *J. Chem. Res. (S)*, 40 (2002).

02JCS(P1)1845 M. Kidwai, S. Saxena, R. Mohan, and R. Venkataramanan, *J. Chem Soc., Perkin Trans. 1*, 1845 (2002).

02JFC133 A. Krishnaiah and B. Narsaiah, *J. Fluorine Chem.*, **113**, 133 (2002).

02JHC1045 M. Kidwai, R. Venkataramanan, and B. Dave, *J. Heterocycl. Chem.*, **39**, 1045 (2002).

02JOC7904 E. Van der Eycken, P. Appukkuttan, W. De Borggraeve, W. Dehaen, D. Dallinger, and C. O. Kappe, *J. Org. Chem.*, **67**, 7904 (2002).

02MI1 A. Lew, P. O. Krutzik, M. E. Hart, and A. R. Chamberlin, *J. Comb. Chem.*, **4**, 95 (2002).

02MI2 J. Hamelin, J. P. Bazureau, and F. Texier-Boullet, in "*Microwaves in Organic Synthesis*" (A. Loupy, ed.), p. 253, Wiley-VCH, Weinheim (2002).

02MI3 C. O. Kappe, *Curr. Opin. Chem. Biol.*, **6**, 314 (2002).

02MI4 M. Andrzejewska, J. Kaminski, and Z. Kazimierczuk, Nucleosides, *Nucleotides Nucleic Acids*, **21**, 73 (2002).

02S223 E. Wellner, H. Sandin, and L. PääKKönen, *Synthesis*, 223 (2002).

02S1578 A. K. Bose, M. S. Manhas, S. N. Ganguly, A. H. Sharma, and B. K. Banik, *Synthesis*, 1578 (2002).

02S1601 O. Belda and C. Moberg, *Synthesis*, 1601 (2002).

02S1669 V. Molteni, M. M. Hamilton, L. Mao, C. M. Crane, A. P. Termin, and D. M. Wilson, *Synthesis*, 1669 (2002).

02S2168 K. S. Deepthi and P. S. N. Reddy, *Synthesis*, 2168 (2002).

02SC147 S. J. Tu, J. F. Zhou, P. J. Cai, H. Wang, and J. C. Feng, *Synth. Commun.*, **32**, 147 (2002).

02SC497 B. K. Karale, V. P. Chavan, A. S. Mane, R. V. Hangarge, C. H. Gill, and M. S. Shingare, *Synth. Commun.*, **32**, 497 (2002).
02SC611 A. R. Hajipour, S. E. Mallakpour, I. Mohammadpoor-Baltork, and S. Khoee, *Synth. Commun.*, **32**, 611 (2002).
02SC659 M. Anniyappan, D. Muralidharan, and P. T. Perumal, *Synth. Commun.*, **32**, 659 (2002).
02SC729 E. Veverkova, M. Noskova, and S. Toma, *Synth. Commun.*, **32**, 729 (2002).
02SC857 K. Mogilaiah, D. S. Chowdary, and P. R. Reddy, *Synth. Commun.*, **32**, 857 (2002).
02SC1549 A. S. Gajare, D. P. Sabde, M. S. Shingare, and R. D. Wakharkar, *Synth. Commun.*, **32**, 1549 (2002).
02SC1639 M. Kidwai and P. Sapra, *Synth. Commun.*, **32**, 1639 (2002).
02SC1803 J. S. Yadav, B. V. S. Reddy, Ch. Venugopal, R. Srinivas, and T. Ramalingam, *Synth. Commun.*, **32**, 1803 (2002).
02SC1899 S. Rostamizadeh and K. Sadeghi, *Synth. Commun.*, **32**, 1899 (2002).
02SC2137 S. -J. Tu, Y. Gao, C. Guo, D. -Q. Shi, and Z. -S. Lu, *Synth. Commun.*, **32**, 2137 (2002).
02SC2161 M. Kidwai, R. Venkataramanan, and B. Dave, *Synth. Commun.*, **32**, 2161 (2002).
02SC2181 S. J. Tu, Z. Lu, D. Shi, C. Yao, Y. Gao, and C. Guo, *Synth. Commun.*, **32**, 2181 (2002).
02SC2391 N. Lingaiah and R. Narender, *Synth. Commun.*, **32**, 2391 (2002).
02SC2395 H. Yang, W. H. Sun, Z. Li, and L. Wang, *Synth. Commun.*, **32**, 2395 (2002).
02SC2633 A. S. Mane, V. P. Chavan, B. K. Karale, R. V. Hangarge, M. S. Gaikwad, and M. S. Shingare, *Synth. Commun.*, **32**, 2633 (2002).
02SC3363 J. -F. Zhou, S. -J. Tu, H. -Q. Zhu, and S. -J. Zhi, *Synth. Commun.*, **32**, 3363 (2002).
02SL519 P. Roboisson, B. Norbergh, J. R. Casimir, and J. J. Bourguignon, *Synlett*, 519 (2002).
02SL907 C. C. Silveira, C. R. Bernardi, A. L. Braga, and T. S. Kaufman, *Synlett*, 907 (2002).
02SL1709 C. Y. Wu and C. M. Sun, *Synlett*, 1709 (2002).
02SL1718 M. C. Bagley and N. Singh, *Synlett*, 1718 (2002).
02SL2037 A. Diaz-Ortiz, A. de la Hoz, A. Moreno, P. Prieto, R. Leon, and M. A. Herrero, *Synlett*, 2037 (2002).
02SL2043 A. A. Abdel-Rahman and E. S. H. El Ashry, *Synlett*, 2043 (2002).
02SL2077 A. Perzyna, R. Houssin, D. Barbry, and J. P. Henichart, *Synlett*, 2077 (2002).
02T887 Y. J. Cherng, *Tetrahedron*, **58**, 887 (2002).
02T997 M. Shanmugasundaram, S. Manikandan, and R. Raghunathan, *Tetrahedron*, **58**, 997 (2002).
02T1125 Y. J. Cherng, *Tetrahedron*, **58**, 1125 (2002).
02T1235 R. S. Varma, *Tetrahedron*, **58**, 1235 (2002).
02T4931 Y. J. Cherng, *Tetrahedron*, **58**, 4931 (2002).
02T8957 S. Manikandan, M. Shanmugasundaram, and R. Raghunathan, *Tetrahedron*, **58**, 8957 (2002).
02TL447 W. M. De Borggraeve, F. J. R. Rombouts, B. M. P. Verbist, E. V. Van der Eycken, and G. J. Hoornaert, *Tetrahedron Lett.*, **43**, 447 (2002).
02TL581 N. S. Wilson, C. R. Sarko, and G. P. Roth, *Tetrahedron Lett.*, **43**, 581 (2002).

02TL1101 J. H. M. Lange, L. J. F. Hofmeyer, F. A. S. Hout, S. J. M. Osnaburg, P. C. Verveer, C. G. Kruse, and R. W. Feenstra, *Tetrahedron Lett.*, **43**, 1101 (2002).

02TL1755 M. Pozarentzi, J. Stephanidou-Stephanatou, and C. A. Tsoleridis, *Tetrahedron Lett.*, **43**, 1755 (2002).

02TL3907 M. E. Theoclitou and L. A. Robinson, *Tetrahedron Lett.*, **43**, 3907 (2002).

02TL3911 F. R. Alexandre, A. Berecibar, and T. Besson, *Tetrahedron Lett.*, **43**, 3911 (2002).

02TL5739 G. Luo, L. Chen, and G. S. Poindexter, *Tetrahedron Lett.*, **43**, 5739 (2002).

02TL6001 G. Priem, M. S. Anson, S. J. F. Macdonald, B. Pelotier, and I. B. Campbell, *Tetrahedron Lett.*, **43**, 6001 (2002).

02TL6169 R. E. Austin, J. F. Okonya, D. R. S. Bond, and F. Al-Obeidi, *Tetrahedron Lett.*, **43**, 6169 (2002).

02TL8371 S. Goswami and A. K. Adak, *Tetrahedron Lett.*, **43**, 8371 (2002).

02TL8551 L. D. S. Yadav, S. S. Singh, and A. Singh, *Tetrahedron Lett.*, **43**, 8551 (2002).

02TL9487 J. R. Harding, J. R. Jones, S. Y. Lu, and R. Wood, *Tetrahedron Lett.*, **43**, 9487 (2002).

03H563 A. Dandia, M. Sati, K. Arya, and A. Loupy, *Heterocycles*, **60**, 563 (2003).

03H1457 H. Yu, H. Kawanishi, and H. Koshima, *Heterocycles*, **60**, 1457 (2003).

03H2775 M. Tsukayama, Y. Kawamura, T. Ishizuka, S. Hayashi, and F. Torii, *Heterocycles*, **60**, 2775 (2003).

03MI1 H. E. Blackwell, *Org. Biomol. Chem.*, **1**, 1251 (2003).

03MI2 A. R. Katritzky and S. K. Singh, *Arkivoc*, **13**, 68 (2003).

03MI3 K. M. Al-Zaydi, R. M. Borik, and M. H. Elnagdi, *Molecules*, **8**, 910 (2003).

03OPP401 A. Dandia, R. Sing, and K. Arya, *Org. Prep. Proc. Intl.*, **35**, 401 (2003).

03S63 L. Dhar, S. Yadav, and S. Singh, *Synthesis*, 63 (2003).

03S262 M. Xia and Y. G. Wang, *Synthesis*, 262 (2003).

03S1039 L. Paolini, E. Petricci, F. Corelli, and M. Botta, *Synthesis*, 1039 (2003).

03S2033 E. Granier, S. Blanchard, I. Rodriguez, C. Jarry, J. M. Leger, P. Caubere, and G. Guillaumet, *Synthesis*, 2033 (2003).

03S2395 L. D. S. Yadav and A. Singh, *Synthesis*, 2395 (2003).

03SL250 P. Nemes, Z. Vincze, B. Balazs, G. Toth, and P. Scheiber, *Synlett*, 250 (2003).

03SL259 M. C. Bagley, D. D. Hughes, and P. H. Taylor, *Synlett*, 259 (2003).

03SL1415 D. C. G. A. Pinto, A. M. S. Silva, L. M. P. M. Almeida, J. R. Carrillo, A. Diaz-Ortiz, A. de la Hoz, and J. A. S. Cavaleiro, *Synlett*, 1415 (2003).

03SL1443 M. C. Bagley, D. D. Hughes, H. M. Sabo, P. H. Taylor, and X. Xiong, *Synlett*, 1443 (2003).

03SL1688 W. J. Chang, W. B. Yeh, and C. M. Sun, *Synlett*, 1688 (2003).

03SL1822 B. U. W. Maes, K. T. J. Loones, G. L. F. Lemiere, and R. A. Dommisse, *Synlett*, 1822 (2003).

03SL1862 P. Stanetty, M. Schnurch, and M. D. Mihovilovic, *Synlett*, 1862 (2003).

03T773 S. Frere, V. Thiery, C. Bailly, and T. Bessona, *Tetrahedron*, **59**, 773 (2003).

03T1413 F. R. Alexandre, A. Berecibar, R. Wrigglesworthа, and T. Bessonb, *Tetrahedron*, **59**, 1413 (2003).

03TL255 S. J. Song, S. J. Cho, D. K. Park, T. W. Kwon, and S. A. Jenekhe, *Tetrahedron Lett.*, **44**, 255 (2003).

03TL1123 Z. Zhao, W. H. Leister, K. A. Strauss, D. D. Wisnoski, and C. W. Lindsley, *Tetrahedron Lett.*, **44**, 1123 (2003).

03TL4369 S. M. Ireland, H. Tye, and M. Whittaker, *Tetrahedron Lett.*, 4369 (2003).

03TL8951 L. D. S. Yadav and R. Kapoor, *Tetrahedron Lett.*, **44**, 8951 (2003).

04H297 M. LIoung, A. Loupy, S. Marque, and A. Petit, *Heterocycles*, **63**, 297 (2004).

04H583 J. Lu, Y. Li, Y. Bai, and M. Tian, *Heterocycles*, **63**, 583 (2004).

04H791 J. Azizian, A. A. Mohammadi, F. Ardakani, A. R. Karimi, and M. R. Mohammadizadeh, *Heterocycles*, **63**, 791 (2004).

04H851 Y. Gong and W. He, *Heterocycles*, **62**, 851 (2004).

04H903 Y. Xu and Q. -X. Guo, *Heterocycles*, **63**, 903 (2004).

04H1417 M. Dabiri, P. Salehi, M. S. Khajavi, and A. A. Mohammadi, *Heterocycles*, **63**, 1417 (2004).

04JCR(S)174 M. A. Al-Shiekh, A. M. Salah El-Din, E. A. Hafez, and M. H. Elnagdi, *J. Chem. Res.* (*S*), 174 (2004).

04JHC1 S. Almazroa, M. H. Elnagdi, and A. M. Salah, *J. Heterocycl. Chem.*, **41**, 1 (2004).

04JOC7794 M. Watanabe, H. Suzuki, Y. Tanaka, T. Ishida, T. Oshikawa, and A. Tori-i, *J. Org. Chem.*, **69**, 7794 (2004).

04JOC7880 E. Petricci, C. Mugnaini, M. Radi, F. Corelli, and M. Botta, *J. Org. Chem.*, **69**, 7880 (2004).

04JOC8118 L. D. S. Yadav and R. Kapoor, *J. Org. Chem.*, **69**, 8118 (2004).

04MI1 V. Roy, R. Zerrouki, P. Krausz, S. Schmidt, and A. H. Aubertin, Nucleosides, *Nucleotides Nucleic acids*, **23**, 1625 (2004).

04S436 H. Pessoa-Mahana, C. D. Pessoa-Mahana, R. Salazar, J. A. Valderrama, E. Saez, and R. Araya-Maturana, *Synthesis*, 436 (2004).

04S1239 H. Hazarkhani and B. Karimi, *Synthesis*, 1239 (2004).

04S1269 R. Nagarajan and P. T. Perumal, *Synthesis*, 1269 (2004).

04SC315 A. V. Koshkin, O. A. Fedorova, V. Lokshin, R. Guglielmetti, J. Hamelin, and F. T. Boullet, *Synth. Commun.*, **34**, 315 (2004).

04SC345 M. Panunzio, M. A. Lentini, E. Campana, G. Martelli, E. Tamanini, and P. Vicennati, *Synth. Commun.*, **34**, 345 (2004).

04SC1141 A. Dandia, K. Arya, and M. Sati, *Synth. Commun.*, **34**, 1141 (2004).

04SC1289 S. Tu, Y. Gao, C. Miao, T. Li, X. Zhang, S. Zhu, F. Fang, and D. Shi, *Synth. Commun.*, **34**, 1289 (2004).

04SC1295 Y. Gao, S. Tu, T. Li, X. Zhang, S. Zhu, F. Fang, and D. Shi, *Synth. Commun.*, **34**, 1295 (2004).

04SL235 M. Gohain, D. Prajapati, and J. S. Sandhu, *Synlett*, 235 (2004).

04SL283 I. Devi and P. Bhuyan, *Synlett*, 283 (2004).

04SL723 E. S. H. El Ashry, E. Ramadan, H. Abdel Hamid, and M. Hagar, *Synlett*, 723 (2004).

04SL803 P. Cledera, J. D. Sanchez, E. Caballero, C. Avendano, M. T. Ramos, and J. C. Menendez, *Synlett*, 803 (2004).

04SL1179 M. Gohain, D. Prajapati, B. J. Gogoi, and J. S. Sandhu, *Synlett*, 1179 (2004).

04SL1309 A. Chetia, M. Longchar, K. C. Lekhok, and R. C. Boruah, *Synlett*, 1309 (2004).

04SL2615 M. C. Bagley, K. Chapaneri, C. Glover, and E. A. Merritt, *Synlett*, 2615 (2004).

04TL417	V. Gracias, J. D. Moore, and SW. Djuric, *Tetrahedron Lett.*, **45**, 417 (2004).
04TL1159	C. -L. Tung and C. -M. Sun, *Tetrahedron. Lett.*, **45**, 1159 (2004).
04TL2405	I. Devi, H. N. Borah, and P. J. Bhuyan, *Tetrahedron Lett.*, **45**, 2405 (2004).
04TL2575	A. Shaabani and A. Bazgir, *Tetrahedron Lett.*, **45**, 2575 (2004).
05AHC1	E. S. H. El Ashry, E. Ramadan, A. A. Kassem, and M. Hagar, *Adv. Heterocycl. Chem.*, **88**, 1 (2005).
05JCR(S)299	E. S. H. El Ashry, E. Ramadan, H. Abdel Hamid, and M. Hagar, *J. Chem. Res.* (*S*), 299 (2005).
05MI1	E. S. H. El Ashry, E. Ramadan, H. Abdel Hamid, and M. Hagar, *Lett. Org. Chem.*, **2**, 136 (2005).
05SC2243	E. S. H. El Ashry, E. Ramadan, H. Abdel Hamid, and M. Hagar, *Synth. Commun.*, **35**, 2243 (2005).
05UP1	E. S. H. El Ashry, L. Awad, H. Abdel Hamid, and I. A. Atta, unpublished results (2005).
05UP2	E. S. H. El Ashry, A. A. Kassem, H. Abdel Hamid, F. F. Louis, Sh. A. N. Kattab, and M. R. Aouad, unbuplished results (2005).
05UP3	E. S. H. El Ashry, N. Rashed, E. Ramadan, S. M. Abdel-Mageed, and N. Rezki, unpublished results (2005).
05UP4	E. S. H. El Ashry, K. F. Atta, S. Aboul-Ela, and R. Beldi, unpublished results (2005).

The Chemistry of Thienothiophenes

V.P. Litvinov

N.D.Zelinsky Institute of Organic Chemistry, Academy of Sciences, Moscow, Russia

I. Introduction

In the last 30 years, annulated heterocyclic systems have attracted considerable attention both from a theoretical standpoint and in view of their various practical applications. This interest is evidenced by a sharply increasing number of publications devoted to various aspects of the chemistry of fused thiophenes. About 300 papers were published over 90 years since the discovery of thienothiophenes in 1886 (1886CB2444). However, since publication of the most recent reviews (76AHC123, 75MI1, 75MI2, 78MI1, 2003MI1, 2004MI1, 2005USC235), the number of such papers has considerably increased, especially in the last 10–15 years. The character of publications has also changed. In recent years procedures for the synthesis of annulated derivatives and their physicochemical properties and reactivity as well as the potentially useful properties of isomeric thienothiophenes and their analogues have attracted growing interest. In particular, the percentage of studies on practical applications of such systems exceeded 30% of the total

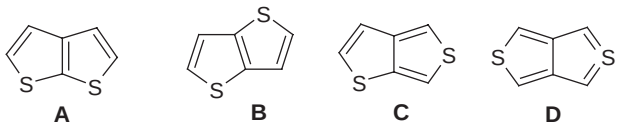
ADVANCES IN HETEROCYCLIC CHEMISTRY
VOLUME 90 ISSN: 0065-2725 DOI: 10.1016/S0065-2725(05)90002-0

number of publications. Here we emphasize investigations performed in the last decade.

II. Methods of Synthesis

Data presented in this section are classified according to the nature of the starting compounds involved in the synthesis of isomeric thienothiophenes.

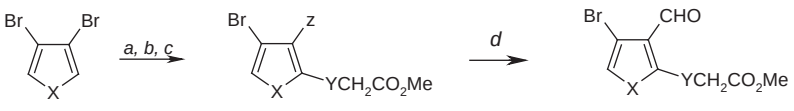
Compounds characterized by three modes of fusion of the thiophene rings, viz., [2,3-*b*] (structure **A**), [3,2-*b*] (**B**) and [3,4-*b*] (**C**), have attracted the most attention. These isomers are refered to as conventional or classical thienothiophenes because structures of the type **D** ([3,4-*c*]-fusion) are much less accessible.



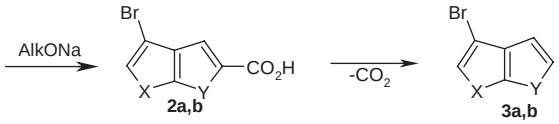
For isomeric thienothiophenes, both general methods of synthesis and original procedures applicable only to the preparation of particular types of compounds have been developed. In recent years, along with conventional methods based on thiophene derivatives as substrates, other approaches using, in particular, cyclopropenethiones, dithiynes and dithiolium salts have been successfully designed. A special section in this review deals with high-temperature synthesis of annulated thienothiophenes and procedures used for the preparation of particular representatives of this class of heterocycles.

A. Thiophene Derivatives in the Synthesis of Thienothiophenes

Bromine derivatives of thiophene are the most widely used for the preparation of isomeric thienothiophenes and related systems. A classical example is illustrated by the following transformation sequence: formylation of 3,4-dibromothiophene (**1**) through lithium derivatives, repeated metallation and treatment with elemental sulfur and methyl bromoacetate. Ring closure of the second heterocycle occurs in the present of sodium alkoxide. Decarboxylation of the resulting 4-bromothieno[2,3-*b*]thiophene-2-carboxylic acid (**2a**) affords 3-bromothieno[2,3-*b*]thiophene (**3a**) (74IZV1570). The reaction with selenium instead of sulfur produced 4-bromoselenolo[2,3-*b*]thiophene-2-carboxylic acid (**2b**) and 4-bromoselenolo[2,3-*b*]thiophene (**3b**).



1a,b



X = Y = S (a); X = Se, Y = S (b); Z = -CH(OLi)NMe_2.

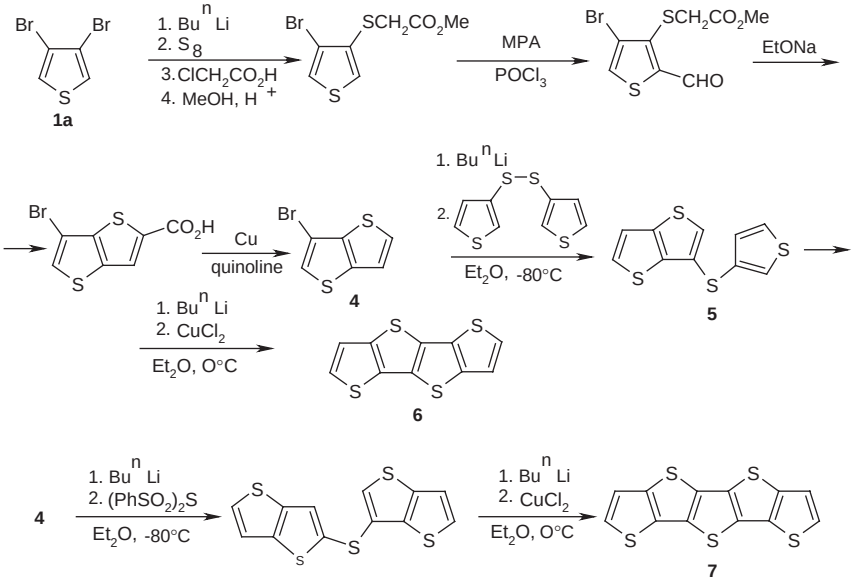
a : 1 eq. Bu^n Li, DMF; 2 eq. Bu^n Li ; - 70°C

b : -70°C; -20°C

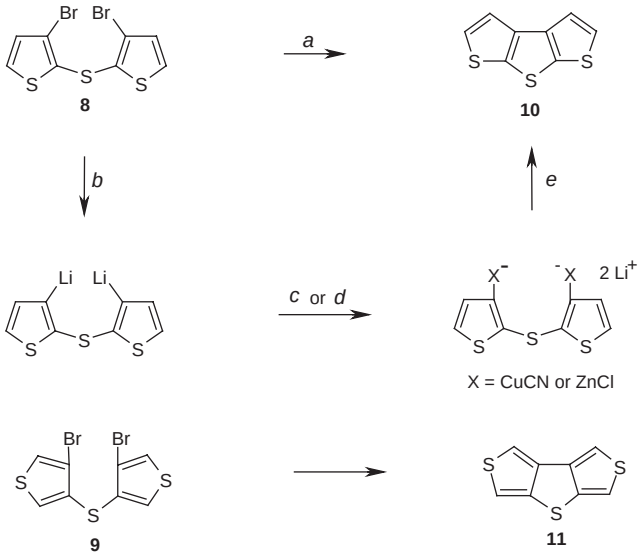
c: $BrCH_2CO_2Me$, -20°C.

d: H^+, O°C

More recently, this approach was applied (89TL3315) to the synthesis of 3-bromothieno[3,2-*b*]thiohene (**4**). It should be noted that bromothienothiophenes have considerable synthetic potential for both transformations into various functional derivatives and synthesis of polyannulated thiophenes. For example, treatment of bromide **4** with Bu^nLi and then with di(3-thienyl) disulfide affords sulfide **5**. Oxidative cyclization of the latter gives tetrathienoacene **6**. Pentathienoacene **7** was prepared according to an analogous scheme.



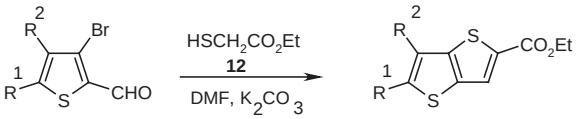
Three approaches to the synthesis of dithieno[2,3-*b*:3′,2′-*d*]thiophene (**10**) and dithieno[3,4-*b*:3′,4′-*d*]thiophene (**11**) starting from di(bromothienyl) sulfides **8** and **9** were developed (97TL4581, 2000H761). One procedure (condensation *a*) involves cyclization of sulfides **8** and **9** with hexamethyldistannane catalysed by a palladium complex. Two other procedures involve lithiation, the formation of organocopper (conditions *b*, *c*, *e*) or organozinc (conditions *b*, *d*, *e*) derivatives and their oxidation by molecular oxygen.



a - $Pd(PPh_3)_4$ (20 mol.%), $(Me_3Sn)_2$ (0.9 equiv.), dioxane, 110-116°C;
b - Bu^nLi, THF, - 78°C; *c* - CuCN; *d* - $ZnCl_2$, - 50°C;
e - 1) O_2; 2) $CuCl_2$, - 70°C.

Conditions	Yield (%)	
	10	**11**
a	75	78
b, c, e	37	40
b, d, e	70	70

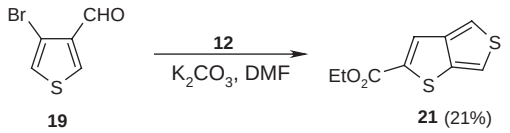
Bromine-substituted thiophenecarbaldehydes were used as the starting compounds in the synthesis of isomeric thienothiophenes (94JCS(P1)2735). The second sulfur-containing ring can be constructed using ethyl thioglycolate (**12**). The reactions of 3-bromine-substituted thiophene-2-carbaldehydes **13**–**15** with ester **12** are most often carried out in DMF in the presence of K_2CO_3 (92JCS(P1)973, 94JCS(P1)2735, 97JCS(P1)3465, 92MM2294, 2000MI1, 2001IZV107). These reactions produce thieno[3,2-*b*]thiophene-2-carboxylates **16**–**18**, whose yields vary substantially depending on the structure of the starting aldehyde. The reaction of 3,4,5-tribromo derivative **15** with ethyl thioglycolate **12** was studied under different conditions. The reaction in boiling anhydrous ethanol in the presence of EtONa afforded ethyl 2,3-dibromothieno[3,2-*b*]thiophene-2-carboxylate (**18**), whereas the reaction in the presence of even traces of water *in situ* was accompanied by hydrolysis of ester **18** to the corresponding carboxylic acid. In liquid ammonia, the reaction proceeds apparently through the replacement of the bromine atom by an $S_{RN}1$ mechanism.



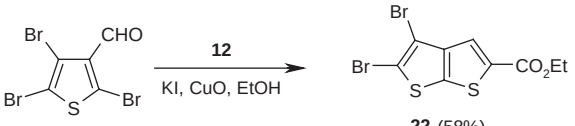
13a,b, 14, 15 **16a,b, 17, 18**

Substrat (product)	R^1	R^2	Reaction conditions	Yield (%)	Ref.
13a (16a)	H	H	DMF, K_2CO_3, 20℃	95	[92JCS(P1)973; 92MM2294; 97JCS(P1)3465
13b (16b)	Me	Br	DMF, K_2CO_3, 20℃	73	[2001IZV107]
14 (17)	Br	H	DMF, K_2CO_3, 20°C	8	[94JCS(P1)2735]
15 (18)	Br	Br	DMF, K_2CO_3, 20°C	61	[94JCS(P1)2735]
15 (18)	Br	Br	EtONa, EtOH (anhydr.), 78°C	72	[94JCS(P1)2735]
15 (18)	Br	Br	NH_3 (liquid.)	66	[94JCS(P1)2735]

Analogously, thienothiophene systems **21** and **22** were derived from thiophene-3-carbaldehydes **19** and **20**, respectively (94JCS(P1)2735) (cf. Ref. (68IZV1828)). Compounds **18**, **21** and **22** provide examples of isomeric thienothiophenes, which were prepared according to the same procedure but are characterized by different modes of fusion of the five-membered sulfur-containing rings.

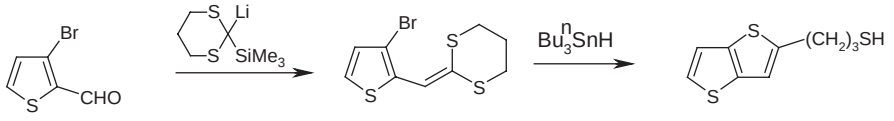


19 **21** (21%)



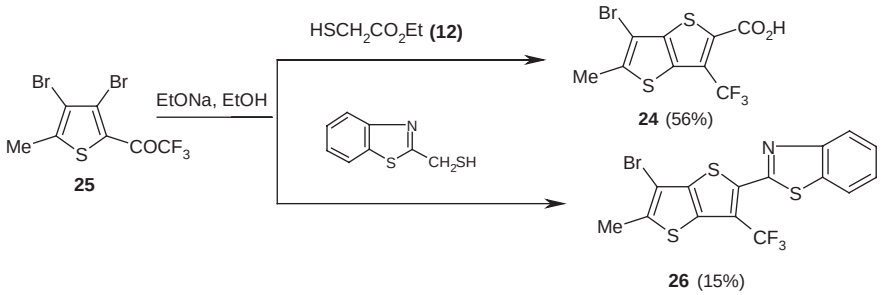
20 **22** (58%)

3-Bromothiophene-2-carbaldehyde **13a** served also as the starting compound in the synthesis of thieno[3,2-*b*]thiophene **23** containing the mercaptopropyl substituent (93TL5653).



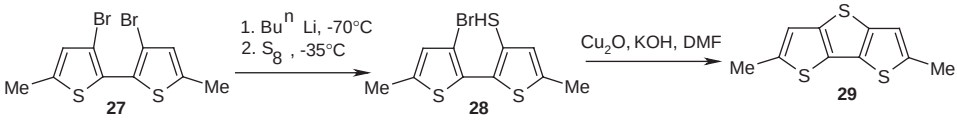
13a **23** (74%)

6-Bromo-5-methyl-3-fluoromethylthieno[2,3-*b*]thiophene-2-carboxylic acid (**24**) was synthesized by the reaction of dibromo-substituted thienyl ketone **25** with ethyl thioglicolate **12** in ethanolic sodium ethoxide.

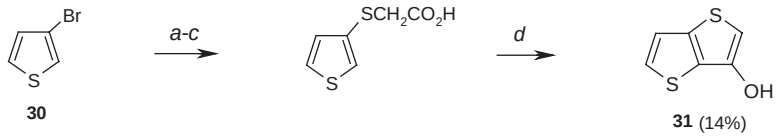


Under analogous conditions, the reaction with 2-mercaptomethylbenzo-thiazole afforded the corresponding 2-(benzothiazol-2-yl)thieno[3,2-*b*]thiophene derivative **26** (2000MI1, 2001IZV107).

Treatment of 3,3′-dibromo-5,5′-dimethyl-2,2′-bithiophene (**27**) with Bu^{n}Li and then with elemental sulfur produced 3-bromo-3′-mercapto-5,5′-dimethyl-2,2′-bithiophene (**28**). In the presence of Cu_2O and alkali, the latter undergoes cyclization to 2,6-dimethyldithieno[3,2-*b*:2′,3′-*d*]thiophene (**29**) (2000MI1, 2002IZV1942). Compounds **26** and **29** were used to design new photochromic substances (2001IZV107, 2000MI1, 2002IZV1942).

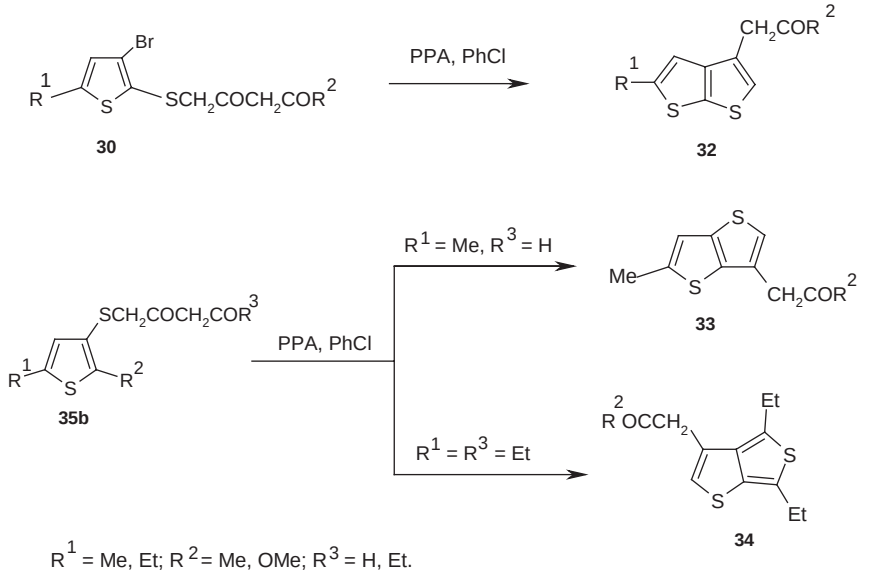


An analogous method was used (76KGS1039) to introduce the thiol group into 3-bromothiophene **30** in the synthesis of 3-hydroxythieno[3,2-*b*]thiophene (**31**).

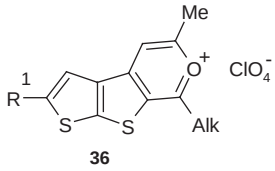


a – Bu^{n}Li, -70°C; *b* – S_8, 20% NH_4Cl; *c* – $ClCH_2CO_2H$, 40-45°C; *d* – H_2SO_4, 95-100°C.

Procedures were developed (81USSR767108, 83KGS37, 2001KGS850) for the preparation of isomeric thienothiophenes **32-34** by cyclization of methyl γ-thienylthioacetoacetates **35a, b** derived from substituted 3-bromothiophenes. Cyclization occurs in chlorobenzene in the presence of polyphosphoric acid (PPA).

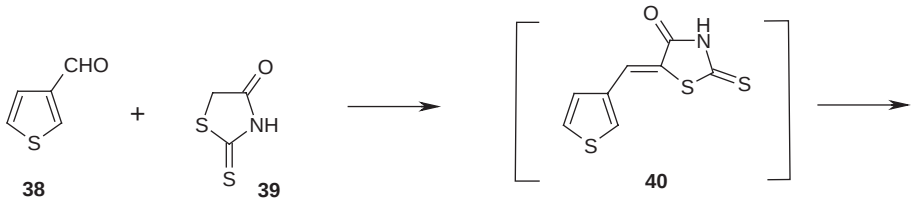


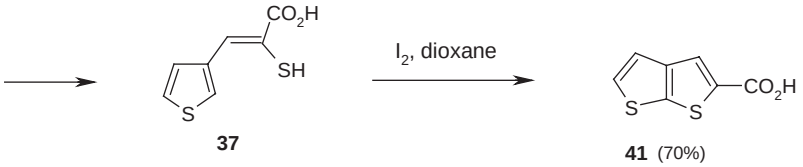
Acylation of thienothiophene derivatives **32** and **33** in an aliphatic acid anhydride – 70% perchloric acid system gives the corresponding pyrylium salts **36** (for compounds **32**, $R^1 = Me$).



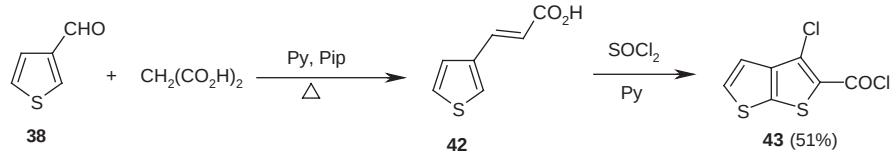
R^1 = Me, Et.

The synthesis of isomeric thienothiophenes and benzothienothiophenes was successfully carried out starting from thiophenecarbaldehydes and their derivatives. Treatment of 2-mercapto-3-(3-thienyl)acrylic acid (**37**), prepared in quantitative yield from thiophene-3-carbaldehyde (**38**) and 2-thioxothiazolidin-4-one (**39**) through intermediate **40**, gave with two equivalents of iodine in dioxane thieno[2,3-*b*]thiophene-2-carboxylic acid (**41**) (74SC29).

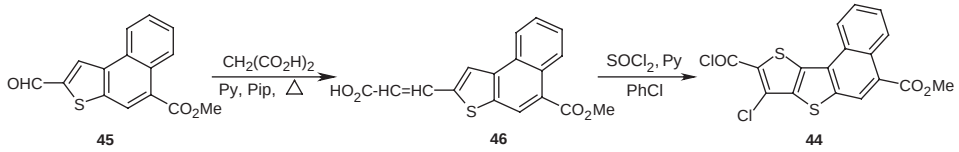




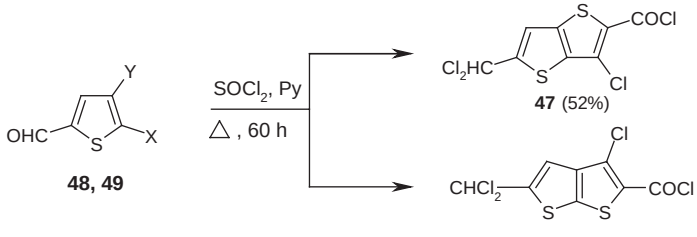
Condensation of thiophene-3-carbaldehyde **38** with malonic acid (Doebner reaction) in a mixture of pyridine (Py) and piperidine (Pip) with heating affords (*E*)-3-(3-thienyl)acrylic acid (**42**), whose treatment with thionyl chloride in Py produces 3-chlorothieno[2,3-*b*]thiophene-2-carboxylic acid chloride (**43**) (72ACS2982, 88JHC1363). Analogously, 3,5-dichlorothieno[3,2-*b*]-2-carboxylic acid chloride was prepared from thiophene-2-carbaldehyde (72ACS2982, 72JHC879, 88JHC1363).



The same methodology was employed in the synthesis of the more complex 3-chloro-6-methoxycarbonylnaphtho[2′,1′:2,3-*b*]thieno[4,5-*d*]thiophene-2-carboxylic acid chloride (**44**). Annulated thiophenecarbaldehyde **45** reacts with malonic acid in boiling Py containing two drops of Pip to give unsaturated acid **46**, which undergoes cyclization to acid chloride **44** upon mixing with thionyl chloride in chlorobenzene with a small admixture of Py (91H2323).

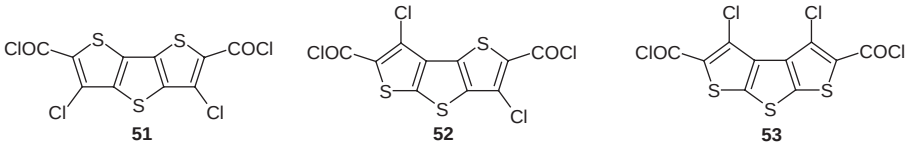


3-Chloro-5-dichloromethylthieno[3,2-*b*]thiophene-2-carboxylic acid chloride (**47**) was synthesized by the reaction of thionyl chloride in Py with 5-formylthiophen-2-ylacrylic acid **48** (75BSF2575). 3-Chloro-5-dichlorometylthieno[2,3-*b*]thiophene-2-carboxylic acid chloride (**50**) was prepared analogously starting from isomer **49**.

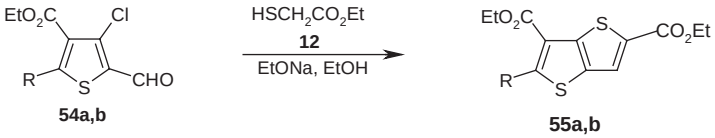


X = CH=CHCO$_2$H, Y = H (48); X = H, Y = CH=CHCO$_2$H (49).

This method was applied to the synthesis of dithienothiophenes **51–53** from isomeric thiophenediacrylic acids (20–40% yields).

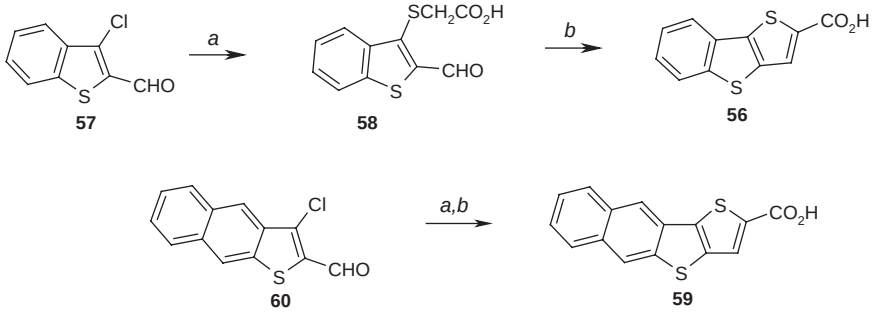


The synthesis of thieno[3,2-*b*]thiophenes and their benzo- and naphthoannulated analogues was carried out starting from 4-chloro-5-formylthiophene-3-carboxylic esters. For example, the reaction of 2-substituted ethyl 4-chloro-5-formylthiophene-3-carboxylates **54a, b** with ethyl thioglycolate **12** afforded the corresponding thieno[3,2-*b*]thiophene derivatives **55a, b** in rather high yields (72KGS427, 81JCS(P1)1078).



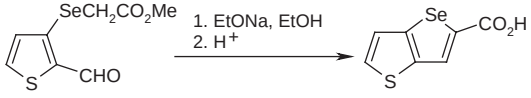
R = Me (a), PhNH (b).

An analogous approach was employed in the synthesis of benzo[*b*]thieno[3,2-*b*]thiophene-2-carboxylic acid (**56**) and naphtho[2,3-*b*]thieno[3,2-*b*]thiophene-2-carboxylic acid (**59**) from substituted benzo[*b*]thiophene-2-carbaldehyde **57** (77MI1) (through thioglycolic acid derivative **58**) and naphtha[2,3-*b*]thiophene-2-carbaldehyde **60**, respectively (71G774).



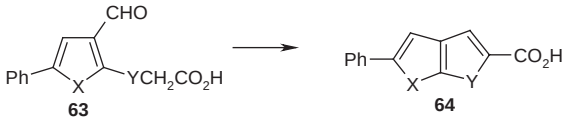
a - $HSCH_2CO_2H$; *b* - aq. KOH, 80-90°C, 30 min.

Substituted thiophenecarbaldehydes were also used in the synthesis of thienothiophene-related systems. For example, cyclization of thiophene-containing methyl selanylacetate **61** in the presence of EtONa in ethanol afforded selenolo[3,2-*b*]thiophene-5-carboxylic acid (**62**) (68IZV1419, 74IZV1575).



61 **62** (76%)

Furo-, pyrrolo-, selenolo- and thieno[2,3-*b*]thiophene-2-carboxylic acids **64** were synthesized from various heterocyclic 2-chalcogenoacetic acids **63** (76ZOR1574).

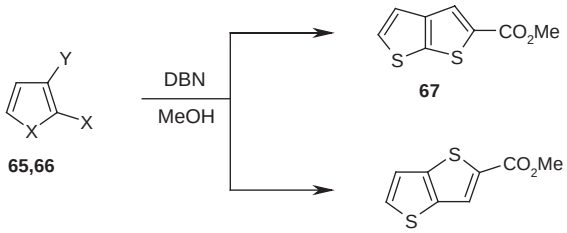


63 **64**

X = NMe, O, S; Y = S, Se.

Substituted selenolo[2,3-*b*]thiophenes can be easily synthesized in two steps from ketene dithioacetal $(MeS)_2C{=}C(COMe)_2$ (2004S451).

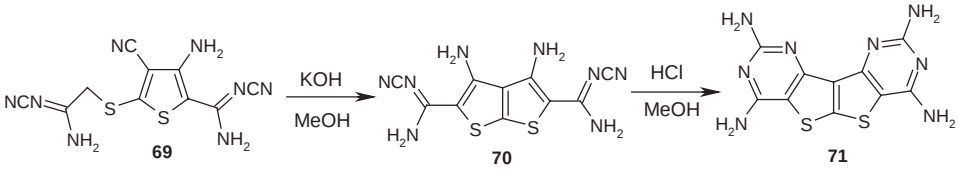
Cyclization of isomeric thiophenes **65** and **66** containing the aldehyde function and the SCH_2CO_2Me group in positions 2 and 3 by reaction with 1,5-diazabicyclo[4.3.0]-non-5-ene (DBN) affords methyl thieno[2,3-*b*]- (**67**) and -[3,2-*b*]thiophene-2-carboxylates (**68**), respectively (91JMC1805).



65,66 **67** **68**

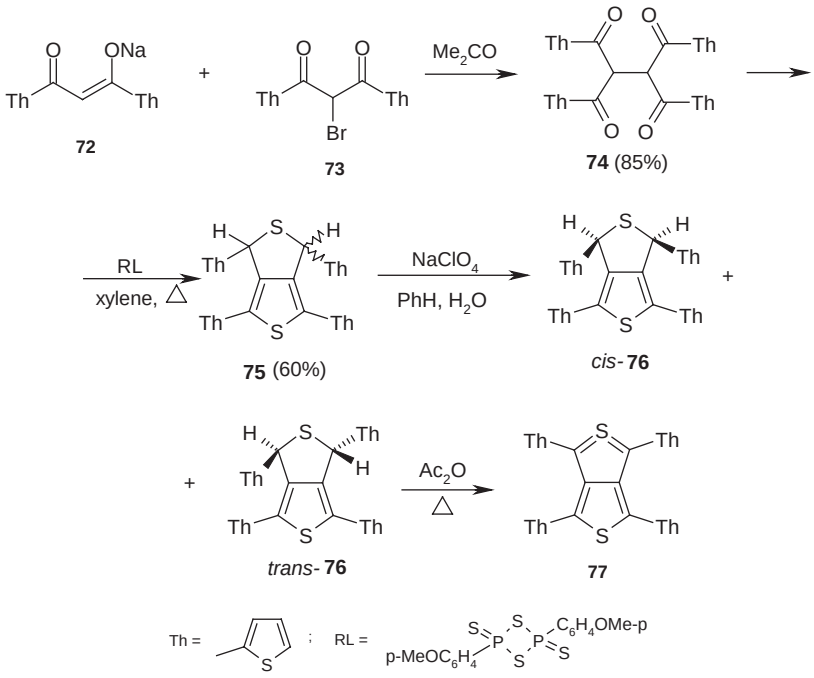
X = SCH_2CO_2Me, Y = CHO (**65**);
X = CHO, Y = SCH_2CO_2Me (**66**).

Intramolecular condensations were also used in the synthesis of derivatives of more complex substances, including thienothiophenes containing various functional groups. The ester and nitrile functions can serve as the "carbonyl component" (76T3055, 90P895). Among examples of the synthesis of the thienothiophene system, worth of mentioning is the transformation of thiophene-4-carbonitrile **69** in a reaction with KOH giving rise to 3,4-diamino-2,5-di[amino(cyanoimine)methyl]thieno[2,3-*b*]thiophene (**70**), which then is cyclized to symmetrical tetracycle **71** (95ZOR127, 96T1011).

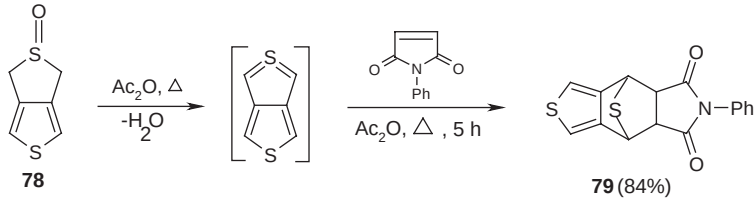


69 **70** **71**

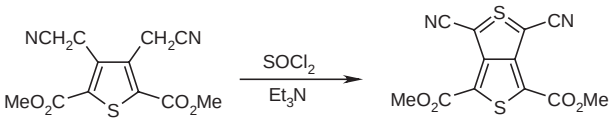
Thiophene derivatives were also used in the synthesis of derivatives of the fourth, the so-called non-classical, isomer of thienothiophene, viz., thieno[3,4-*c*]thiophene (85TL1983, 91JOC78). For example, the reaction of a sodium salt of dithenoylmethane (**72**) and bromodithenoylmethane (**73**) in acetone produced 1,1,2,2-tetra-2-thenoylethane (**74**). Sulfonation of the latter with Lawesson's reagent (RL) in boiling xylene afforded a mixture of two stereoisomeric 1,3-dihydrothieno[3,4-*c*]thiophenes (**75**). This mixture was oxidized without purification and then chromatographed on silica gel (CCl_4 as the eluent) to isolate individual *cis*- and *trans*-sulfoxides **76**. Dehydration of an unseparated mixture of isomers **76** in boiling acetic anhydride under nitrogen produced 1,3,4,6-tetra-2-thienylthieno[3,4-*c*]thiophene (**77**) in 84% yield, whereas the yield of the product in an analogous transformation of the *cis*-isomer of **76** decreased to 68% (91JOC78).



Unsubstituted thieno[3,4-*c*]thiophene was synthesized for first time by Pummerer dehydration of 1*H*,3*H*-thieno[3,4-*c*]thiophene-2-oxide (**78**) (85TL1983). This compound was characterized using chemical traps, for example, as adduct **79** with *N*-phenylmaleimide (88CC959).

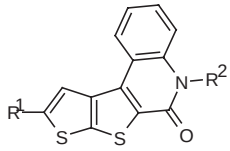


The reaction of thienyldinitrile **80** with thionyl chloride in the presence of triethylamine gives thieno[3,4-*c*]thiophene **81** containing only electron-withdrawing substituents (2000TL8843, 2002JOC2453). This compound is very stable in the solid state. The use of selenium oxychloride furnished the corresponding cyano-substituted selenolo[3,4-*c*]thiophene (2002JOC2453).



80 **81** (70%)

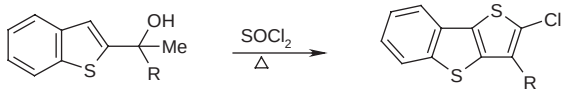
The multistep synthesis involving aldol condensation of thiophene-3-carbaldehyde **38** with malonic acid or the Heck reaction using 3-bromothiophene **30** or 4-bromothiophene-2-carboxylate produced thieno[3′,2′:4,5]thieno[2,3-*c*]quinolones **82**, which exhibit high antitumour activity (2002CPB656).



82

R^1 = H, MeO_2C, PhHCO, $Me_2N(CH_2)_3NH$, $Me_2N(CH_2)_3NPh$;
R^2 = H, $Me_2N(CH_2)_3$.

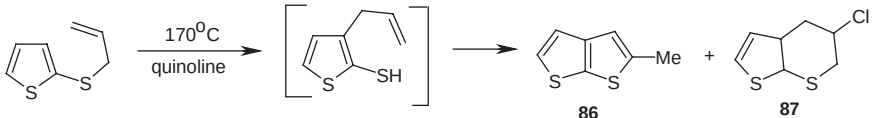
Benzothiophenes **83** containing a tertiary alcoholic group undergo cyclization in the presence of thionyl chloride (91JHC109) to afford benzo[*b*]thieno[3,2-*b*]thiophenes **84**.



83 **84**

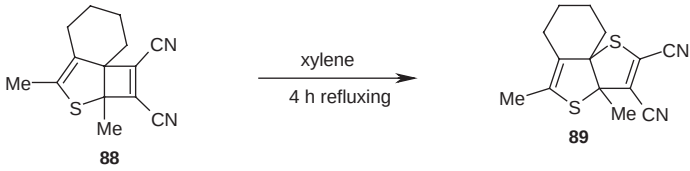
R = Pr^i, Bu^t.

Isomeric thienothiophenes can also be synthesized from other thiophene derivatives. In the study of the 3,3-sigmatropic rearrangement of allyl 2-thienyl sulfide (**85**), 2-methylthieno[2,3-*b*]thiophene (**86**) and 3-chloro-3,4-dihydro-2*H*-thieno[2,3-*b*]thiopyran (**87**) were isolated in a total yield of up to 60% (77ZOR2624, 79KGS1062, 82DOK97).



85 **86** **87**

Refluxing sulfur-containing tricyclic dinitrile **88** in xylene was found to give 3*a*,5-dimethyl-3*aH*-6,7,8,9-tetrahydrobenzo[*c*]thieno[3,2-*b*]thiophene (**89**) (82JOC977).

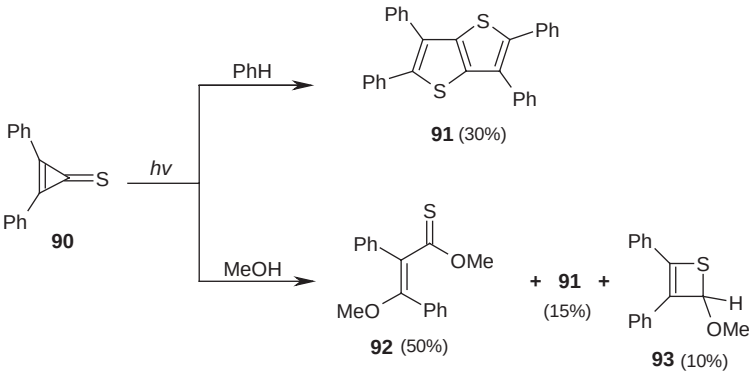


Analysis of the above methods for the synthesis of thienothiophenes and their analogues based on thiophene derivatives demonstrates that mono- and dibromo-substituted thiophenes are most often successfully used as the starting compounds. It should be noted that intramolecular cyclization of compounds derived from the above-mentioned thiophenes serves as the key step. In this step, vicinal carbonyl functions (generally, formyl or acyl) interact with fragments containing an activated methylene group.

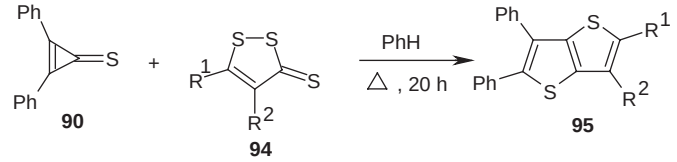
B. Cyclopropenethiones in the Synthesis of Thienothiophenes

Cyclopropenethiones are transformed into thienothiophenes both under irradiation and on heating. However, this method has not received wide acceptance because the starting compounds are difficult to prepare and also because of the low yields.

Photodimerization of 2,3-diphenylcyclopropenethione (**90**) in benzene (71TL4993) occurs regioselectively to give the expected 2,3,5,6-tetraphenylthieno[3,2-*b*]thiophene (**91**). This reaction in methanol afforded methyl 1-methoxy-2-phenylthiocinnamate (**92**) as the major product; in addition, thienothiophene **91** and 3,4-diphenyl-2-methoxythiethane (**93**) were isolated as by-products (82JOC3550, 85JOC3732).



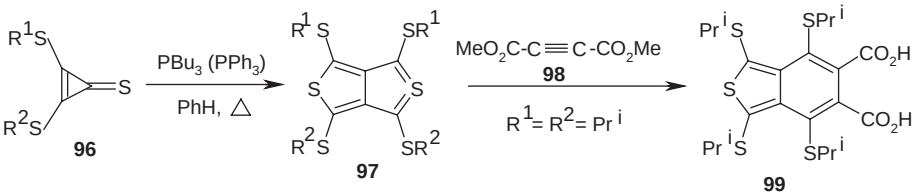
Refluxing cyclopropenethione **90** with 4,5-disubstituted 1,2-dithiol-3-thiones **94** in anhydrous benzene in the dark is accompanied by the elimination of two sulfur atoms to form thieno[3,2-*b*]thiophenes **95** (82LA315).



$R^1 = R^2$ = Me, Ph; R^1-R^2= $(CH_2)_4$, $(CH{=}CH)_2$.

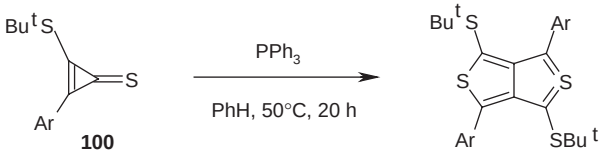
Refluxing 1,2-dithyol-3-thione **94** ($R^1 = R^2 = Ph$) with powdered copper in chlorobenzene (6.5 h) led to its cyclization to thienothiophene **91** in 39% yield (81LA1729, 81LA1928).

In the presence of triphenyl- or tributylphosphine, 2,3-di(alkylthio)cyclopropenethiones **96** are dimerized (refluxing in benzene under nitrogen, 4 h) to 1,3,4,6-tetra(alkylthio)thieno[3,4-*c*]thiophenes (**97**) in moderate yields (85JA5801, 88JHC559). The authors also demonstrated that thienothiophene **97** ($R^1 = R^2 = Pr^i$) is involved in a cycloaddition with dimethyl acetylenedicarboxylate (**98**) to form 5,6-dimethoxycarbonylbenzo[*c*]thiophene (**99**).



R^1 = Pr^i, Bu^t; R^2= Me, Et, Pr^i, Bu^t.

More recently (96CL421, 98JOC163), 1,4-bis(*tert*-butylthio)-3,6-diarylthieno[3,4-*c*]thiophenes **101** were prepared by treatment of cyclopropenethiones **100** with triphenylphosphine.



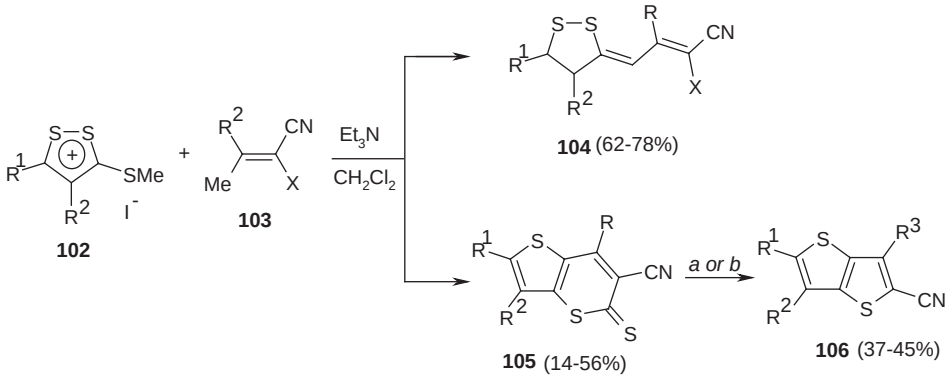
Ar = Ph, thien-2-yl.

An analogous procedure involving the reaction of cyclopropenethiones with tributylphosphine was employed in the synthesis of substituted thieno[3,2-*b*]thiophenes (88AG597).

C. Dithiynes in the Synthesis of Thienothiophenes

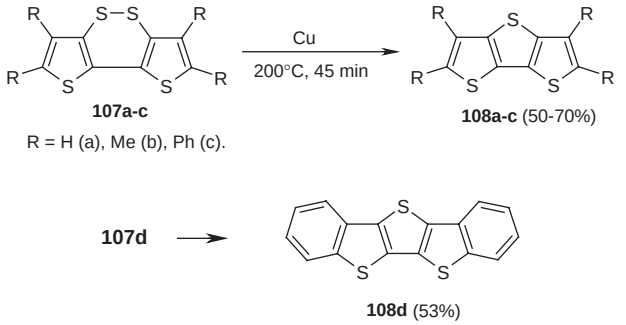
The use of dithiynes for the preparation of thienothiophenes is exemplified by four types of reactions. For example, 3-methylthio-1,2-dithiolium ions **102** react with

malonic acid derivatives **103** to give γ-dithiolydene nitriles **104** and 6-cyanothieno[3,2-*b*]thiopyranothiones **105**. Oxidation of the latter with H_2O_2 in acetic acid or successive treatment of **104** and **105** with NaOH and $BrCH_2CN$ affords 2-cyanothieno[3,2-*b*]thiophenes **106** (82BSF342 This method was applied to the synthesis of a rather broad range of nitrile-containing thienothiophenes promising in view of further modifications.

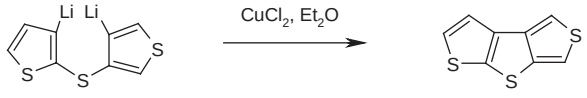


R^1 = H, Bu, SMe, Ph, 4-$MeOC_6H_4$; R^2, R^3 = Ph, 4-$MeOC_6H_4$;
X = CN, CO_2Et ; a - H_2O_2, AcOH ; b - 1) NaOH, 2) $BrCH_2CN$.

Heating dithienoannulated 1,2-dithiynes **107a–c** with powdered copper (200 °C, 45 min) afforded dithieno[3,2-*b*:2′,3′-*d*]thiophenes **108a–c** (94AG(E)739, 97T7509). An analogous transformation of benzoannulated dithiyne **107d** (R–R=(CH=CH)$_2$) produced bis(benzo[4,5]thieno)[3,2-*b*:2′,3′-*d*]thiophene (**108d**) (94CB401).

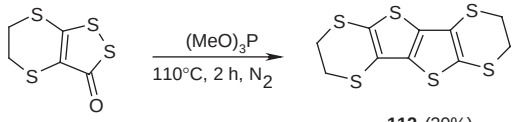


Unsubstituted dithienothiophene **108a** was synthesized earlier by treating 2,2′-dilithium 3,3′-dithienyl sulfide with copper dichloride in diethyl ether (65ZOR1282). This method was also successfully applied to oxidative cyclization of the corresponding dilithium dithienyl sulfide **109**, giving rise to dithieno[2,3-*b*:3′,4′-*d*]thiophene (**110**) (29% yield) (71JOC1645). The above dithieno[2,3-*b*:3′,2′-*d*]thiophene (**10**) (32%) and dithieno[3,4-*b*:3′,4′-*d*]thiophene (**11**) (31%) were synthesized analogously (see Section II.A) (71JOC1645).



109 **110** (29%)

Heating a suspension of 4,5-ethylidenedithio-1,2-dithiol-3-one (**111**) in trimethylphosphite under nitrogen (110 °C, 2 h) afforded 2,3:5,6-bis(ethylidenethio)thieno[3,2-*b*]thiophene (**112**) (95BCJ1193).



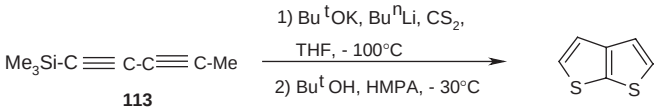
111 **112** (20%)

Almost all the above reactions gave products in low yields. Hence, this approach is of theoretical rather than preparative interest.

D. Carbon Disulfide in the Synthesis of Thienothiophenes

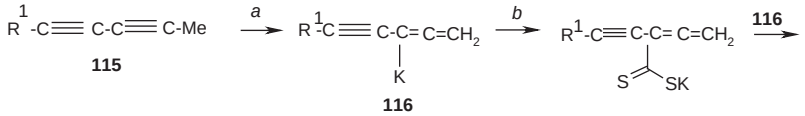
Methods based on the reactions of carbon disulfide with compounds containing conjugated triple-bonded systems or an active methylene group are successfully employed in the synthesis of thienothiophenes. Generally, these procedures involve many steps, which require a thorough preparation and purification of the reagents and solvents.

Unsubstituted thieno[2,3-*b*]thiophene was synthesized in satisfactory yield from trimethylsilylpenta-1,3-diyne (**113**) under very mild conditions. In this procedure, the reagents should be added in a reverse order: *n*-butyllithium is initially added to a suspension of Bu^{t}OK in dry THF at −100 °C followed by the addition of alkyne at −80 °C, CS_2 at −100 °C and a solution of Bu^{t}OH in dry HMPA at −30 °C (93BCJ2033).

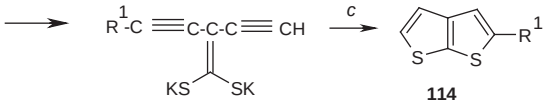


113 (47%)

A one-pot procedure was developed for the synthesis of thieno[2,3-*b*]thiophenes **114** using diynes **115** and CS_2 as the building blocks (in 44–48% yields) (81MI1, 83CC1056, 91SC145). Allene derivative **116** was detected as an intermediate.



115 **116**



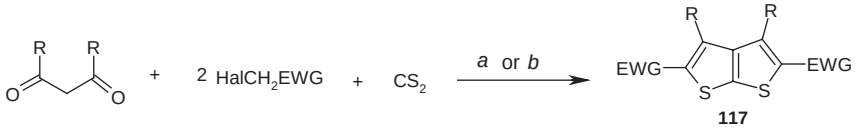
114

R^1 = Me_3Si (H for **114**), Alk, $N(Alk)_2$, SAlk ;

a - Bu^nLi, Bu^tOK, THF, C_6H_{14}; *b* - CS_2, - 100°C; *c* -Bu^tOH;

HMPT is hexamethylphosphorous trianide.

A technologically convenient one-pot synthesis of 2,5-functionalized thieno[2,3-*b*]thiophenes **117** starting from 1,3-diketones uses carbon disulfide and alkylating agents containing electron-withdrawing groups. The reaction proceeds either in dry DMF in the presence of anhydrous KF as a promoter for condensation (36–67% yields) (99S2030) or under phase-transfer catalysis conditions (78–93% yields) (93BCJ2011) (see also Ref. (92PS15)).



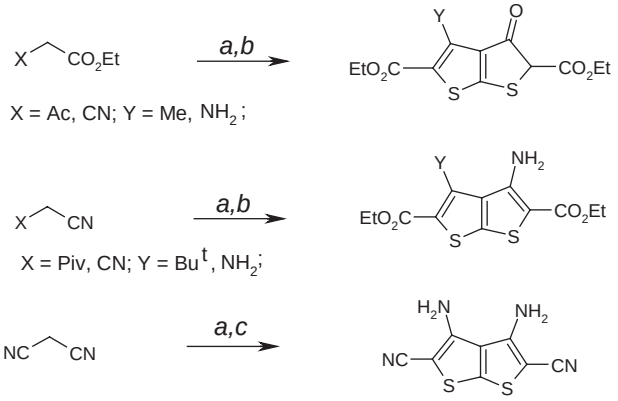
117

R = Me, Ph, 4-MeC_6H_4.

Hal = Br, Cl; EWG = CN, COMe, CO_2Et, CONHPh, CONH-thiazol-2-yl.

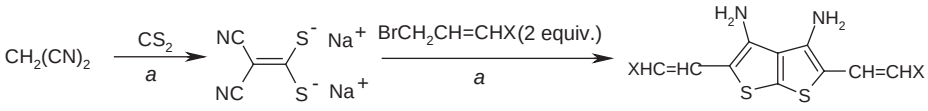
a - KF, DMF; *b* - K_2CO_3, Bu_4NBr, PhH, H_2O.

More recently (2001JHC1167), this approach was extended to the synthesis of oxo- and amino-substituted thieno[2,3-*b*]thiophenes. Compounds containing an active methylene group (3-keto esters, malononitrile, ethyl cyanoacetate or 3-ketonitrile) were used as the starting reagents, and ethyl bromoacetate or bromoacetonitrile served as the alkylating agent. The yields of thienothiophenes were 61–87%.



a - CS_2, K_2CO_3, DMF; *b* - $BrCH_2CO_2Et$ (2 equiv.); *c* - $BrCH_2CN$ (2 equiv.); Piv = Bu C(O).

The reactions of carbon disulfide with malononitrile in the presence of sodium methoxide in methanol followed by treatment of the resulting dicyanodithioacetate **118** with γ-bromocrotonic acid derivatives can also be assigned to this reaction type (90LA115). These reactions give diamino-substituted thienothiophenes **119** as the final products.

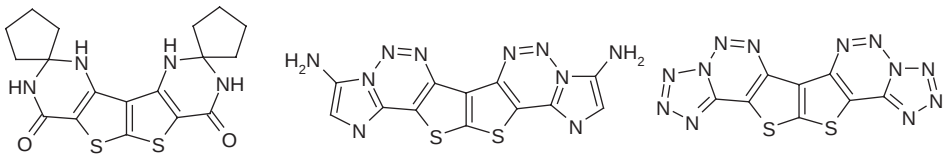


118 **119**

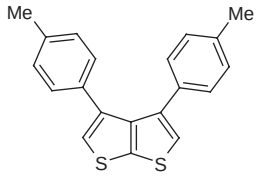
X = CN, CO_2Me; *a* - MeONa, MeOH.

Dinitrile **118** was also used in the synthesis of other thieno[2,3-*b*]thiophene derivatives (86MI1). Various tri- and tetra-substituted thieno[2,3-*b*]thiophenes were prepared according to modifications (74T93, 80ZC96, 92LA387, 95CCC1578).

Tetracondensed thienothiophenepyrimidines, -triazines and -imidazolotriazines were prepared from 3,4-diaminothieno[2,3-*b*]thiophene-2,5-dicarboxamide and CS_2, carbonyl compounds, ethyl chloroformate, dithioacetal, oxalyl chloride, etc. (2003PS1211).



The synthesis of *peri*-substituted 3,4-diaryl-thienothiophene **120** from $(4\text{-}MeC_6H_4CH_2)_2CO$ through the corresponding ketene dithioacetal, Dieckmann cyclization, hydrolysis and decarboxylation was described (2000SC1695).

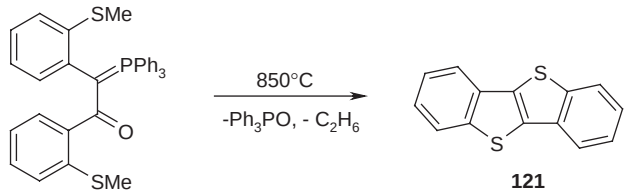


120

E. High-Temperature Synthesis

High-temperature synthesis of sulfur-containing heteroaromatic systems has attracted attention of researchers (predominantly Russian) in the last 30 years. This method uses both a broad range of starting substrates (aliphatic, aromatic and heteroaromatic compounds) and various sulfur donors (elemental sulfur, hydrogen sulfide and dialkyl sulfides).

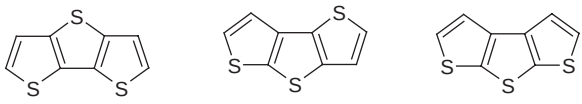
Friedmann was the first to describe the formation of thienothiophenes under pyrolytic conditions in 1916 (16CB277, 16CB1344, 16CB1352, 16CB1551). The reaction of aliphatic or aromatic hydrocarbons with sulfur proceeds at 270–320 °C and high pressure. More recently, this method was applied to the synthesis of benzo[*b*]thieno[3,2-*b*]benzo[*b*]thiophene (**121**) in yields up to 50% starting from benzyl bromide and its derivatives (66KGS529, 89ZOR2382), 1,2,3-trichloro-1,2-diphenylethane (70KGS457) or *o*-halo-toluenes (74ZOR811) at 200–280 °C. Compound **121** was also prepared in 36% yield by tandem radical cyclization of 2-methylthiophenyl-substituted phosphorus yield **122** under conditions of flash vacuum pyrolysis at 850 °C (95SL53, 98JCS(P1)3973).



122 **121**

In addition, thienothiophene **121** was synthesized by gas-phase pyrolysis of benzotrichloride at 400 °C in a hydrogen sulfide atmosphere (67% yield) (83ZOR1079).

1,2-Dichloroethylene reacts with hydrogen sulfide in the gas phase at 420–520 °C in a quartz tubeto produce a complex mixture in which thieno[2,3-*b*]thiophene and thieno[3,2-*b*]thiophene were detected (in a total yield of 4.5%) (80ZOR399, 81ZOR1103). Thieno[2,3-*b*]thiophene was prepared by the gas-phase reaction of 2-chlorothiophene with hydrogen sulfide and acetylene at 600 °C (93ZOR2246). The reaction with dimethyl selenide instead of acetylene afforded a mixture of dithienothiophene **108a** and dithieno[3,2-*b*;2,3-*d*]thiophene (**123**) (3% yield) (86ZOB2087). The formation of dithienothiophene **10** along with other products was observed upon thermolysis (500–600 °C) of 2,2′-dithienyl sulfide under an atmosphere of nitrogen and hydrogen sulfide (85KGS1134), whereas dithienothiophenes **10** and **108a** were generated in a hydrogen sulfide atmosphere (86KGS1614).



108a **123** **10**

Thieno[2,3-*b*]thiophene was also prepared by the high-temperature reaction of 2-chlorothiophene with acetylene and hydrogen sulfide (92SL137, 95MI1) or dimethyl sulfide (95MI1) and by the reaction of thiophene-2-thiol with acetylene (89KGS1565). An analogous reaction of 2-chlorothiophene with a mixture of diethyl di- and trisulfides produces a mixture of thieno[2,3-*b*]thiophene and thieno[3,2-*b*]thiophene in 10–32% yields (88KGS1041). This reaction in the presence of

acetylene affords a mixture of thienothiophenes in somewhat higher yield (36%) (95ZOR925).

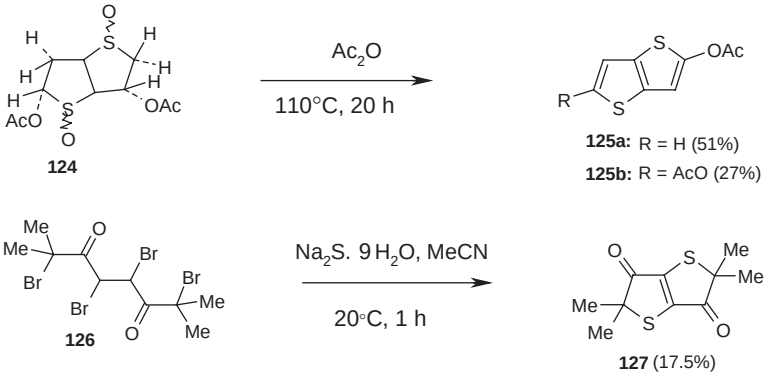
A mixture of thiophene and isomeric thienothiophenes (total yield of 85%) was prepared by the gas-phase reaction of dimethyl sulfide, diethyl disulfide, diethyl trisulfide and diethyl tetrasulfide with acetylene (89ZOR2588). It was also found that gaseous allyl 2-thienyl sulfide is transformed into a mixture of thiophene-2-thiol, bis(2-thienyl) sulfide and 2-methylthieno[2,3-*b*]thiophene at 350–410 °C; in the presence of acetylene, the reaction gives these products along with thieno[2,3-*b*]thiophene (91KGS1312). Thermolysis (at 540 °C) of a mixture of di(prop-l-enyl) sulfide and 2-chloro(or bromo)thiophene affords a mixture of thieno[2,3-*b*]thiophene and thieno[3,2-*b*]thiophene (91ZOR354).

The advantage of this method is that the starting compounds are readily available. Among the drawbacks are the use of special apparatus, the formation of a large number of by-products in almost all reactions and low yields of the desired compounds.

F. Other Methods for the Synthesis of Thienothiophenes and their Analogues

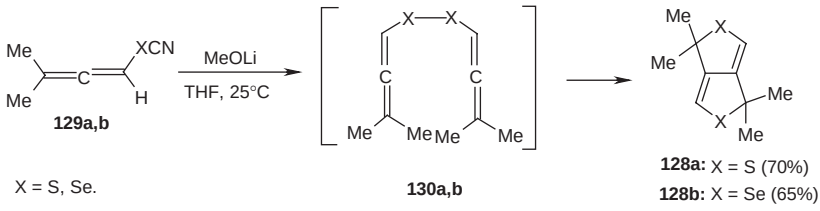
There are a few original procedures that were used to prepare particular representatives of this class of compounds and their selenium- and tellurium-containing analogues. The most interesting procedures are considered below.

Among other approaches to the synthesis of thienothiophenes, the following are worth of mentioning: the Pummerer rearrangement of disulfoxide **124** giving a mixture of 2-acetylthieno[3,2-*b*]thiophenes **125a, b** (71T5055) and the reaction of 2,4,5,7-tetrabromo-2,7-dimethyl-3,6-octanedione (**126**) with sodium sulfide hydrate yielding 2,2,5,5-tetramethyl-2,3,5,6-tetrahydrothieno[3,2-*b*]thiophene-3,6-dione (**127**) (77CB1421).

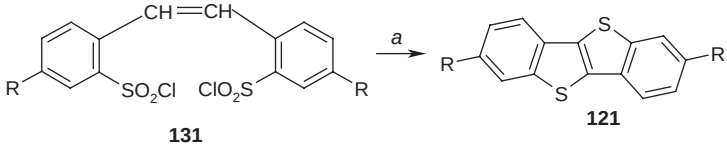


Substituted tetrahydrothieno[3,4-*c*]thiophene (**128a**) and its selenium analogue (**128b**) were synthesized by the reactions of lithium methoxide with γ,γ-dimethylallenyl thio(or seleno)cyanates **129a, b** (80TL3617, 90T5759, 2002TL9615). The multistep mechanism involves the formation of bis(dimethylallenyl) chalcogenides

130a, b as the key intermediates, which undergo successive [3,3]-sigmatropic rearrangement and double Michael addition of a chalcogen-containing group.

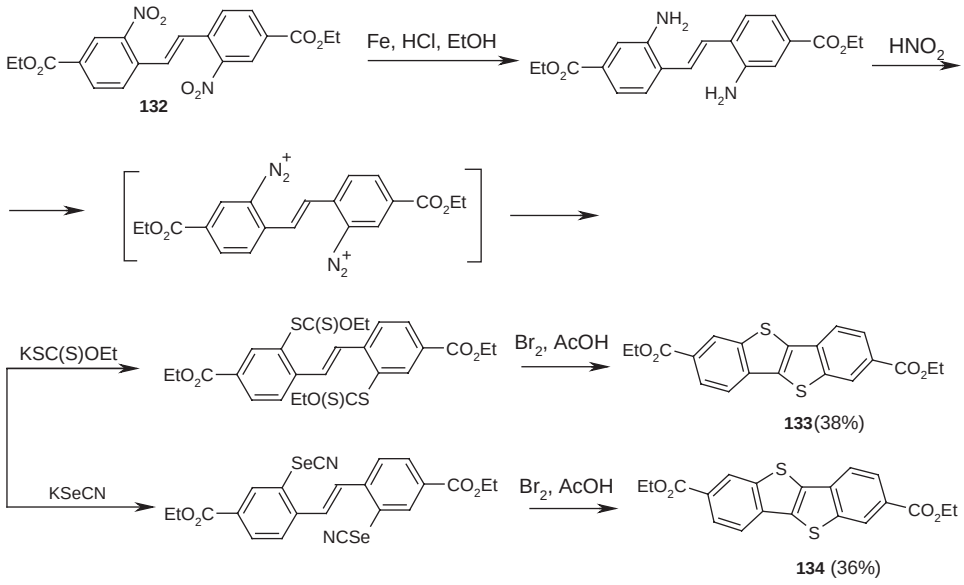


A new procedure was developed for the synthesis of benzoannulated thienothiophene based on reduction of stilbene-2,2′-disulfochloride (**131**) with concentrated hydroiodic acid in acetic acid (80ZOR425, 80ZOR430, 81MI2, 81USSR755785). This approach is applicable also to the synthesis of 2,7-disubstituted derivatives of thienothiophenes **121** starting from the corresponding 4,4′-disubstituted disulfonylchlorides.

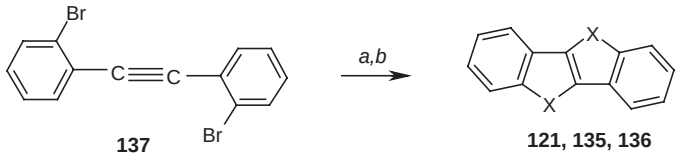


R = H (79%), NH_2; *a* - 55% aq. HI, 100°C, 8 h.

Diethyl 2,2′-dinitro-(*E*)-stilbene-4,4′-dicarboxylate **132** proved to be a convenient starting compound in the synthesis of diethyl benzo[*b*]thieno[3,2-*b*]benzo[*b*]thiophene-2,7-dicarboxylate (**133**) and its selenium analogue **134** (93JOC5209).



Sulfur-, selenium- and tellurium-containing heteroaromatic systems **121**, **135** and **136** were prepared by successive treatment of 2,2′-dibromodiphenylacetylene (**137**) with *tert*-butyllithium and chalcogens in anhydrous THF at −80 °C under argon (98JHC725).



137 **121, 135, 136**

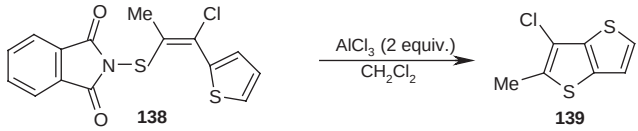
X = S (**121**, 49%), Se (**135**, 52%), Te (**136**, 55%);

a - Bu^{t}Li, THF, - 80°C, Ar; *b* - chalcogen (S, Se or Te).

A selenium modification of the Claisen rearrangement of propargylselenochalcogenophenes was employed in the synthesis of fused bicyclic systems, viz., thieno[2,3-*b*]-2*H*-selenopyran, thieno[3,2-*b*]-2*H*-selenopyran, 5-methylselenolo[2,3-*b*]tellurophene and 5-methylselenolo[3,2-*b*]thiophene (2000Sl215).

The reactions of sulfur with dimethylformamide dimethylacetal (96JPR403) and 2,5-dimethylhex-3-yne-2,5-diol (94H143) give substituted thieno[3,2-*b*]thiophenes.

Sulfonamide **138** with two equivalents of aluminium chloride produces 3-chloro-2-methylthieno[3,2-*b*]thiophene (**139**) in satisfactory yield (94S521).



138 **139**

Methyl 3-hydroxythieno[2,3-*b*)thiophene-2-carboxylates were also synthesized by cyclization of substituted methyl 3-hydroxythiophene-2-carboxylates (91MI1).

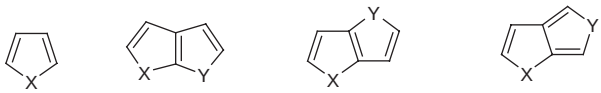
Therefore, the above data demonstrate the diversity of synthetic approaches to thienothiophene derivatives.

III. Reactivity and Chemical Transformations

Heteroatoms in five-membered π-excessive heteroaromatic compounds are responsible for the chemical behaviour of the molecules as a whole. The heteroatoms not only give electrons to form an aromatic π-electron system but also determine the direction of the attack of electrophilic or nucleophilic agents. In fused π-excessive heterocycles containing two or more heteroatoms, the reactivity of compounds and their physical properties are substantially affected by both the mutual arrangement of the heteroatoms and the electronic effects associated with their nature.

A. Reactivity

The first studies of the reactivity of thienothiophenes and their analogues by quantum-chemical methods were carried out in the mid-1970s (74CS49, 76AHC123, 78MI1). More recently (80KGS199, 82MI1), the reactivity of thiophene, selenophene, various isomeric thienothiophenes, selenolothiophenes, selenoloselenophenes and their various C-protonated forms (σ complexes) in electrophilic substitution reactions was estimated by the semiempirical LCAO SCF MO method for all valence electrons (CNDO/2). The charges on the carbon atoms Q_c (static index) and the localization energy Λ^+ (dynamic index; in the CNDO/2 approximation) were used as the reactivity indices. This index is determined as $\Lambda^+ = E_{total}M - E_{total}MH^+$, where $E_{total}M$ and $E_{total}MH^+$ are the total energies of the aromatic molecule and its σ complex with a proton, respectively. The method of reactivity indices supplemented by a "pseudoatom" approach (pseudoatoms simulate an electrophilic agent) provides a correct interpretation of experimental data on electrophilic substitution in fused heteroaromatic systems containing various heteroatoms. In addition, the values of Q_c and Λ^+ (relative to position 3 in thiophene) indicate that the direction of electrophilic attack depends on the nature and size of the attacking species. This effect is mainly responsible for the difference in the reactivity of substrates.



140,141 **142-144** **145-147** **148-151**

140: X = S; **141**: X = Se; **142**: X = Y = S; **143**: X = S, Y = Se; **144** X = Y = Se;
145: X = Y = S; **146**: X = S, Y = Se; **147**: X = Y = Se; **148**: X = Y = S;
149: X = Se, Y = S; **150**: X = S, Y = Se; **151**: X = Y = Se.

The results of calculations made it possible to arrange the relative reactivities of different positions in compounds **140–151** in electrophilic substitution reactions in the following theoretical series: C(4) (**150**) > C(4) (**148**) > C(4) (**151**) > C(4) (**149**) > > C(6) (**150**) > C(6) (**148**) > C(6) (**151**) C(6) (**149**) > C(2) (**146**) > > C(2) (**145**) > C(5) (**146**) > C(2) (**147**) > C(2) (**143**) > C(2) (**149**) > (**142**) > C(2) (**148**) > C(2)(**144**) > C(2) (**151**) > C(5) (**143**) > C(2) (**150**) > C(2) (**140**) > C(2) (**141**) > C(3) (**149**) > C(3)(**143**) > C(3) (**148**) > C(3) (**144**) > C(3) (**151**) > C(3) (**142**) > C(3) (**150**) > C(4) (**143**) > C(3) (**146**) > C(3) (**145**) > C(3) (**147**) > C(6) (**146**) > C(3) (**147**) > C(3) (**140**) (78MI1).

This series was confirmed experimentally. For example, the following series of reactivities of different positions in these compounds was obtained in studies of acetylation, formylation and chlorination of thiophene (**140**), thieno[2,3-*b*]thiophene (**142**) and thieno[3,2-*b*]thiophene (**145**): C(2) (**145**) > C(2) (**142**) > C(2) (**140**) > C(3) (**142**) > C(3) (**145**) > C(3) (**140**) (72CS137). In formylation, position 4 in thieno[3,4-*b*]thiophene (**148**) was found (70RTC77) to be more readily subjected to the attack of an electrophilic species compared to position 6.

The detritiation rate was studied for thieno[2,3-*b*]thiophene (**142**), thieno[3,2-*b*]thiophene (**145**), dithieno[2,3-*b*:3′,2′-*d*]thiophene (**10**), dithieno[3,2-*b*:2′,3′-*d*]thiophene (**108a**) and dithieno[2,3-*d*:2′,3′-*d*]thiophene (**123**), which are specially labelled with the ^{3}H isotope at each position, in trifluoroacetic acid or its mixture with acetic acid (82JCS(P2)295, 82JCS(P2)301). All thiophene systems were demonstrated to be rather active in electrophilic substitution reactions. The reactivity of the corresponding α and β positions slightly increases on going from thiophene to thienothiophenes and increases to an even larger extent on going from thienothiophenes to dithienothiophenes.

The comparative reactivities in electrophilic substitution of selenolo[3,2-*b*]thiophene (**143**) and -selenophene (**144**) with respect to thieno[3,2-*b*]thiophene (**142**) were studied by the method of competitive reactions (80CS206). The reactivity was found to change in the following order: **144** > **143** > **142**. This series agrees well with a higher substitution rate in selenophene compared to thiophene in acetylation, formylation and chlorination reactions.

Competitive metallation of two-component systems, viz., thieno[3,2-*b*]thiophene (**142**) and selenolo[3,2-*b*]thiophene (**143**), selenolothiophene **143** and thiophene (**140**), selenolothiophene **143** and selenophene (**141**), thiophene (**140**) and selenophene (**141**), was investigated (74IZV1575). The reactions were carried out with a deficient amount of $Bu^{n}Li$ in anhydrous diethyl ether at 25 ± 1 °C followed by hydrolysis with heavy water. Mass-spectrometric analysis of the products demonstrated that the relative reactivities of the compounds increase in the following order: **143** > **142** > **141** > **140** (74IZV1575).

The reactivities of thieno[2,3-*b*]thiophene (**142**) and selenolo[2,3-*b*]thiophene (**143**) were also compared using competitive acetylation of their mixture with thiophene (**140**) or selenophene (**141**) by acetyl chloride in the presence of tin chloride ($CHCl_3$, 25 °C) (76ZOR1574). The selenophene rings were found to be more reactive than the thiophene ring.

The above examples demonstrate that the theoretical estimates of the reactivities of the compounds in electrophilic substitution reactions most typical of aromatic systems agree well with the experimental data.

B. Chemical Transformations

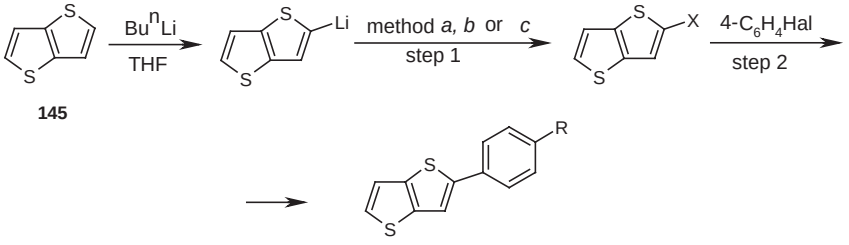
In the last 20 years, studies of chemical transformation of isomeric thienothiophenes have been aimed primarily at examining the possibilities of using these substrates in the synthesis of new polyannulated heteroaromatic systems and compounds possessing practically useful properties. These compounds can exhibit both electron-withdrawing and -donating properties and they were used in the synthesis of numerous charge-transfer complexes. Thienothiophene derivatives have found application as medicines, pesticides, conducting polymers, liquid and clathrate crystals, organic conductors or superconductors, photosensitive receptors, materials for optoelectronics (nonlinear optical chromophores), dyes, etc. The most typical reactions of this class of compounds (metallation, condensation and photochemical cyclizations) clearly illustrate their high synthetic potential.

1. *Metallation*

Lithiation (generally, with *n*-butyllithium) is most often and successfully used in the synthesis of various functionalized thienothiophenes. The lithium intermediates thus formed can react with various electrophiles.

For example, thieno[3,2-*b*]thiophene (**142**) (68ACS63, 69ACS2704, 71ACS27, 73CS190, 94JHC(P1)2603, 94MI1, 96H1927, 96JCS(P2)1377) and its alkyl derivatives (67ZOB2220, 94MI1, 96JCS(P2)1377, 96T471) are readily metallated with *n*-butyllithium at the α position, which can be used for the preparation of α-substituted thienothiophenes. This method was employed to introduce such substituents as Br (69ACS2704), I (96H1927), MgBr (96T471), ZnCl, $SnBu_3$, $B(OH)_2$) (94JHC(P1)2603), SeMe, TeMe (96JCS(P2)1377), SR (R = Me, *n*-$C_{18}H_{37}$) (94MI1), SMe (73CS190), SEt (67ZOB2220), SO_2Me, SO_2NH_2 (94MI1), CHO (71ACS27) and CO_2Me (94MI1).

Lithium derivatives of thieno[3,2-*b*]thiophene (**145**) were used in the synthesis of 2-arylthieno[3,2-*b*]thiophenes **152** through various organometallic (or -boron) intermediates (94JCS(P1)2603).



145 **152**

R = H, NO_2, CN, CO_2Me, SO_2Me;Hal = Br, I.

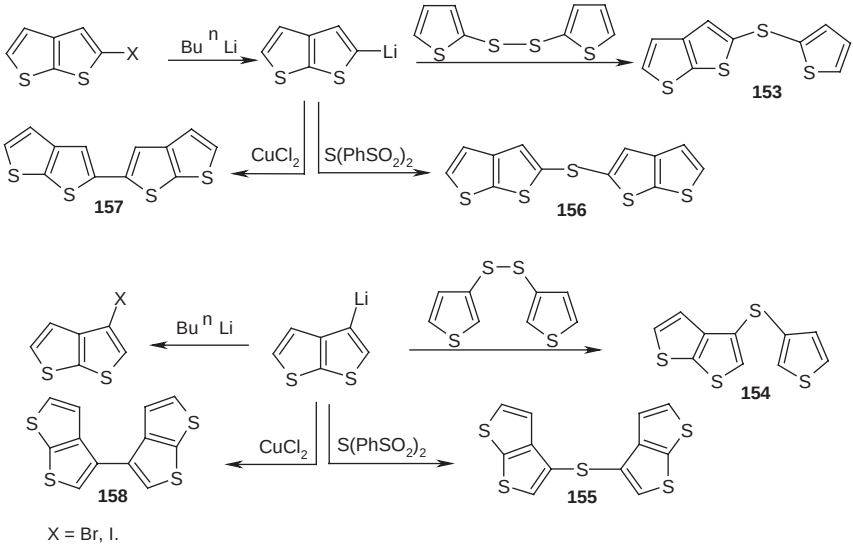
Method	X	Reaction conditions		Yields (%)
		Step 1	Step 2	
a	ZnCl	$ZnCl_2$, THF	$Pd(dba)_2$, DMF	10 - 85
b	$Bu(OH)_2$	$B(OBu^n)_3$, THF	$Pd(PPh_3)_4$, $Ba(OH)_2$, DME	40 -55
c	$SnBu_3^n$	Bu_3^nSnCl, THF	$Pd(PPh_3)_4$, dioxane	< 60

dba is dibenzylideneacetone, DME is 1,2-dimethoxyethane.

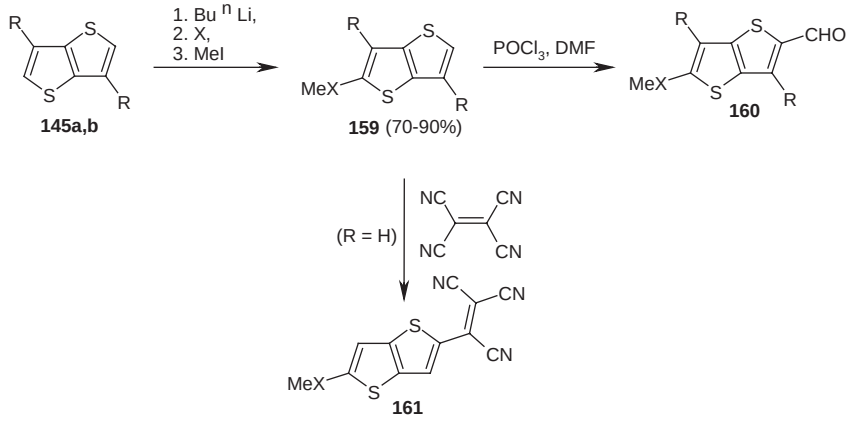
Metallation of thieno[3,2-*b*]thiophene **145** with two equivalents of Bu^{n}Li affords the 2,5-dilithium derivative, whose treatment with various reagents (CO_2, DMF, $(MeS)_2$, $(PhS)_2$, $(Me_3Si)_2$ and $(Bu^tMe_2Si)_2$) gives the corresponding disubstituted thienothiophene (68ACS63, 85ZN1199, 2001IZV107).

Halogen-lithium exchange reactions provide an approach to thienothiophene sulfides **142** and **145**, which were used in the synthesis of tetrathienocene **6** and pentathienocene **7** (see Section II.A) (89TL3315, 92JCS(P2)765).

Lithium intermediates served as the starting compounds in the synthesis of the corresponding 2(α)- or 3(β)-substituted derivatives of thienyl sulfides **153** and **154**, thieno[2,3-*b*]thienyl sulfides **155** and **156** and thieno[2,3-*b*]thienylthieno[2,3-*b*]thiophenes **157** and **158** (79BSB325).

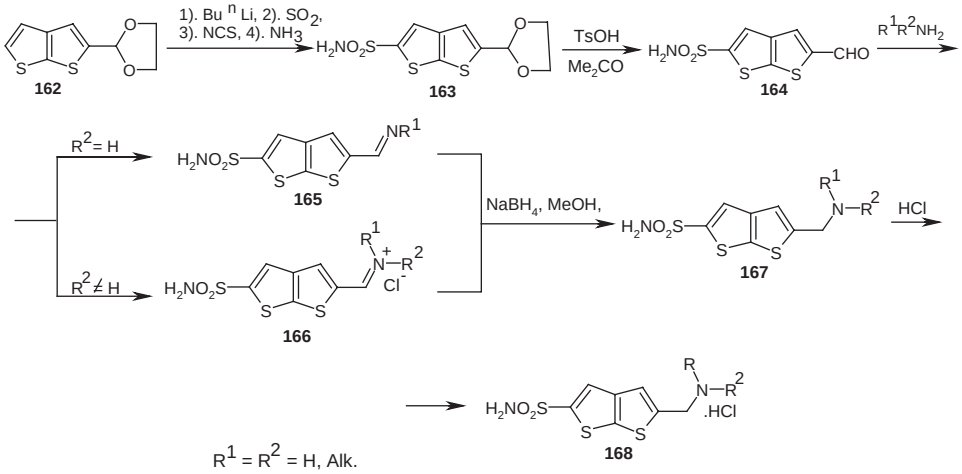


Lithiation of thieno[3,2-*b*]thiophenes **145a, b** gives 2-lithium derivatives, whose treatment with chalcogens and iodomethane affords chalcogenides **159** (96JCS(P2)1377). Vilsmeier–Haack formylation of the latter produces aldehydes **160**, whereas the reaction with tetracyanoethylene (TCNE) in DMF affords 5-tricyanovinyl derivatives **161**.

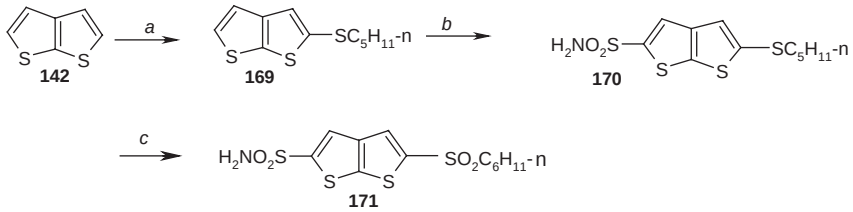


Organolithium derivatives served as intermediates in the synthesis of 5-amino-substituted thieno[2,3-*b*]- and -[3,2-*b*]thiophene-2-sulfonamides possessing biological

activities. These compounds are carbonic anhydrase inhibitors (CAIs) (91JMC1805, 99JHC249) and non-peptide fibrinogen receptor antagonists (99JMC2409). For example, the introduction of the sulfamoyl group into the dioxolane derivative of thieno[2,3-*b*]thiophene **162** can be efficiently performed by metallation with *n*-butyllithium at position 5 followed by treatment of the reaction mixture with SO_2, *N*-chlorosuccinimide (NCS) and ammonia. The acetal protection in the resulting 5-[l,3]dioxolan-2-ylthieno[2,3-*b*]thiophene-2-sulfonamide **163** was removed (91JMC1805) by transacetalation giving rise to aldehyde **164** in high yield. The latter reacts with various primary and secondary amines to form imines **165** or immonium salts **166**, respectively, whose reduction with sodium borohydride affords tertiary amines **167**. Transformations of the amines into hydrochlorides **168** produced water-soluble salts, which were tested for biological activities. The same synthetic approach was applied to the synthesis of the corresponding thieno[3,2-*b*]thiophene analogues.



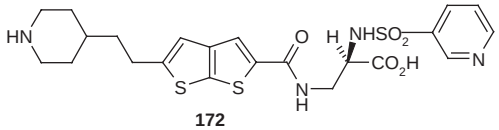
The reaction of thieno[2,3-*b*]thiophene (**142**) with Bu^{n}Li affords a lithium intermediate, whose treatment with elemental sulfur and bromopentane produces sulfide **169**. Regioselective *N*-sulfonation of the latter was successfully carried out by successive reactions with Bu^{n}Li, SO_2 and hydroxylamino-*O*-sulfonic acid. Selective oxidation of sulfide **170** with potassium peroxymonosulfate afforded sulfone **171** (99JHC249).



a - 1) Bu^{n}Li, 2) S_8; *n* - $C_5H_{11}Br$; *b* - 1) Bu^{n}Li, 2) SO_2, 3) hydroxylamino-*o*-sulfonic acid;

c - K_2SO_3.

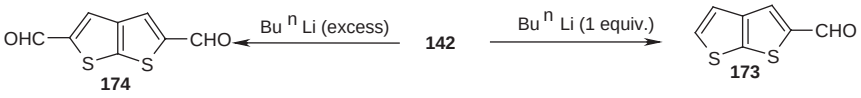
An analogous approach was employed in the synthesis of sulfonamide **172**, which is a potential non-peptide fibrinogen receptor antagonist (99JMC2409).



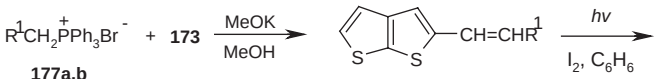
172

Metallation was involved also as the first step in the synthesis of di-, tri- and tetramers of 3,6-disubstituted thieno[3,2-*b*]thiophene (**145**) and selenolo[3,2-*b*]selenophene (**147**) (96T471). These compounds are of practical interest. Many thiophene oligomers exhibit biological activity, which is enhanced upon exposure to visible light (88MI1).

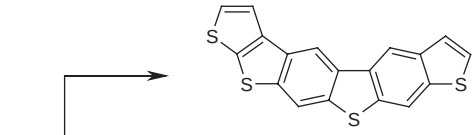
Metallation of thieno[2,3-*b*]thiophene (**142**) followed by the reactions of the resulting mono- and dilithium derivatives with dimethylformamide afforded aldehydes **173** and **174**, which served as the starting compounds in the synthesis of heterohelicenes **175a, b** and **176a, b** (73JA3692).



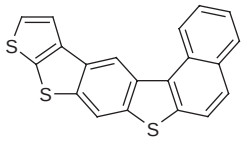
174 **173**



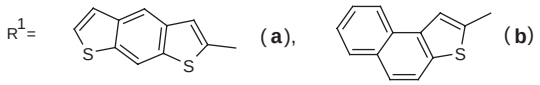
177a,b **178a,b** (57-95%)

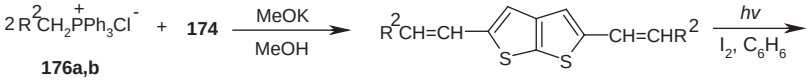


175a (69%)

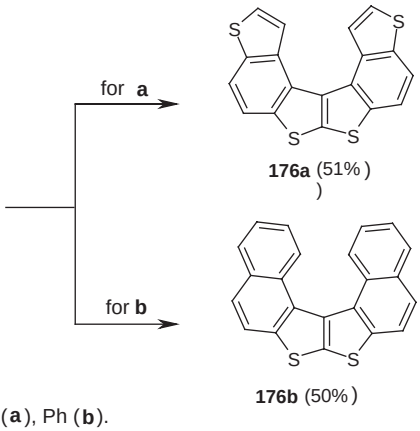


175b (60%)





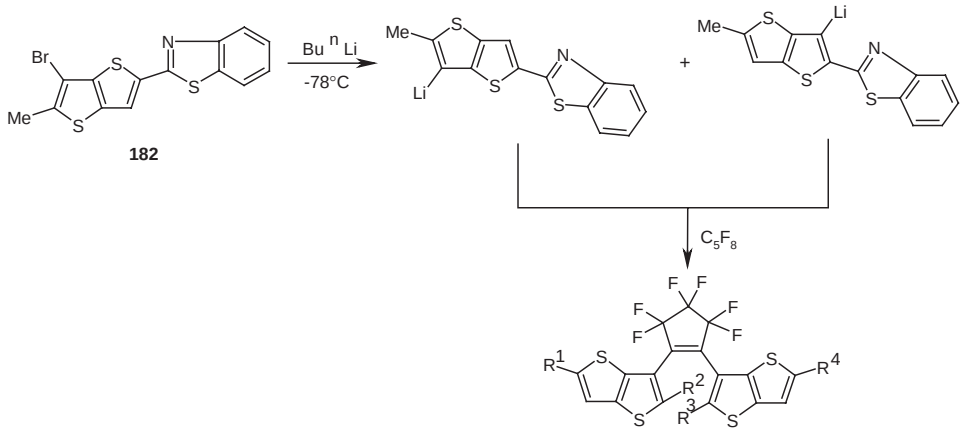
176a,b **180a,b** (50-69%)



R^2 = 2-Th (**a**), Ph (**b**).

The Wittig reaction of aldehyde **173** with phosphonium salts **177a, b** gives alkenes **178a, b**, and the double Wittig reaction of dialdehyde **174** with phosphonium salts **179a, b** affords alkenes **180a, b**. Irradiation of suspensions of alkenes **178a, b** and **180a, b** in benzene in the presence of iodine produces heterohelicenes **175a, b** and **176a, b**.

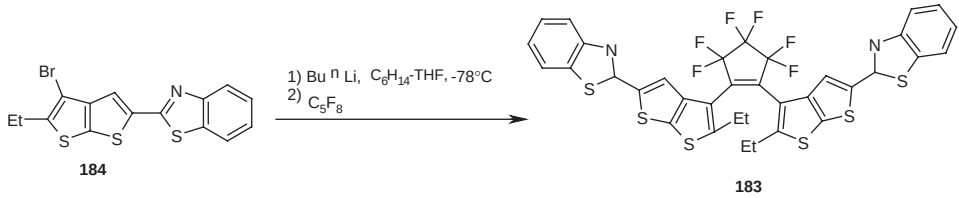
With the aim of synthesizing new photochromic dihetarylethenes, viz., 5-substituted l,2-bis(thieno[3,2-*b*]thiophen-3-yl)perfluorocyclopentenes **181a–c**, 2-(benzothiazol-2-yl)-6-bromo-5-methylthieno[3,2-*b*]thiophene (**182**) was subjected to metallation. A mixture of lithium derivatives produced by this reaction was treated with octafluorocyclopentene (C_5F_8) (2000MI1, 2001IZV107).



$R^1 = R^4$ = Z, $R^2 = R^3$ = Me (**a**); $R^1 = R^3$ = Z, $R^2 = R^4$ = Me (**b**); $R^2 = R^3$ = Z, $R^1 = R^4$ = Me (**c**).

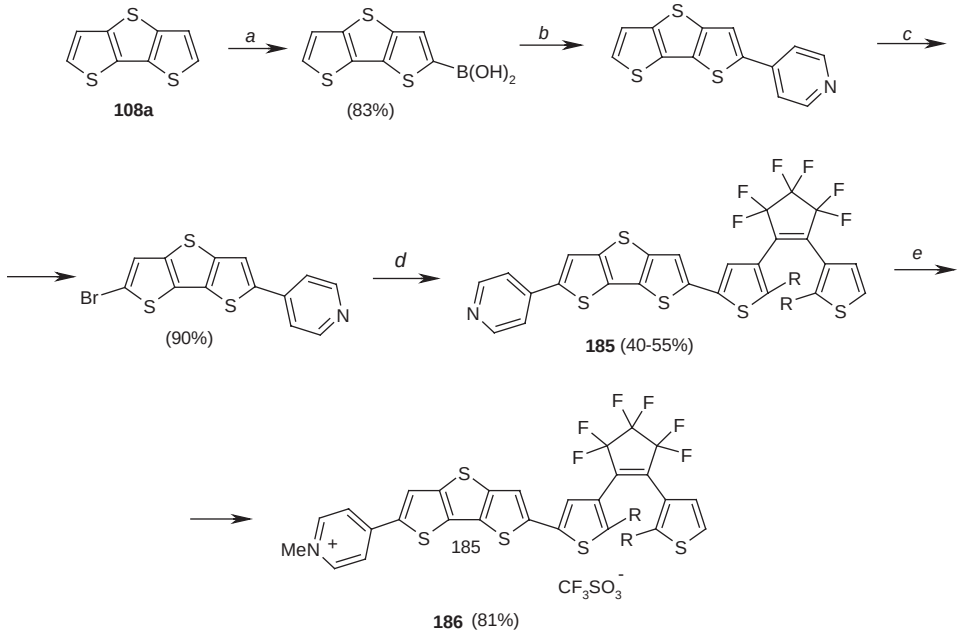
Z = 2-benzothiazol-2-yl

The thieno[2,3-*b*]thiophene analogue of compound **181**, viz., 1,2-bis{2-ethyl-5-(benzothiazol-2-yl)thieno[2,3-*b*]thiophen-3-yl}hexafluorocyclopentene (**183**), was synthesized according to an analogous procedure starting from (5-benzothiazol-2-yl)-3-bromo-2-ethylthieno[2,3-*b*]thiophene (**184**) (2005KGS360).



184 **183**

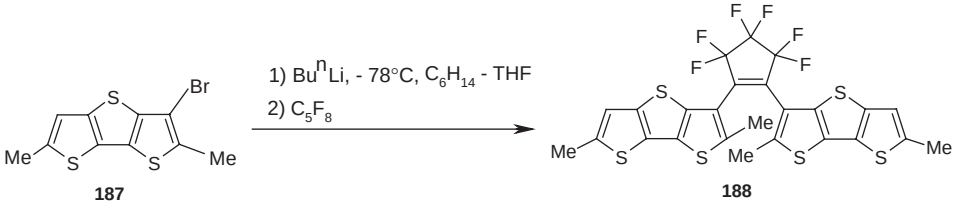
Dithieno[3,2-*b*:2′,3-*d*]thiophene (**108a**) served as a building block in the design of photochromic materials for optical memory. Photochromic compounds **185** and **186** were prepared in satisfactory yields by successive transformations involving initial metallation of dithienothiophene **108a** with Bu^{n}Li at −78 °C (95AG(E)1119).



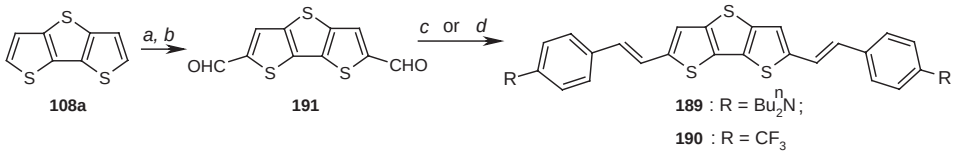
108a (83%) (90%) **185** (40-55%) **186** (81%)

a - 1) Bu n Li, -78°C; 2) $B(OBu^i)_3$, *b* - 4-bromopyridine, $Pd(PPh_3)_4$, Na_2CO_3, THF ; *c* - NBS, $CHCl_3$-AcOH ;
d - 1,2-bis[2-hexyl-5-(dihydroxyboryl)thiophen-3-yl]hexafluorocyclopentene, $Pd(Ph_3)_4$, Na_2CO_3, H_2O-THF;
e - CF_3SO_3Me, CH_2Cl_2 ; R = *n*-hexyl; NBS is *N*-bromosuccinimide.

Photochromic 1,2-bis(2,6-dimethylthieno[3,2-*b*:2′,3′-*d*]thiophen-3-yl)hexafluorocyclopentene (**188**) was synthesized [18] starting from 3-bromo-2,6-dimethylthieno[3,2-*b*:2′,3′-*d*]thiophene (**187**) according to a procedure described in the studies (2000MI1, 2001IZV107).



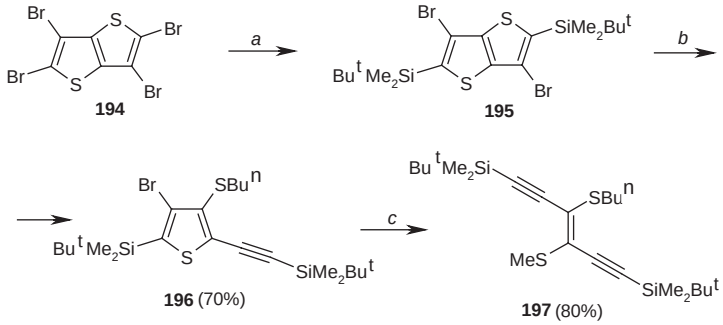
An analogous methodology was employed in the synthesis of new quadrupole photophores **189** and **190**, which have high two-photon excited fluorescence. Conjugated dithienothiophene **108a** was used as the starting compound. The reactions of dialdehyde **191** (see Ref. (99MI1)) with phosphonium salt **192** (2.1 equiv.) or phosphonate **193** (2.2 equiv.) in the presence of phase-transfer catalysts (99CP51) afforded compounds **189** and **190**, respectively, in 80–90% yields (99CC(C)2055). After crystallization, these compounds were isolated as pure *E*-isomers.



a - Bu^{n}Li, THF, - 78°C; *b* - DMF, - 78°C; *c* - 4-Bu$_2$NC$_6$H$_4$CH$_2$P$^+$Ph$_3$I$^-$ (**192**), Bu^{t}OK, CH_2Cl_2, 20°C, 5 h;

d - 4- $F_3CC_6H_4CH_2P(O)(OEt)_2$ (**193**), NaH, THF, 20°C, 24 h.

Polyfunctional thiophenes and enediynes were synthesized through the cleavage of the heterocycle in 3-lithiated thieno[2,3-*b*]- and -[3,2-*b*]thiophenes, 3,4-dilithiated thieno[2,3-*b*]thiophenes and 3,6-dilithiated thieno[3,2-*b*]thiophenes (97CC(C)2355, 99JCS(P1)1273, 2001IZV107). For example, tetrabromothieno[3,2-*b*]thiophene (**194**) (89BCJ1547) was successively treated with 2 equiv. of *n*-butyllithium (THF, 20 °C) and 2 equiv. of Bu^{t}Me$_2$SiCl to prepare dibromide **195**, which was treated with 1 equiv. of *n*-butyllithium. The corresponding bromothiophene **196** was isolated by flash chromatography on silica gel. Treatment of **196** with Bu^{n}Li (1 equiv.) and excess iodomethane afforded enediyne **197**. Both steps of ring opening can be carried out without isolation of intermediates (99JCS(P1)1273).



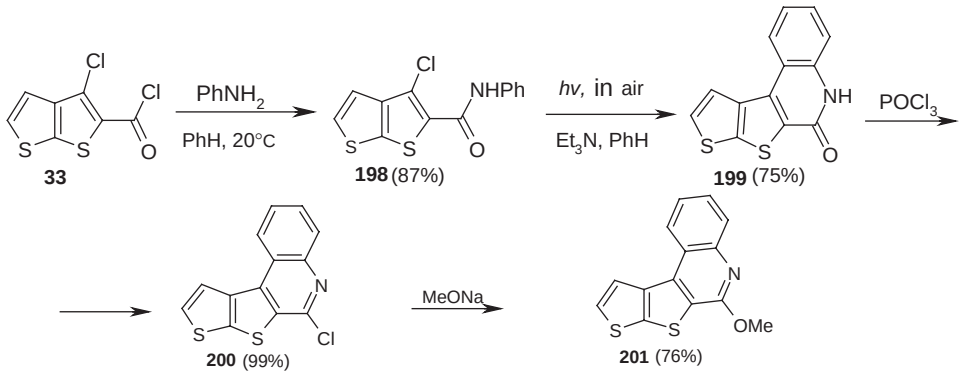
a - 1) $Bu^n Li$ (2 equiv.), THF, 20°C, 2) $Bu^t Me_2SiCl$ (2 equiv.);

b - $Bu^n Li$ (1 equiv.), - 78°C; *c* - $Bu^n Li$ (1 equiv.), O°C, MeI.

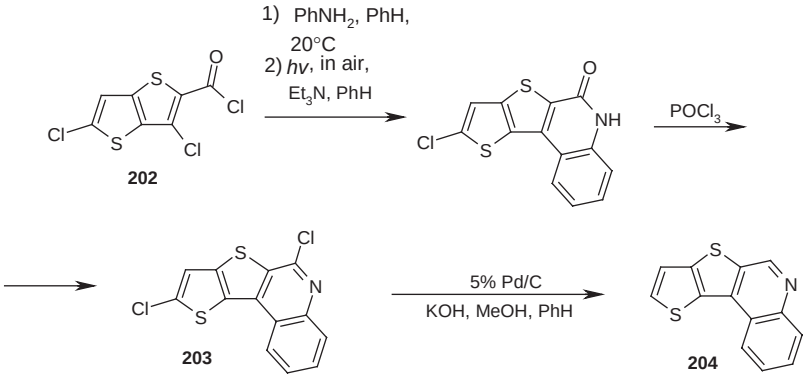
The above reactions exemplify the wide range of applications of metallation of thienothiophenes, which allows one to prepare new derivatives of this class of heterocycles, including those having useful properties.

2. *Photocyclization*

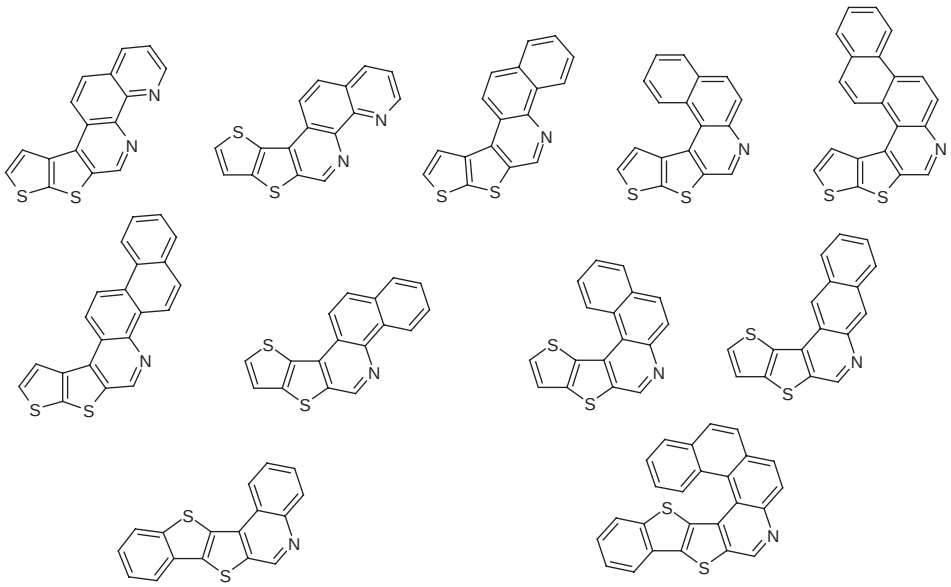
In the last decade, photocyclization (84MI1) of thienothiophenes and their derivatives (primarily amides) has attracted considerable attention as a convenient method for the synthesis of sulfur-containing polyannulated heterocyclic systems (88JHC1363, 91H2323, 91JHC737, 95H1659, 95JHC317, 95JHC659, 96JHC119, 96JHC185, 98JHC144). Two examples of the synthesis of such compounds are given below. The reaction of aniline with 3-chlorothieno[2,3-*b*]thiophene-2-carboxylic acid chloride **43** produced *N*-phenylthieno[2,3-*b*]thiophene-2-carboxamide **198** (72ACS2982, 88JHC1363). Photocyclization of the latter in benzene containing a small amount of triethylamine gave thieno[3′,2′:4,5]thieno[2,3-*c*]quinolin-2-one (**199**), whose chlorination with $POCl_3$ afforded 6-chlorothieno[3′,2′:4,5]thieno[2,3-*c*]quinoline (**200**). The reaction of compound **200** with sodium methoxide produced the corresponding methoxy derivative **201**. All steps of this transformation sequence gave products in good yields.



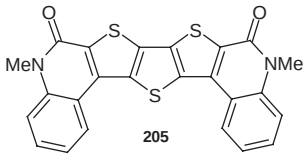
6,9-Dichlorothieno[2′,3′:4,5]thieno[2,3-*c*]quinoline (**203**) was synthesized from 3,5-dichlorothieno[3,2-*b*]thiophene-2-carboxylic acid chloride (**202**). Catalytic dechlorination of **203** afforded unsubstituted thieno[2′,3′:4,5]thieno[2,3-*c*]quinoline (**204**) (88JHC1363).



This procedure was employed to prepare various polyannulated thienothiophene- and benzo[*b*]thiophene-containing systems starting from thieno[2,3-*b*]- and -[3,2-*b*]thiophene-2-carboxylic acid chlorides (95H2691, 95JHC317, 96JHC119, 96JHC185, 98JHC1441). The structures of these compounds are given below.



Dithieno[3,2-*b*:2′,3′-*d*)thienyl[2″,3″-*c*:2″,3″-*c*′]-5,10-*N*,*N*″-dimethylquinoline-6,9-dione (**205**) was synthesized by double photochemical dehydrohalogenation of the corresponding thieno[3,2-*b*:2′,3′-*d*]thiophene-2,6-dicarboxanilide (95H2691).



205

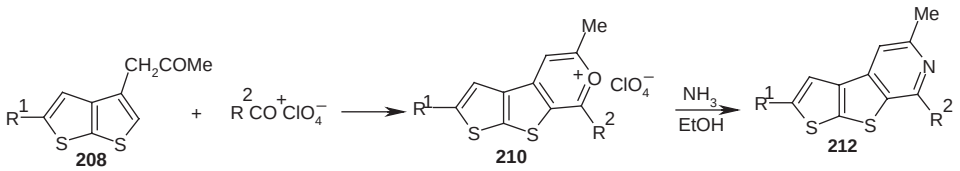
Conjugated thiophene polymers are of interest because of their electrical and optical properties. In this connection, photochemical polymerization of dithieno[3,2-*b*:2′,3′-*d*]thiophene **108a** and dithieno[3,4-*b*:3′,4′-*d*]thiophene **11** was studied. Irradiation of solutions containing dithienothiophene and an electron acceptor (e.g., *p*-dinitrobenzene, CCl_4) gives rise to polythienothiophenes with molecular mass of $\sim 10^4$. The radical cation of the starting thienothiophene is efficiently generated by photo-induced electron transfer from the excited state of the monomer to an electron acceptor. The subsequent coupling reaction affords polymers (95SM309, 96CL285).

3. *Fused Thienothiophenes and their Reactions*

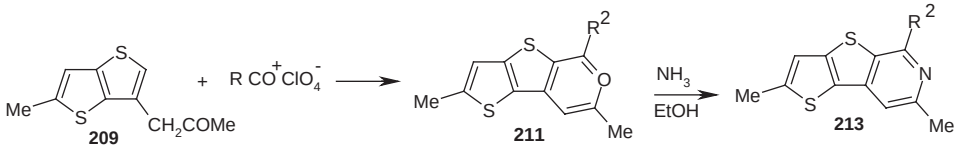
To construct additional heterocycles fused to the thienothiophene system, a number of approaches other than the above-mentioned photocyclizations were used. For example, heating 2-acetylamino-3-hydroxythieno[3,2-*b*]thiophene (**206**) in the presence of P_2S_5 afforded 2-methylthieno[3,2-*b*]thieno[3,2-*d*]thiazole (**207**) (76KGS1039). Isomeric 2-methylthieno[2,3-*b*]thieno[3,2-*d*]thiazole was prepared by oxidation of 2-thioacetylaminothieno[2,3-*b*]thiophene with $K_3Fe(CN)_6$ in aqueous alkali (65KGS619).

206 207

Acylation of 3-acetonyl-5-alkylthieno[2,3-*b*]thiophenes **208** and 3-acetonyl-5-methylthieno[3,2-*b*]thiophenes (**209**) in a mixture of aliphatic acid anhydride and perchloric acid (actually, acylium perchlorate) was demonstrated (79KGS1424) to occur at the free a position followed by cyclization and formation of perchlorates of tricyclic pyrylium salts **210** and **211** (yields >80%). The latter are transformed into thieno[2′,3′:5,4]- (**212**) and -[2′,3′:4,5]thieno[2,3-*c*]pyridines **213** in yields higher than 90% by passing ammonia through their suspensions.

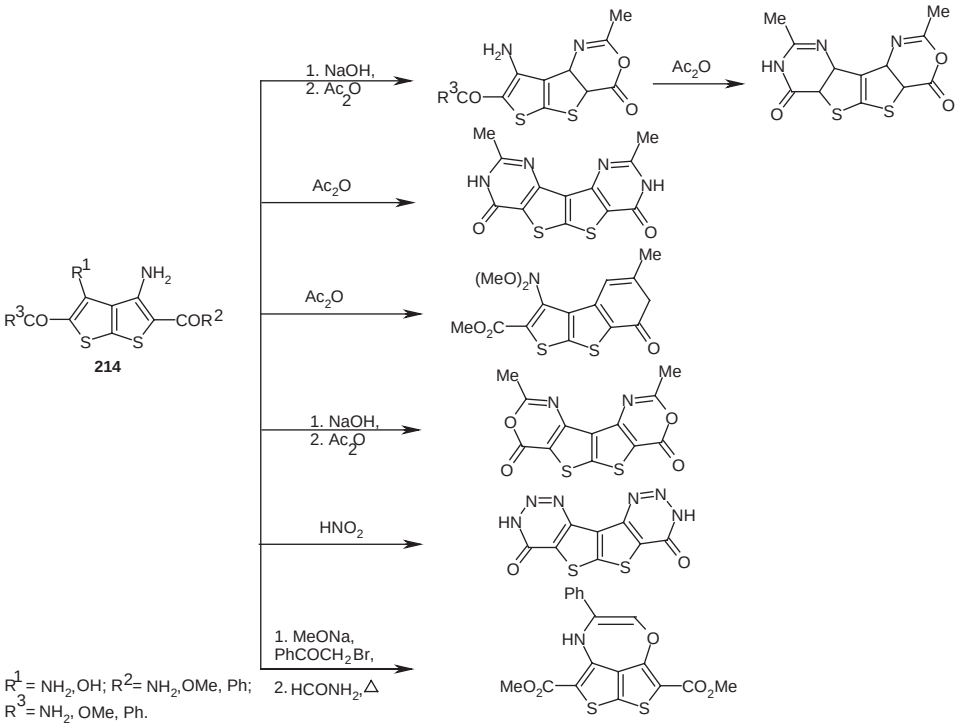


208 210 212



R^1= Me, Et; R^2= Me, Et, Bu^n.

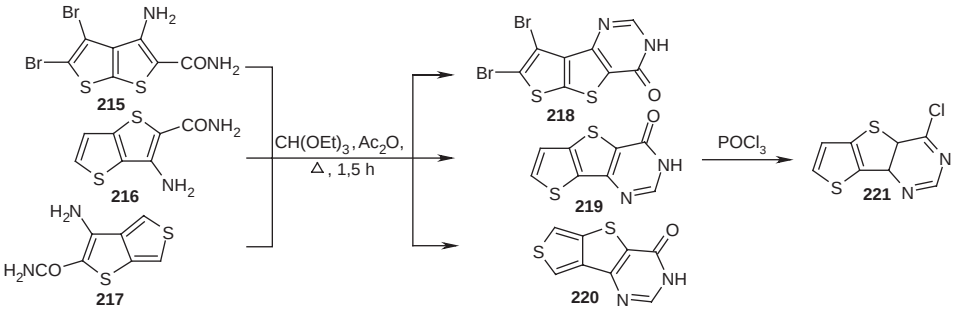
Functionalized thieno[2,3-*b*]thiophenes **214** were transformed according to conventional procedures into the following tri- and tetracyclic systems: thienopyrimidines, thieno-l,3-oxazines, bis(thieno-l,2,3-triazines), dithieno-1,4-oxazepines (90P895) (presented in Schemes) and fused thieno[2,3-*b*]thiophenes containing Py, pyrimidine, thiazine, thiazole, oxadiazole, isoxazole, pyrazole, pyridazine, piperazine, pyrrolopiperazine and other heterocyclic fragments (92PS73, 2000PS259, 2000PS45, 2000PS57).



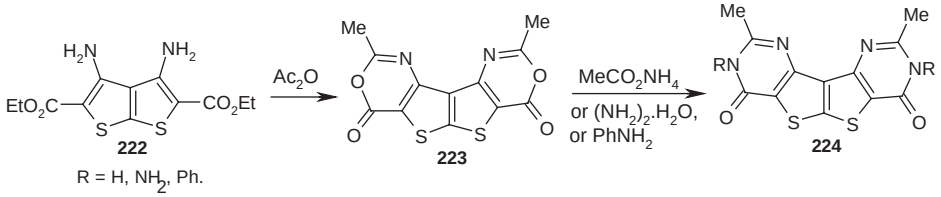
R^1 = NH_2, OH; R^2= NH_2, OMe, Ph;
R^3= NH_2, OMe, Ph.

The reactions of thienothiophenes **215–217** containing the amino- and carboxamide groups in adjacent positions with triethyl orthoformate in boiling acetic anhydride produce thieno[2′,3′:4,5]- (**218**), thieno[3′,2′:4,5]- (**219**) and thieno

[3′,4′:4,5]thieno[3,2-*d*]pyrimidin-7(6*H*)-ones (**220**), respectively (94JCS(P1)2735). The reaction of thienopyrimidine **219** with $POCl_3$ affords 7-chloro derivative **221**.

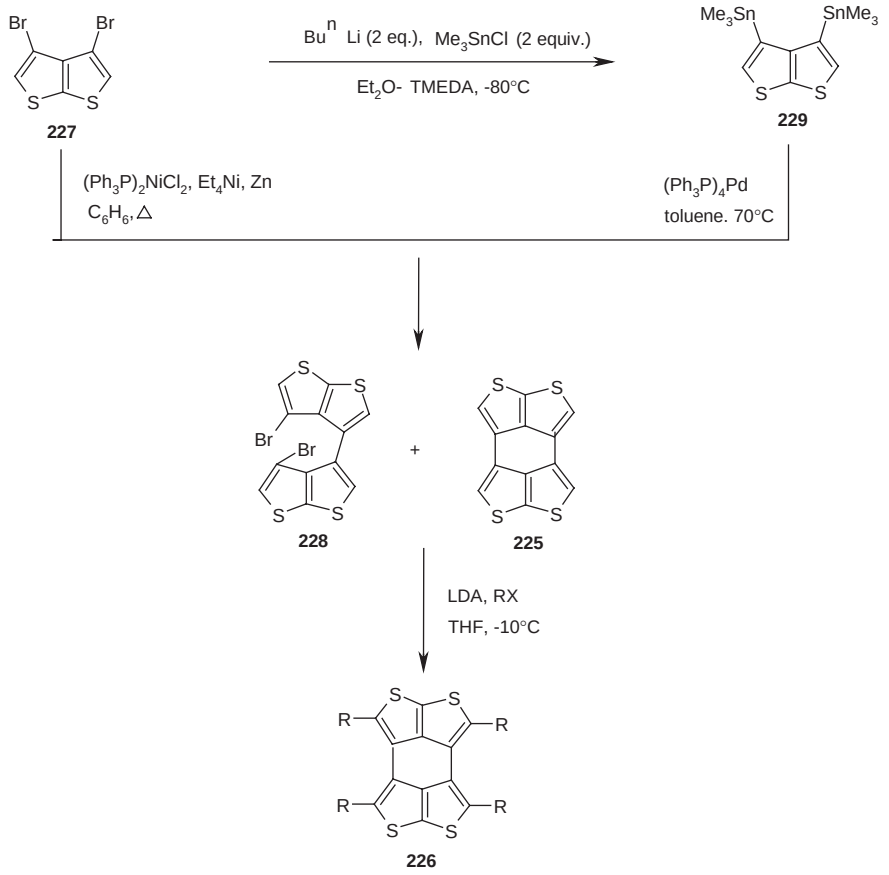


Treatment of diethyl 3,4-diaminothieno[2,3-*b*]thiophene-2,5-dicarboxylate (**222**) with acetic anhydride afforded symmetrical tetracyclic derivative **223**, whose reactions with ammonium acetate, hydrazine hydrate or aniline produced its nitrogen analogues **224** (92PS73).



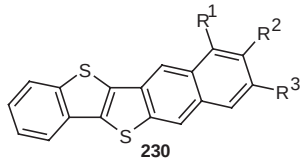
2,3,6,7-Tetrathiabenzo[l,3-*cd*:4,6-*c′d′*]dipentalene (**225**) and its derivatives **226** are new fused polynuclear heteroarenes isoelectronic with perylene. Dipentalene **225** was prepared for the first time by dimerization of thieno[2,3-*b*]thiophene (**142**) (92PS73). More recently, it was found that catalytic reduction of 3,4-dibromothieno[2,3-*b*]thiophene (**227**) with an excess of activated zinc in the presence of bis(triphenylphosphine)nickel(II) chloride and tetraethylammonium iodide afforded only 4,4′-dibromo-3,3-bis(thieno[2,3-*b*]thiophene) (**228**) (in a maximum yield of 28%) (89AG1254). However, the reaction in the presence of a larger amount of the nickel catalyst afforded also dipenatlene **225**. Optimization of the reaction conditions made it possible to increase the yield of the latter to only 14%. An alternative procedure was employed to transform thienothiophene **227** into trimethylstannyl derivative **229**. The reaction of thienothiophene **227** with organotin intermediate **229** in the presence of the palladium triphenylphosphine complex afforded dipentalene **225** (13% yield). Derivatives **226** were prepared by lithiation of

dipentalene **225** followed by the reaction with the corresponding alkyl iodide or dialkyl disulfide (86MI1).



The oxidation potential of heteroarene **225** is equal to that of perylene, and compound **225** forms an analogous complex with iodine having rather high conductivity ($0.11\,S\,cm^{-1}$). However, it appeared that complexes of all derivatives **226** with iodine have low conductivity. In addition, compounds **225** and **226** form charge-transfer complexes with strong electron acceptors, such as 7,7,8,8-tetracyanoquinodimethane (TCNQ), 2,3,5,6-tetrafluoro-7,7,8,8-tetracyanoquinodimethane ($TCNQF_4$), 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ) and l,l,2,3,4,4-hexacyano-l,3-butadiene (HCBD) (86MI1, 89AG1254). However, the majority of these π complexes are low-conducting powdered polymers, whereas complexes of tetrakis(methylthio) derivatives **226** (R = SMe) form crystalline radical-cation salts with a conductivity of about $10^{-3}\,S\,cm^{-1}$.

Friedel–Crafts condensation of benzo[*b*]thieno[3,2-*b*]thiophene-2-carboxylic acid chloride with *m*- and *p*-xylene affords ketones, which undergo Elbs pyrolysis (420 °C, 15 min) to form pentacyclic derivative **230** (2000JA1082). Analogous products were prepared from benzo[*b*]thieno[3,2-*b*]thiophene and (di)methyl homologues of benzoyl chloride.



230

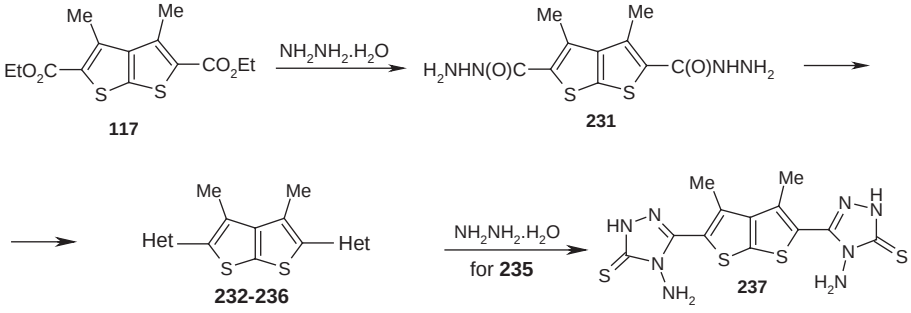
$R^1 = R^2 = R^3 = H$; $R^1 = Me$, $R^2 = R^3 = H$; $R^2 = Me$, $R^1 = R^3 = H$; $R^3 = Me$, $R^1 = R^2 = H$.

Cyclization of benzo[*b*]thieno[3,2-*b*]thiophene-2-butyric acid in the presence of P_2O_5 gives benzo[*b*]thieno[3,2-*b*]benzo[*b*]thiophene (**121**) in 80% yield (92BCJ1855).

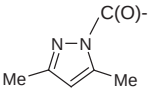
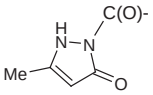
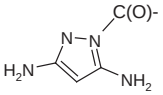
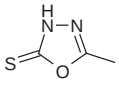
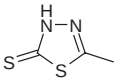
4. *Other Transformations*

This section deals with the most interesting reactions of thienothiophenes giving rise to various sulfur-containing heterocyclic systems.

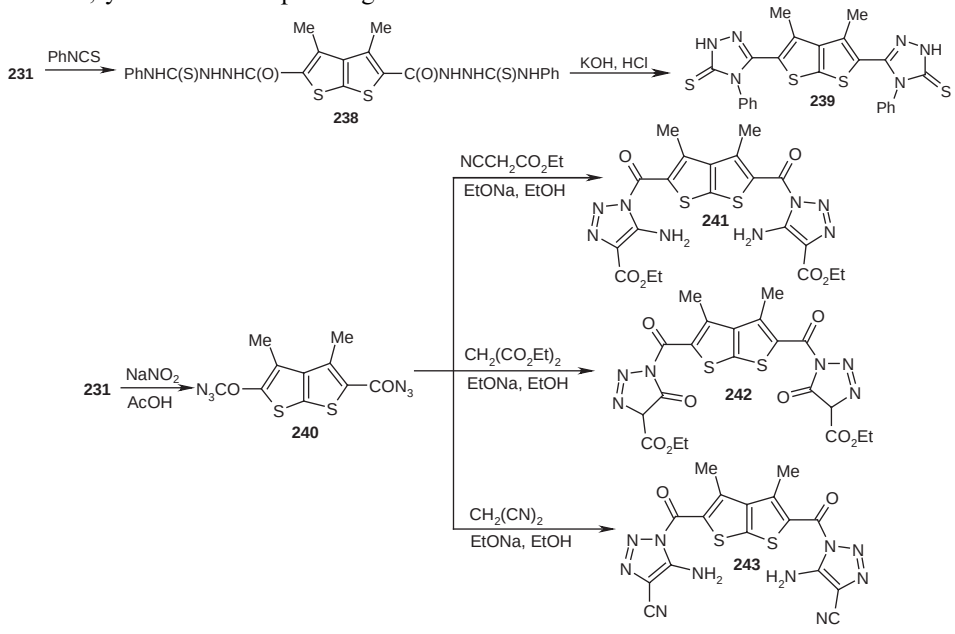
The reaction of diethyl 3,4-dimethylthieno[2,3-*b*]thiophene-2,5-dicarboxylate (**117**, R = Me, EWG = CO_2Et) with hydrazine hydrate afforded dihydrazide **231**, which was subjected to various transformations. For example, the reactions with acetylacetone, ethyl acetoacetate or malononitrile (93BCJ2011) are accompanied by the closure of the exocyclic pyrazole ring to form the corresponding derivatives **232–234**. The reaction of dihydrazide **231** with carbon disulfide in the presence of KOH followed by decomposition with dilute HC1 or concentrated H_2SO_4 produces di(oxadiazole) (**235**) or di(thiadiazole) derivative (**236**). Condensation of di(oxadiazolyl)thienothiophene **235** with hydrazine hydrate affords di(triazolyl)thienothiophene **237**.



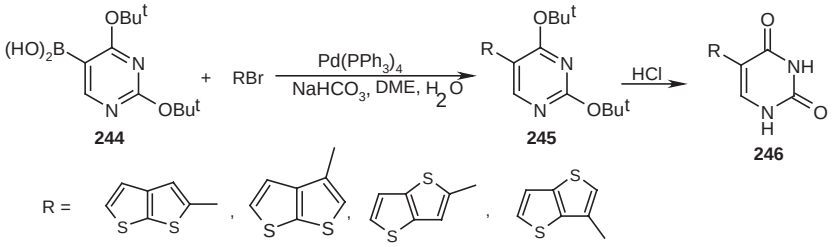
117 **231** **232-236** **237**

Compound	Het	Reaction conditions	Yield (%)
232		CH_2Ac_2, fusion	88
233		$AcCH_2OEt$, EtOH, AcOH	79
234		$CH_2(CN)_2$, EtOH, Pip	73
235		1) CS_2, KOH, 2) HCl	82
236		1) CS_2, KOH, 2) H_2SO_4	85

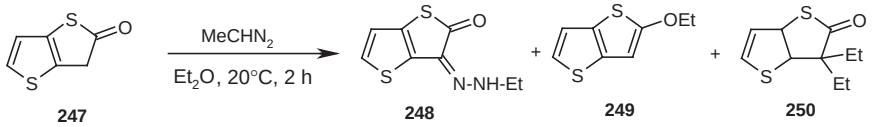
Dihydrazide **231** was also used in the synthesis of thienothiophenes containing triazole substituents. For example, the reaction with phenyl isothiocyanate in ethanol produces di(*N*-phenylthiocarbamoyl)carbohydrazide **238**, whose treatment with KOH followed by acidification affords compound **239**. Diazotization of dihydrazide **231** with 10% sodium nitrite in acetic acid gives diazide **240**. The reactions of the latter with compounds containing the active methylene group, viz., ethyl cyanoacetate, malononitrile or diethyl malonate, in the presence of sodium ethoxide, yield the corresponding ditriazole derivatives **241–243**.

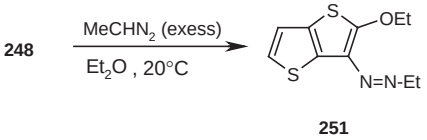


In the presence of zero-valent palladium complexes as the catalyst, 2,4-di-*tert*-butoxypyrimidine-5-boronic acid (**244**) reacts with the bromine derivatives of thieno[2,3-*b*]- (**142**) and thieno[3,2-*b*]thiophene (**145**) (90JHC2165, 91JHC1623). This reaction was used to introduce fragments of isomeric thienothiophenes at position 5 of 2,4-di-*tert*-butoxypyrimidine. The resulting compounds **245** were transformed into uracils **246** in quantitative yields.

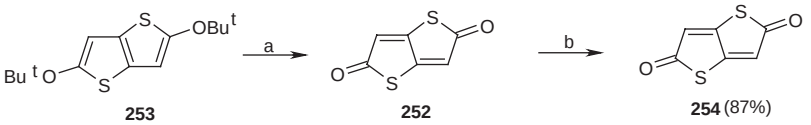


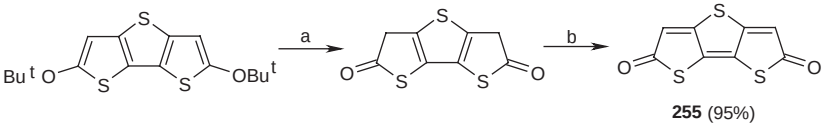
After the reaction of thieno[3,2-*b*]thiophen-2(3*H*)-one (**247**) with diazoethane in diethyl ether, thieno[3,2-*b*]thiophene-2,3-dione 3-ethylhydrazone (**248**), 2-ethoxythieno[3,2-*b*]thiophene (**249**) and 3,3-diethylthieno[3,2-*b*]thiophen-2-one (**250**) were isolated from the reaction mixture (75JOC3392). The reaction of hydrazone **248** with diazoethane yielded 2-ethoxy-3-ethylazothieno[3,2-*b*]thiophene (**251**).





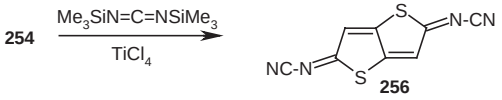
Dehydrogenation of dione **252**, which was prepared by treatment of 2,5-di(*tert*-butoxy)thieno[3,2-*b*]thiophene (**253**) with *p*-toluenesulfonic acid, with DDQ in dioxane gave 2,5-dioxothieno[3,2-*b*]thiophene (**254**) (91CL1117). 2,6-Dioxo-thieno[3,2-*b*]thieno[2′,3′-*d*]thiophene (**255**) was prepared according to an analogous procedure.



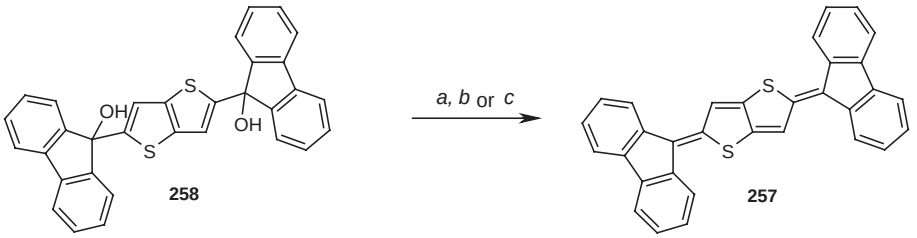


a: TsOH, C_6H_6, △, 2 h; b: DDQ, dioxane, △, 5 h.

Dicyanodiimide **256** and its various derivatives were synthesized starting from dione **254**. These compounds form high-conducting charge-transfer complexes (90AG(E)204).

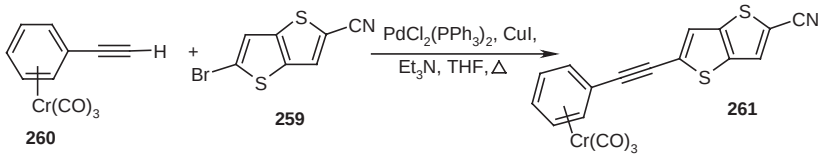


Fluorenylidene derivative **257** was synthesized from diol **258** according to three procedures: by heating without a solent (35% yield) and by irradiation for 5–10 h in the solid state (~10%) or in a solution in CH_2Cl_2 (86%). Irradiation was carried out using a high-pressure mercury lamp through a Pyrex filter (91TL4367).



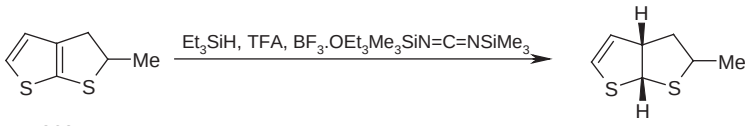
a - > 200°C; *b* - *hv*; *c* - CH_2Cl_2.

Recently, the first example of Pd-catalysed coupling of bromothienothiophene **259** with the chromium tricarbonyl complex of phenylacetylene (**260**) giving rise to complex **261** has been published (2000TL3607).



Catalytic liquid-phase oxidation of 3-methylthieno[2,3-*b*]- and -[3,2-*b*]thiophenes in the presence of cobalt acetate and NaBr in acetic acid (90–110 °C) gave rise to thieno[2,3-*b*]thiophene-2-carboxylic acid (**41**) and the 3-formyl derivative, respectively (75KGS492). The kinetic data provide evidence that electron transfer from the peroxy radical to Co^{2+} is the rate-determining step.

Ionic hydrogenation of 2-methyl-2,3-dihydrothieno[2,3-*b*]-thiophene (**262**) affords *cis*-2,8-dithiabicyclo[3.3.0]octane (**263**) (79MI1).



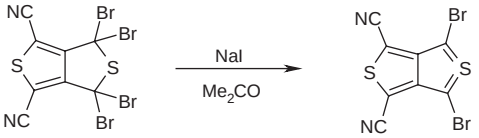
262 **263** (25%)

Et_3SiH, TFA - is trifluoroacetic acid.

Desulfurization of methyl 5,6-dibromo-3-chlorothieno[3,2-*b*]thiophene-2-carboxylate with a Ni–Al melt in a 10% NaOD–D_2O solution produced methyl heptanoate containing 96% of deuterium (94MI2).

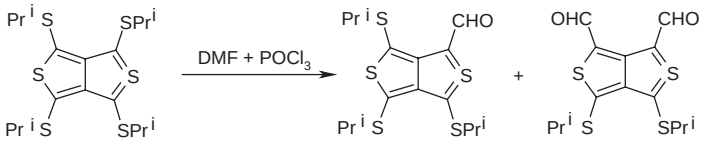
As mentioned above, thieno[3,4-*c*]thiophene is most difficult to synthesize compared to all other isomeric thienothiophenes. A few of its derivatives are known: tetraphenyl- (67JA3639, 73JA2558, 73JA2561), tetrakis(alkylthio)- (85JA5801), tetra(2-thienyl)- [42], tetrabromo-, l,3-dibromo-4,6-dicyano-, 1,3-dibromo-4,5-bis (methoxycarbonyl)- (94JOC2223), 1,4-bis(*tert*-butylthio)-3,6-diphenyl- and 3,6-di (2-thienyl)thieno[3,4-*c*]thiophenes (98JOC163).

The synthesis of l,3-dibromo-4,6-dicyanothieno[3,4-*c*]thiophene (**264**) by the reaction of tetrabromide **265** with Nal in acetone is the first example of the synthesis of a stable thieno[3,4-*c*]thiophene derivative (89CC223).



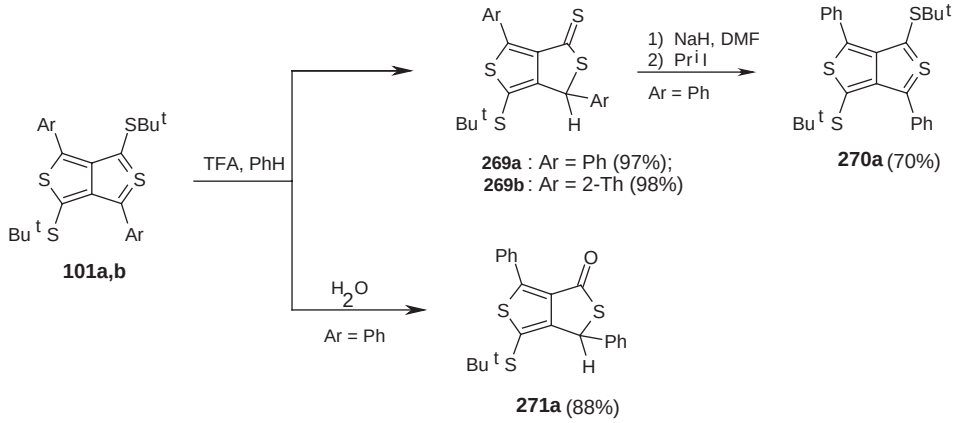
265 **264**

Mono- (**266**) and diformyl derivatives **267**, which were prepared by formylation of 1,3,4,6-tetrakis(isopropylthio)thieno[3,4-*c*]thiophene (**268**) with the Vilsmeier reagent, also proved to be rather stable (76TL2581).



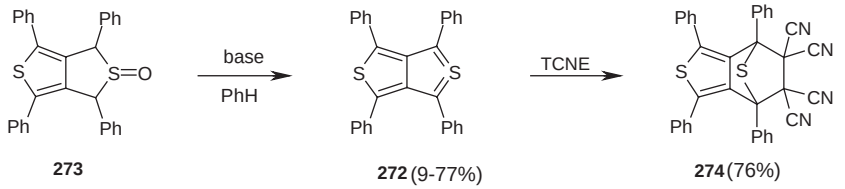
268 **266** (33%) **267** (14%)

The reactions of thienothiophenes **101a, b** with trifluoroacetic acid are accompanied by protonation of the thienothiophene system, resulting in Bu^t–S bond cleavage to form the corresponding thieno[3,4-*c*]thiophene-1(*3H*)-thione (**269a, b**) (96CL421, 98JOC163). Treatment of thienothiophene **269a** with sodium hydride and isopropyl iodide leads to regeneration of the thieno[3,4-*c*]thiophene system to give l-(*tert*-butylthio)-3,6-diphenyl-4-(isopropylthio)thieno[3,4-*c*]thiophene (**270a**). The reaction of thienothiophene **101a** with trifluoroacetic acid in the presence of 10 equiv. of water is accompanied by elimination of one sulfur-containing group to form 4-(*tert*-butylthio)-3,6-diphenylthieno[3,4-*c*]thiophen-l(3*H*)-one (**271**).

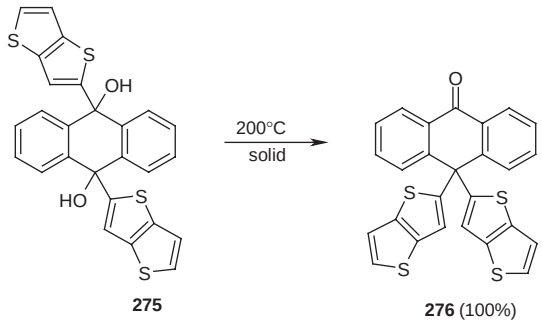


Cycloaddition of thienothiophenes **101a, b** to *N*-phenylmaleimide and dimethyl acetylenedicarboxylate was described (98JOC163).

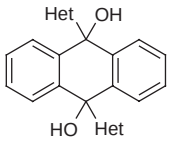
1,3,4,6-Tetraphenylthieno[3,4-*c*]thiophene (**272**) was derived from a mixture of *cis*- and *trans*-sulfoxides **273** by dehydration with bases ($Ba(OH)_2$, MeMgBr, EtMgBr, MeLi and LDA). Product **272** was isolated either directly or as adduct **274** with TCNE (76TL2581).



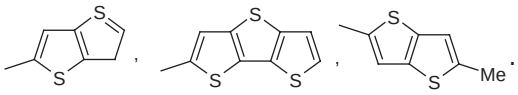
The reactions of thienothiophene derivatives in the absence of a solvent were also described. For example, the solid-state thermally induced rearrangement of 9,10-dihydroxy-9,10-bis(thieno[3,2-*b*]thiophen-2-yl)-9,10-dihydroanthracene (**275**) occurs at 240 °C and gives 10,10-bis(thieno[3,2-*b*]thiophen-2-yl)anthrone (**276**) (2000JA1082).



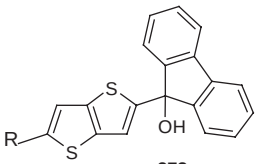
(Thienothienyl)anthracenes **277** were subjected to analogous transformations to prepare the corresponding anthrones.



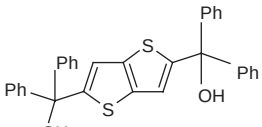
277

Het = 

(Hydroxyfluorenyl)thieno[3,2-*b*]thiophenes **278a–c** and their diphenyl analogue **279** were subjected to methanolysis (2001JOC803). Substitution of the hydroxy function with the methoxy group requires specific reactions conditions for each substrate.



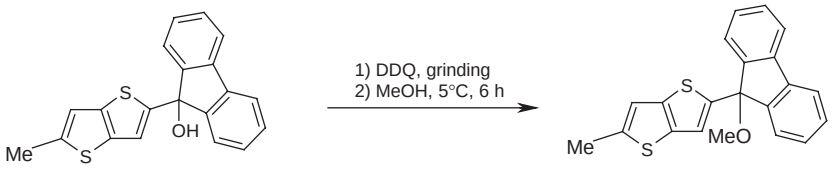
278



279

R = Me (***a***), Cl (***b***), 9-hydroxyfluoren-9-yl (***c***).

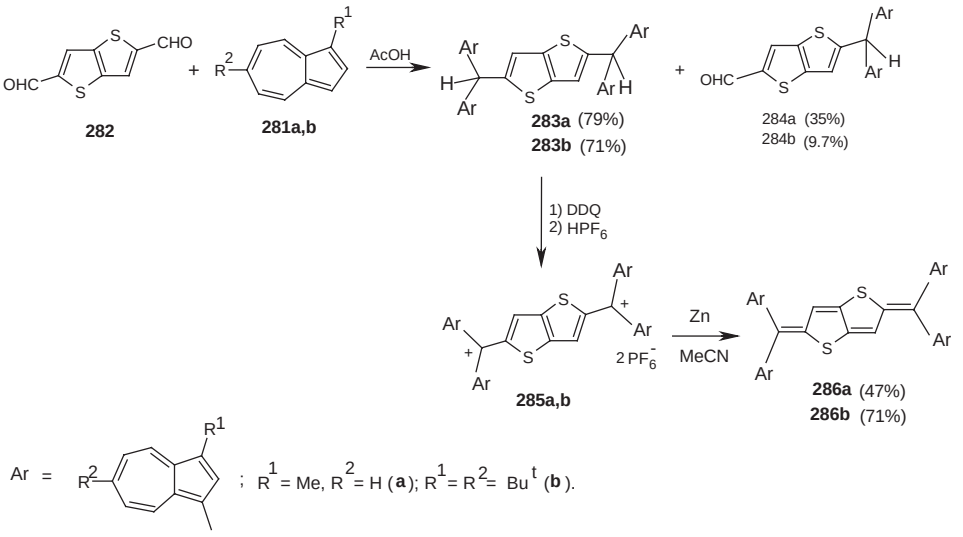
For example, 2-(9-methoxyfluoren-9-yl)thieno[3,2-*b*]thiophene (**280**) was prepared by careful by grinding an equimolar mixture of 5-(9-hydroxyfluoren-9-yl)-2-methylthieno[3,2-*b*]thiophene (**278a**) with DDQ followed by storage of the resulting dark-green powder in methanol at a temperature below 5 °C for 6 h.



278a **280** (42%)

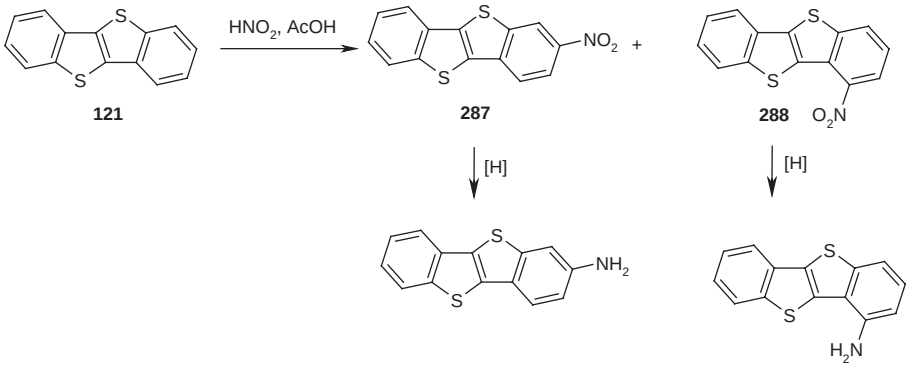
The reaction of 1-methyl- or l,6-di-*tert*-butylazulenes (**281a, b**) with 2,5-diformylthieno[3,2-*b*]thiophene (**282**) in acetic acid afforded diazulenylmethylthieno[3,2-*b*]thiophenes **283a, b** along with products **284a, b** resulting from the reaction at one aldehyde group (2001JOC2470). The reaction of thienothiophenes

283a, b with 2 equiv. of DDQ produced dications, which were isolated as stable hexafluorophosphates **285a, b** by treating the reaction mixture with a 60% HPF_6 aqueous solution. Treatment of salts **285a, b** with zinc powder in acetonitrile afforded 2,5-bis[di(azulenyl)methylene]-2,5-dihydrothieno[3,2-*b*]thiophenes (**286a, b**).

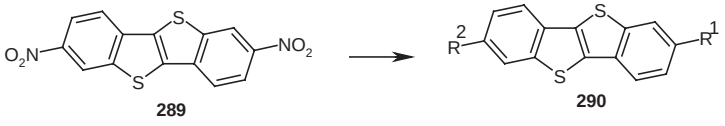


Electrophilic substitution reactions were studied for thienothiophenes annulated with one or two benzene rings. For example, benzo[*b*]thieno[2,3-*b*]- and -[3,2-*b*]thiophenes and their 3-methyl derivatives undergo bromination, Vilsmeier–Haack formylation and Friedel–Crafts acylation at position 2. These results agree well with their calculated electron densities (71G774, 70JCS243, 71JCS463, 71JCS1308). When these compounds contain a methyl group at position 2, bromination occurs at position 3, whereas the direction of acylation of 2-methylbenzo[*b*]thieno[2,3-*b*]thiophene depends on the reaction conditions and the reaction produces either a 3- or 6-acetyl derivative. Bromination of 3-formyl-substituted benzo[*b*]thienothiophenes affords 2-bromo derivatives, whereas the reactions with 2-formyl-substituted derivatives are accompanied by a loss of the formyl group to give, respectively, 2,3-dibromobenzo[*b*]thieno-[2,3-*b*]- or 2,6-dibromobenzo[*b*]thieno[3,2-*b*]thiophenes. Nitration of 2-formyl derivatives also leads to the replacement of the formyl group and the formation of 2-nitro derivatives as the major product (71JCS1308).

Nitration of benzo[*b*]thieno[3,2-*b*]benzo[*b*]thiophene **121** containing two fused benzene rings with concentrated nitric acid ($d = 1.51\ g\,cm^{-3}$) in acetic acid produced 2- (**287**) and 4-nitro derivatives (**288**), which were reduced to the corresponding amines (80ZOR438).



Earlier (69USP3433874), it has been reported that nitration of benzo-thienobenzothiophene **121** with a mixture of nitric and acetic acids led to substitution at the carbon atoms in both rings to give 2,7-dinitrodibenzo[*b*]thieno[3.2-*b*]thiophene **289** in low yield. The latter was transformed according to conventional synthetic procedures into derivatives **290** containing various electron-donating and electron-withdrawing substituents (80ZOR430).

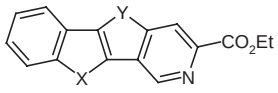


289 **290**

$R^1 = R^2 = NH_2$; $R^1 = NH_2$, $R^2 = NO_2$; $R^1 = R^2 = Cl$; $R^1 = R^2 = Br$; $R^1 = OH$, $R^2 = Cl$; $R^1 = NH_2$, $R^2 = Cl$; R^1 – NO_2, $R^2 = OH$; $R^1 = OMe$, $R^2 = NO_2$; R^1 - NH_2, $R^2 = OMe$; R^1 - $R^2 = NHAc$; $R^1 = R^2 = NHCOCF_3$; $R^1 = NO_2$, $R^2 = NHCOCF_3$; $R^1 = NHAc$, $R^2 = Cl$; R^1 - NHAc, $R^2 = OMe$.

Nitration of 2-benzoyl- and 4-acetylaminobenzo[*b*]thieno[3,2-*b*]thiophenes with nitric acid occurs predominantly at the *o*-position with respect to the substituent to give the nitro derivative, whose deacylation and reduction afford 1,2- and 3,4-diaminobenzo[*b*]thieno[3,2-*b*]benzo[*b*]thiophenes in high yields (89MI1).

Thermal decomposition of azidoacrylates, which were prepared by condensation of ethyl azidoacetate with heteroaromatic aldehydes, produced a series of the previously unknown fused heteroaromatic analogues of isoellipticine **291** (98HEC227).



291

X, Y = S, Se.

The above-considered transformation convincingly demonstrates a high synthetic potential of thienothiophene derivatives.

IV. Molecular Structures and Physical Properties

Theoretical aspects of the structures, reactivities and physicochemical properties of isomeric thienothiophenes have attracted considerable attention. Early reviews are available (76AHC123, 76MI1) and other publications (see, for example, Refs (67CCA119, 67TL2889, 67TL5257, 67ZN1475, 68JMS181, 68TCA247, 69TL239)).

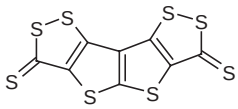
A. Structures

In the last 25 years, X-ray diffraction analysis has been particularly widely used (along with other methods) to determine the structures of thienothiophenes. For example, the crystal structures of the following compounds were established by X-ray diffraction: 3,4-dibromothieno[2,3-*b*]thiophene (86MI1), 2,2,5,5-tetramethyl-2,3,5,6-tetrahydrothieno[3,2-*b*]thiophene-2,6-dione (**127**) (the main chromophoric system of the thioindigo-like dye having the *trans*-(*S*)-*trans*-(*S*)-*trans*-configuration) (77CB1421, 78CB3233), (5-benzoyloxymethyl)thieno[2,3-*b*]thiophene-5-sulfamide 6,6-dioxide (99JHC249), nitronyl nitroxide and imino nitroxide free radicals bound to isomeric thieno[2,3-*b*]- and -[3,2-*b*]thiophenes (95JOC2092), 2,3:5,6-bis(ethylenedithio)thieno[3,2-*b*]thiophene (95BCJ1193), 1,2-bis{2-methyl-5-(2-benzothiazolyl)-6-trifluoromethylthieno[3,2-*b*]thiophen-3-yl}hexafluorocyclopentane (93TL5653), 2,5-bis(dicyanomethylene)-2,5-dihydrothieno[3,2-*b*]thiophene (84MI1) and the 3,6-dimethylselenolo[3,2-*b*]thiophene dimer (96T471).

Recently, it has been demonstrated that 2,5-bis(9-hydroxyfluoren-9-yl)thieno[2,3-*b*]- and -[3,2-*b*]thiophenes form crystalline inclusion guest–host complexes with EtOH, Pr^{n}OH, Pr^{i}OH, DMSO, Me_2SO and benzene, and the structures of these clathrates were established by X-ray diffraction (92CC1381, 92MCL75, 94AM654, 94CC2351, 94MCL81, 94TL5883, 98CC(C)1965, 95JOC6342, 99CSJ1395).

The structures of l,3,4,6-tetraphenylthieno[3,4-*b*]thiophene (**272**) (83JA1705), l,4-bis(*tert*-butylthio)-3,6-diphenylthieno[3,4-*c*]thiophene, 4-(*tert*-butylthio)-3,6-diphenylthieno[3,4-*c*]thiophene-l(3*H*)-thione, 4-*(tert*-butylthio)-3,6-diphenylthieno[3,4-*c*]thiophen-l(3*H*)-one (98JOC163), and Pt and Au complexes of polyyne polymers on the base of 2,5-bis(trimethylsylilethenyl)thieno[3,2-*b*]thiophene were also characterized by X-ray diffraction (2004AX(C)o1202).

Study of the crystal structure of sulfur-containing heterocyclic compound **292**, prepared by the reaction of diethyl dihydroxythieno[2,3-*b*]thiophene-2,5-dicarboxylate with Lawesson's reagent in the presence of sulfur, revealed the presence of a three-dimensional *S*–*S* interaction (93ZN1621).



292

The π-electron structure of thiophene, isomeric thienothiophenes and other fused sulfur-containing compounds (58 compounds, including those annulated with the

benzene and naphthalene rings) was detected by correlating the degree of sulfur participation with the ability to propose resonance structures involving the whole hydrocarbon part of the molecule (80T2711).

Bicyclic conjugated systems consisting only of five-membered heterocycles were studied theoretically. The authors used the topological resonance energy (TRE) as a new aromaticity index (77CCA107), which correctly predicts the aromatic behaviour of all groups of isomeric heteroaromatic systems, including thienothiophenes. These isomers are referred to as positional isomers, because they formally differ only in the position of σ-bivalent heteroatoms and can be considered as a special group in accordance with the mode of their annotation. The calculated TREs agree well with the experimental values (77CCA107, 77JA1692).

The geometries, electronic structures and electronic spectra of stilbene derivatives and chromophores based on dithienothiophenes are systematically studied by AM1 and INDO/CI method. On the basis of correct UV–Vis spectra, the position and strength of the two-photon absorption can be predicted (2001MI1).

To study the effect of the nature of the heteroatom on the aromatic system, the photoelectron spectra of thieno[2,3-*b*]thiophene (**142**), thieno[3,2-*b*]thiophene (**145**) (73T3085), thieno[2,3-*b*]selenophene (**143**), selenolo[3,2-*b*]selenophene (**147**), thieno[2,3-*b*]pyrrole, selenolo[2,3-*b*]pyrrole, pyrrolo[2,3-*b*]pyrrole and selenolo[3,2-*b*]pyrrole (77JOC2230) were measured and analysed. The replacement of the sulfur atom with selenium causes slight changes in all characteristics in accordance with the simple excitation theory. The replacement of the sulfur or selenium atom with the NH group influences the π-electron system. In this case, an increase in the resonance integral of the bonds including the heteroatom is compensated by a strong destabilizing inductive effect due to N–H bond polarity. The efficient electronegativity of the NH group was found to differ only slightly from that of the sulfur atom (77JOC2230).

Thieno[3,2-*b*]thiophene (**145**), thieno[3,2-*b*]thieno[2′,3′-*d*]thiophene (**108a**), thieno[2″,3″:4′,5′]thieno[2′,3′-*d*]-thieno[3,2-*b*]thiophene (**6**) and dithieno[2,3-*d*:2′,3′-*d*′]thieno[3,2-*b*:4,5-*b*′]thiophene (**7**) were studied by gas-phase and solid-state photoelectron spectroscopy (99CP51). For tetrathienocene **6**, the ionization energy for the gas phase (7.22 eV) differs substantially from that for the solid state (4.86 eV), resulting in an increase in the polarization energy by 2.36 eV, which is larger than the calculated value (1.83 eV). This phenomenon was interpreted in terms of intramolecular orbital interactions for the solid state of polythienothiophene **6**. This interaction is not observed for lower homologues (thienothiophenes **145** and **108a**).

Recently, among isomeric thienothiophenes, thieno[3,4-*c*]thiophenes have attracted the most attention from both the theoretical and spectroscopic points of view as 10 π-electron heterocycles having a non-classical structure (68T2567, 70JA1453, 72AX(B)1336, 74JA1817, 76JA7187, 78JA3893, 83JA1705, 83JA1979, 86JA4303, 88JA1793, 98JOC163). Examination of the photoelectron and UV–Vis absorption spectra of 1,3,4,6-tetraphenylthieno[3,4-*c*]thiophene (**240**) (78JA3893) confirmed the singlet aromatic ground state of the molecule predicted by quantum-chemical calculations (83JA1705) (by the MINDO/3 method without allowance for *d*-orbital interactions).

In the π-electron approximation of the MO LCAO SCF method, a procedure was developed on the basis of the Longuet–Higgins model to account for the d-orbitals of the sulfur atoms. The chemical shifts in the ^{1}H and ^{13}C NMR spectra, the lowest singlet–singlet and singlet–triplet transitions and the dipole moments of a series of sulfur-containing heterocyclic systems, including thieno[2,3-*b*]thiophene (**142**), thieno[3,2-*b*]thiophene (**145**) and thieno[3,4-*c*]thiophene, were calculated (81MI3). These results are in agreement with experimental data.

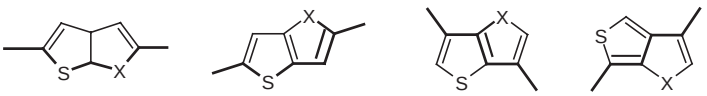
The multiplicity of the ground state, *p*-stability (''aromaticity''), the order and energy of the electron-excited and ionic states of thieno[3,4-*c*]thiophene were studied (93ZN1621). In particular, this compound was demonstrated to have ''aromaticity'' analogous to that of thiophene, but it is much less stable due to a specific structure of its highest occupied molecular orbital.

B. NMR Spectra

NMR spectroscopy along with and combined with other physicochemical methods is widely used to study the chemical structures of thienothiophenes and their hetero-analogues. In the study (82CS75), CNDO/2 calculations were carried out for selenophene and [2,3-*b*]-, [3,2-*b*]- and [3,4-*b*]-annulated selenolothiophenes **143, 144, 146** and **149–151**. Correlations between the calculated electron density and experimental ^{77}Se NMR chemical shifts in the spectra of these compounds were revealed. The chemical shifts were demonstrated to depend substantially on both the total and π-electron density on the selenium atom.

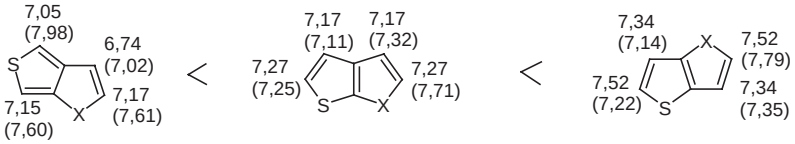
The ^{1}H, ^{13}C and ^{77}Se NMR spectra of selenolo[2,3-*c*]thiophene (**149**) (81IZV1285), selenolo[2,3-*b*]selenophene (**144**) (76CS159), selenolo[3,2-*b*]selenophene (**146**) (74CS236), selenolo[3,4-*b*]selenophene (**151**) (80T3317) and a series of 2-substituted selenolo[2,3-*b*]selenophenes (83CS22) and -[3,2-*b*]selenophenes (84JMS345) were measured and analysed.

The ^{1}H NMR spectra of isomeric thienothiophenes, selenolothiophenes and their derivatives (70ACS105, 70RTC77, 73JPR850) revealed long-range spin–spin coupling through five and six bonds located in a ''direct zigzag'' system. This phenomenon is analogous to that observed in a series of other bicyclic systems including sulfur, nitrogen and oxygen atoms (see, for example, Ref. (65TL2393)).



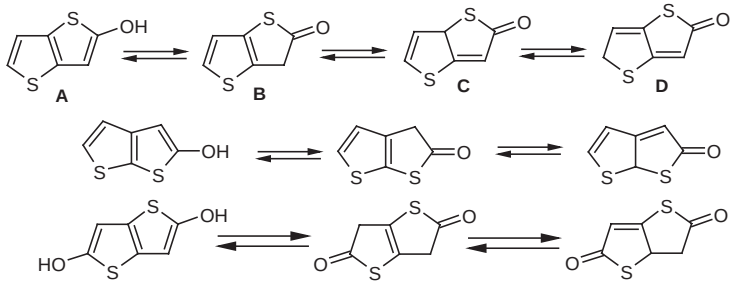
X = S, Se.

It was also concluded that the signals for the α- and *β*-protons of isomeric thieno- and selenolothiophenes are characteristic of different modes of fusion of heterocyclic rings (76MI1). The chemical shifts of annulated thiophenes with X = S are given below (the values for X = Se are given in parentheses).

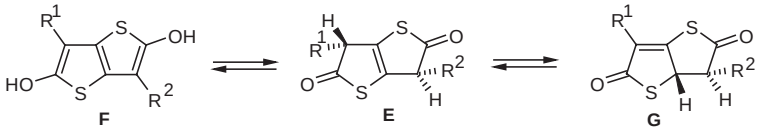


The spectra of isomeric selenolothiophenes are characterized also by spin–spin coupling between the ^{77}Se atom (spin 1/2) and protons of the selenophene fragment (73JPR850) analogous to that observed in selenides of the thiophene series (71ZOR1257).

Tautomerism of 2-hydroxythieno[2,3-*b*]- and -[3,2-*b*]thiophenes, 2,5-dihydroxythieno[3,2-*b*]thiophene and their alkyl- and aryl-substituted derivatives was also examined by NMR spectroscopy (75JOC3384, 78JOC2197). These compounds were demonstrated to occur predominantly as thiolactones rather than in the hydroxy form. For the thieno[2,3-*b*]thiophene system, this equilibrium is completely shifted to thieno[2,3-*b*]thiophen-2(3*H*)-ones, whereas the forms **B** and **D** were found for [3,2-*b*]-fused systems. The effect of the nature and positions of the substituents on the tautomeric equilibrium was discussed.



Alkyl- and aryl-substituted 2,5-dihydroxythieno[3,2-*b*]thiophenes appeared to occur exclusively as dithiolactones. In no case was the hydroxy form of these compounds detected (78JOC2197). NMR spectroscopy demonstrated that 2,3-dihydrothieno[3,2-*b*]thiophene-2,5-dione (**E**) is a favourable structure. Tautomer **F** was detected only for the unsubstituted compound. However, this tautomer is readily transformed into tautomer **E**. For 6-substituted compounds, two stereoisomers of the form **G** are observed; these stereoisomers have opposite configurations at the C(6) atom.

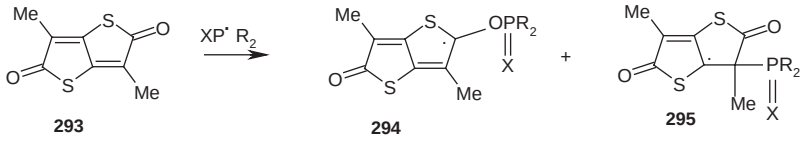


R^1 = H, Me, Bu^t, Ph; R^2 = H, Me, Ph.

The effects of the nature and positions of the substituents on stability of tautomeric forms were discussed.

C. ESR Spectra

The reactions of the diphenylphosphoryl ($OP \cdot Ph_2$) and diethoxyphosphoryl [$OP \cdot (OEt)_2$] radicals with 3,6-dimethylthieno[3,2-*b*]thiophene-2,5-dione (**293**) were studied by ESR spectroscopy (85CJC917). Both reactions produce the oxygen-containing (**294**) and cyclic (**295**) adducts. The hyper-fine coupling constants of the former adducts are close to those of analogous oxygen-containing adducts of Group IVB organometallic radicals (80JOM145). The attack can occur on the carbon atoms at positions 3, 6 or 4, 5 of the ring. In the former case, the structure of the adduct is similar to that of the substituted allylic system, and the ESR spectra would be expected to show methyl splitting with a constant of ~10 Hz. The reactions of dione **293** with the $SP \cdot Et_2$ and $P \cdot Ph_2$ radicals afforded predominantly derivatives **294**, although the ESR signals of cyclic adduct **295**, which was generated simultaneously with **294**, were recorded.



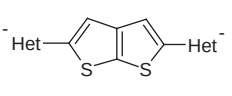
293 294 295

X = O: R = Ph, PEt; X = S: R = Et; X is absenr, R = Ph.

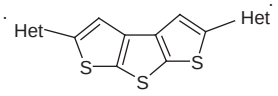
The hyperfme coupling constants for paramagnetic adducts of the $M \cdot R_3$ (M = Si, Ge, Sn) radicals with dithienyl and bis(thieno[2,3-*b*]- and -[3,2-*b*]thienyl) ketones were measured and compared with those of the diarylhydroxymethyl radicals. These results were confirmed by INDO calculations and indicate that the $2p_z$ orbital is involved in the O–M bond in dithienyl derivatives (79JCS(P2)1568).

Complexation of dibenzo-18-crown-6 ether with 3,6-dimethylthieno[3,2-*b*] thiophene-2,5-dione **293** (77JCS(P2)1327), homolytic aromatic silylation of 2-cyanothieno[2,3-*b*]- and -[3,2-*b*]thiophenes (79G395), addition of silyl radicals to 3,6-dimethylthieno[3,2-*b*]thiophene-2,5-dione and 5-benzylidene-3,6-dimethylthieno[3,2-*b*]thiophen-2-one (86JA4993) and the conformational behaviour of the dithieno[3,2-*b*:2′,3′-*d*]-thiophene-2,6-dicarbaldehyde radical anions (78JCS(P2)212) were studied by ESR spectroscopy.

Diradical species **296–299**, in which two nitronyl nitroxide (ONC = NO) or imino nitroxide (NCNO) radical centres are bound to the thieno[2,3-*b*]thiophene and thieno[2,3-*b*]thieno[3′,2′-*d*]thiophene chromophores, were investigated. Their intramolecular exchange coupling in frozen solutions and the magnetic sensitivity at low temperatures were examined by ESR spectroscopy (95TL5543, 96T6893).



296, 297



298, 299

The ESR spectra of mononitronyl nitroxide and imino nitroxide free radicals bound to isomeric thieno[3,2-*b*]- (**145**) and -[2,3-*b*]thiophenes (**142**) were measured in toluene at room temperature (69TL239).

D. UV Spectra

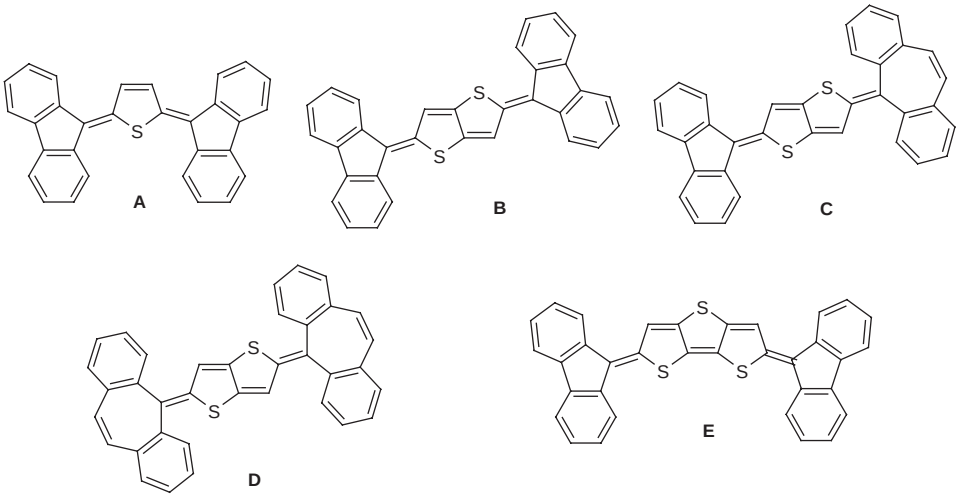
The nature and properties of the ground and first low-lying excited states of the thieno[3,2-*b*]thiophene (**145**) molecule were investigated in a series of spectroscopic studies (56MI1, 70MI1, 71MI1, 73CR365, 75MI3, 76CP297).

The first UV spectrum of thienothiophene **145** in the gas phase was recorded in 1956 (56MI1). However, some details of the spectrum have remained uninterpreted because of the complicated spectral pattern. Only 20 years later, a complete spectroscopic study, including IR and UV–Vis spectroscopy, of this compound was carried out both in the gas phase and in the crystalline state (77JCP51). Two systems of intense absorption bands at 36 000–40 000 cm^{-1} were assigned to two electron transitions in the excited state, whereas a very weak band observed in the spectrum of the crystal at 34394 cm^{-1} was assigned to a singlet–triplet transition caused by spin-orbital coupling. Calculations by the LCAO method with the STO/3G basis set (69JCP2657) confirmed the assignment of the electron transitions.

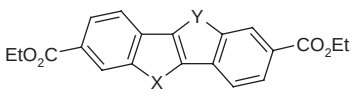
The possibility of using the liquid-crystal linear dichroism (LCLD) technique for the assignment of electron transitions was exemplified by two models of chromophores with high (phenylthiol) and low (thienothiophene **145**) symmetry (82JCS(P2)447). The LCLD spectrum of the thienothiophene chromophore revealed a new band, not been observed earlier, and confirmed the theoretical results (69JCP2657).

The thieno[3,2-*b*]thiophene (**145**), selenolo[3,2-*b*]thiophene (**146**) and selenolo[3,2-*b*]selenophene (**151**) charge-transfer complexes based on TCNE were studied by UV and IR spectroscopy. The absorption spectra recorded in CCl_4 and CH_2Cl_2 show numerous charge-transfer bands (82CS214). A comparison with photoelectron spectra of other donors demonstrated that these bands appear due to transitions from two different occupied orbitals of the donor to unoccupied orbitals of the acceptor. The calculated ionization potentials of the donors are consistent with the photoelectron spectroscopic data.

The quinoid compounds **A**, **B** and **E** have similar UV spectra, although the absorption maximum is shifted to longer wavelengths by approximately 50 nm with increasing number of thiophene rings (91CL1117). The observed absorption maxima agree with the values calculated by the Pariser–Parr–Pople (PPP) method with allowance for restricted configuration interactions. For the **B–C–D** series, the long-wavelength band is shifted to higher frequencies on going from the first to the last compound, in spite of an increase in π-conjugation in this series. This may be a consequence of steric interactions between the phenyl fragment and the quinoid thienothiophene system, resulting in a deviation of the seven-membered ring from the plane. The discrepancy between the observed and calculated electron transitions for the long-wavelength band in compounds **C** and **D** also confirms a non-planar structure of the total π-system of these molecules.



The UV spectra of 3,6-dimethylthieno[3,2-*b*]thiophene, 3,6-dimethylselenolo [3,2-*b*]selenophene, their dimers, trimers and tetramers (96T471), 2,2,5,5-tetra-methylthieno[3,2-*b*]thiophene-3,6-dione (68TCA247, 77CB1421), and derivatives of benzo[*b*]thieno[3,2-*b*]benzo[*b*]thiophene **121** (80ZOR425) and compounds **300–305** (93JOC5209) were measured and analysed.



300-305

X = Y = NMe(300);X = Y = S (301);X - Y = Se(302);X - NMe, Y = S (303); X - NMe, Y = Se (304); X = S, Y = Se (305).

The strongest absorption maximum in the UV–Vis spectra of compounds **300–305** is observed between 331 nm (for **301**) and 354 nm (for **300**); the longest-wavelength absorption is most intense, and the maximum is observed between 367 nm (for **301**)

and 426 nm (for **300**). All compounds, except for **302**, show fluorescence. Compound **300** shows strong fluorescence, whereas compounds **301** and **305** exhibit relatively weak fluorescence due, apparently, to the effect of the heavy atom.

The UV spectra of a homologous thienocene series show a shift of the long-wavelength band to the red region characterized by a good linear correlation with the number of thiophene rings. A comparison of the UV spectra of heterohelicenes **175a, b** and **176a, b** (56JA4765, 66JCP1126, 71JA2968) with the spectra of benzohelicenes (56JA4765, 66JCP1126) demonstrated that the longest-wavelength band (α band) is shifted to higher frequencies (by approximately 30 nm), whereas the positions of the second and third bands (*p* and *β* bands, respectively) are only slightly different.

The twist angles of the phenyl ring relative to the plane of the bicyclic fragment in 2-phenylthieno(or selenolo)[2,3-*b*]thiophenes, -furans and analogous *N*-methylpyrroles were determined from absorption spectra and data on molecular refraction (77ZOB1623).

V. Fields of Application

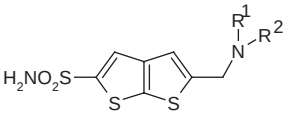
Earlier, the practical use of thienothiophenes has been limited primarily to the preparation of polymethine dyes, transition metal complexes (76AHC123), as well as the synthesis of *N*-(aminoalkyl)thieno[3,2-*b*]thiophene-2-carboxamide derivatives, which were proposed as antidepressants and antitumour agents (73USP3733322), and the synthesis of benzo[*b*]thienobenzo[*b*]thiophenes, which are used as pesticides (67USP3278552, 71JCS1308). In recent years, the applications of these compounds have been substantially extended due to the synthesis of numerous derivatives. The introduction of pharmacophoric substituents into thienothiophene molecules and the use of these compounds in the synthesis of annulated systems gave rise to new types of biological activities. The discovery of unusual optical, electrical and complexation properties made it possible to prepare new materials for modern technology.

A. Biological Activity

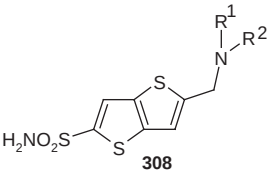
Since many thiophene-containing compounds, including annulated compounds, exhibit biological activities (80JMC878, 81JHC1277, 84P4, 89MI2), the structure–activity relationships for this series of heterocycles have attracted considerable attention. Studies are aimed both at using thienothiophenes as building blocks and searching for new types of biological activity of fused systems containing various central fragments (90P895, 80ZC96).

For example, 5-substituted thieno[2,3-*b*]- and -[3,2-*b*]thiophene-2-sulfonamides **306–312** were synthesized and proposed as glaucoma medicines (89USP4806592, 90USP4894390, 90USP4929549, 91JHC13, 91JMC1805, 92EUP480692, 92EUP480745,

99JHC249). In the cited studies, the substituents at position 5 were varied to increase solubility in water and achieve pK_a minimizing binding of the iris pigment. The best results were obtained in tests of compound **306** [$R^1 = (CH_2)_2O(CH_2)_2OMe$, $R^2 = (CH_2)_2OMe$] (91JMC1805).

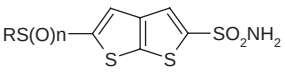


306 : X = H_2 ;
307 : X = O

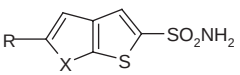


308

R^1= Me, $(CH_2)_2OH$, $(CH_2)_2(OH)CH_2OH$, $(CH_2)_3NMe_2$, $(CH_2)_2S(O)Me$, $(CH_2)_2O(CH_2)_2OMe$, $(CH_2)_2N(CH_2CH_2)_2O$, $(CH_2)_2N(CH_2CH_2)_2S$; R^2= H, Me, $(CH_2)_2OH$, $(CH_2)_2OMe$.



309 : n = 0;
310 : n = 2

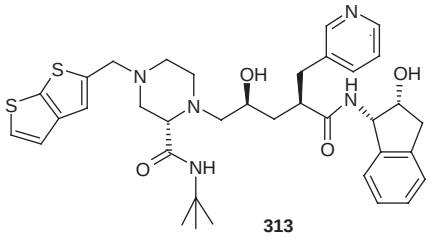


311 : X = S;
312 : X = SO_2;

R = n-C_5H_{11}, $(CH_2)_3)H$, $(CH_2)_3N(CH_2CH_2)_2O$.

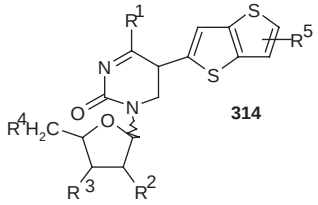
The results of pharmacological studies of the potential non-peptide fibrinogen receptor antagonist, viz., thieno[2,3-*b*]thiophene-based compound **172**, were reported (71JCS1308, 95PCT9504531).

A series of thieno[2,3-*b*]thiophene-based HIV protease inhibitors were synthesized and tested (94BMC2769, 95BMC185). At low concentrations, these inhibitors are efficient against HIV, and some of them provide satisfactory plasma level in animals upon peroral administration. Among compounds of this series, compound **313** proved to be the most promising ($IC_{50} = 0.12$ nM and $IC_{9S} = 6$–12 nM) (94BMC2769).



313

Pyrimidine nucleosides **314** containing the thieno[3,2-*b*]thiophene substituent hold promise against HIV and hepatitis B and were patented (90PCT8912061).

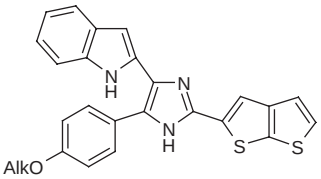


314

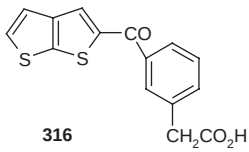
R^1 = OH, NH_2; R^2 = H, F, OH, OMe; R^3 = H, F, OH;
R^4 = OH, $(CH_2)nP(O)(OMe)_2$; R^5 = H, C_1-C_{10}-Alk, Hal.
n = 0, 1.

2-(Thienothienylglycyl)cephalosporin (85JMC1896, 86USP4581352) and 2-(thienothienylphenyl)carbapenam derivatives (93USP5143914) possess antibacterial properties.

Patents covered procedures for the preparation of 4(5)-(3-indolyl)imidazoles **315**, which are used as medicines for the treatment of central nervous system disorders, cerebrovascular dementia, senility and memory disturbance or for improvement of learning ability (99JAP11199582), the synthesis of thieno[2,3-*b*]thienyl-containing carboxylic acids **316** and their derivatives used as analgetics, inflammation and thrombosis inhibitors (77GEP2703624, 79FRP2378783) and the synthesis of thieno[3,2-*b*]thiophene-2-carboxamides used as cyclooxygenase and lipoxygenase inhibitors (88USP4720503).

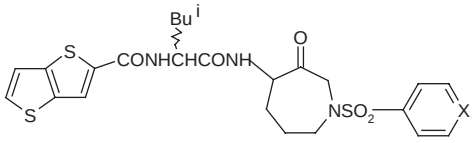


315



316

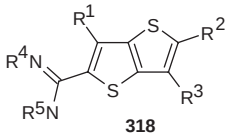
Thieno[3,2-*b*]thiophene-2-carboxamides **317**, which were prepared as mixtures of diastereomers and separated by high-performance liquid chromatography, were patented as cysteine protease inhibitors (98PCT9822494, 2001PCT0134153, 2001PCT0134154, 2001PCT0134159, 2001PCT0134565).



317

X-N.N^+-O^-.

Amidines of the thieno[3,2-*b*]thiophene series **318** were patented as urokinase inhibitors (94EUP568289).



318

R^1 = H, NH_2, Hal; R^2, R^3 = H, Hal, HO, NH_2 , NO_2; R^4, R^5 = H.C_1-C_6-Alk.

Thieno[2,3-*b*]- and -[3,2-*b*]thiophene-2-carboxylic acids and their benzo[*b*]annulated analogues were synthesized and their lipid-reducing properties were investigated (78APS368). A number of hydrazides and sulfonamides of the thienothiophene series were patented as pesticides (85EUP146263, 92EUP483647).

It was found that the smell of heated food includes odours of compounds formed by the reaction of thienothiophene-containing 4-hydroxy-5-methyl-3(2*H*)-furanones with cysteine or H_2S (2001MI3). Thieno[3,2-*b*]thiophene derivatives were used in combinatorial synthesis to compile chemical libraries with the aim of examining the biological action of these compounds (96TL1003).

B. Other Areas of Practical Applications

Sulfur-containing heteroaromatic compounds, particularly, fused compounds having an extensive conjugated system can be used as building blocks for preparing organic conductors (87MI1, 89PS187, 91JA7064, 91SM403), magnetic (91SM3287) and photosensitive receptors (93JAP04338761), materials for optoelectronics (91MI1, 91MI2), etc. These compounds most often belong to charge-transfer complexes (82MI2, 88CRV201, 93CC345). A rational combination of conducting polymers (86MI2) and magnetic materials (91JA2764, 91MI3) requires the presence of precursors containing functional groups, which can enhance π-conjugation in the system as a results of condensation.

1. *Complexation Properties of Isomeric Thienothiophenes*

Isomeric thienothiophenes and their derivatives are of considerable interest as electron donors or acceptors for the design of new types of charge-transfer complexes and as ligands coordinating metal ions. As mentioned above (see Section IV.D), charge-transfer complexes of some five-membered fused heteroaromatic systems with TCNE were studied by UV and IR spectroscopy and their relative stabilities were discussed using the association constants and enthalpies of formation (82CS214).

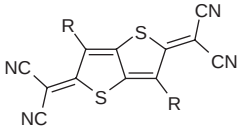
Thieno[2,3-*b*]thiophene and -[3,2-*b*]thiophene containing two 9-hydroxyfluoren-9-yl groups as substituents form charge-transfer complexes with 1,2,4,5-tetracyanobenzene (TCNB), which show fluorescence in the solid state (96MCL159, 98CC(C)1965). Benzo[*b*]thieno[3,2-*b*]thiophene forms charge-transfer complexes with various organic acceptors (90MI2).

In recent years, dithienothiophenes have attracted considerable attention because these compounds have three various types of π-conjugation, which play a decisive role in their donor ability (89TL3315, 91CC1268, 92CC1381, 93PAC127, 94CC1765, 94TL5883, 97TL4581, 94TL7589, 97SM1851, 99JCS(P1)1273, 99PCT9912989, 2000H761). Two higher homologues of fused polythiophenes, viz., thienocenes **6** and **7**, which are isoelectronic with chrysene and picene, respectively, but contain much less peripheral hydrogen atoms, were also used as precursors of organic conductors (89PS187, 89TL3315, 92JCS(P2)765).

As mentioned above (see Section III.B.3, and Ref. (91JAP03038588)), 2,3,6,7-tetrathiabenzo[l,3-*cd*:4,6-*c′d′*]dipentalene (**225**) and its derivatives **226** form charge-transfer complexes with strong electron acceptors (TCNQ, $TCNQF_4$, DDQ and HCBD), most of which have a low conductivity.

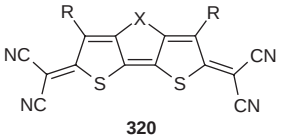
A new fused thienothiophene, 2,3:5,6-bis(ethylenedithio)thieno[3,2-*b*]thiophene (**112**), was used to prepare conducting organic salts (95BCJ1193).

Examples of the use of 2,5-bis(dicyanomethylene)-2,5-dihydrothieno[3,2-*b*]thiophenes (**319**) and -2,6-dihydrothieno[3,2-*b*:2′,3′-*d*]thiophenes **320** as electron acceptors were reported, and the resulting charge-transfer complexes have a very high (up to metallic) conductivity (99JCS(P1)1273).



319

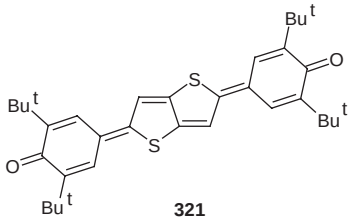
R = H, Br.



320

X = S (R = H, Br); X = SO, SO_2 (R = H).

2,5-Bis(3,5-di-*tert*-butyl-4-oxocyclohexa-2,5-dien-2-ylidene)-2,5-dihydro-l,4-dithiapentalene (**321**) is also a promising electron acceptor for the formation of complexes (90CC1196).



321

Synthesis of a new class of cofacially oriented neutral of donor–acceptor thienothiophenes was described to probe the presence of through-space charge-transfer interaction (2004JMS107). Dinuclear complexes of Group VIB (Cr, Mo and W) (2001IC(E)233, 2002MI1) and Group VIII (Pt) (2002JOM56, 2003JOM39) metal

ions with 3,6-dimethylthieno[3,2-*b*]- and dithieno[3,2-*b*:2′,3′]thiophene as ligands were synthesized and studied.

2. *Thienothiophenes as Liquid and Clathrate Crystals*

In the last 15 years, the liquid-crystalline properties of azomethines, azines, vinylenes and hexatrienes containing the thiophene or thieno[3,2-*b*]thiophene fragment were examined. Their thermal and optical properties were compared with those of analogous compounds of the benzene series (85ZN1199, 89MI3). Taking into account particular characteristics, these compounds were proposed as materials for various purposes of modern technology.

Certain thieno[2,3-*b*]- and -[3,2-*b*]thiophene derivatives can be used in liquid-crystalline mixtures for electro-optical switches and evaluation devices (85GEP3342631, 96GEP4422488, 98NJC771).

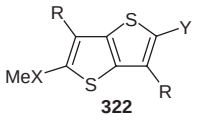
Benzo[*b*]thieno[3,2-*b*]benzo[*b*]thiophene-2,7-dicarboxylate derivatives exhibit properties of smectic liquid crystals, whose stability depends on the length and nature of terminal chains. Samples of these liquid crystals show pronounced photoconducting behaviour (2000LC321).

LCLD of the thieno[3,2-*b*]thiophene molecule was examined (82JCS(P2)447).

Recently (89TL3315, 91CL1117, 92CC1381, 92CC1661, 92CL1689, 92JCS(P1)761, 92JCS(P2)765, 92MCL75, 94AM654, 94CC2351, 94MCL81, 94TL5883, 95JOC6342, 98CC(C)1965, 98MCL185, 99CSJ1395), a series of new compounds possessing host-type complexation properties, for example, 2,5-bis(9-hydroxyfluoren-9-yl)thieno[3,2-*b*]thiophene (**278c**), were introduced into crystals of complexes. Such compounds are referred to as ''clathrate crystals'' [348].

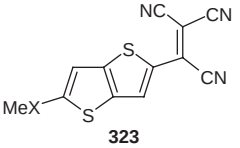
3. *Materials for Nonlinear Optics*

The recently discovered physical and chemical properties of thieno- and dithienothiophenes make it possible to use these fused heteroaromatic compounds for the design of new nonlinear optical materials. For example, the following two conjugated chromophoric charge-transfer systems were synthesized (96JCS(P2)1377): thieno[3,2-*b*]thiophenes **322**, which contain simultaneously electron-donating and electron-withdrawing substituents, and trinitriles **323**, which are heteroaromatic chromophores due to formation of charge-transfer complexes. The first hyperpolarizability (β) of these compounds was determined by electric-field-induced second-harmonic (EFISH) generation; the replacement of the oxygen atom with sulfur leads to a substantial increase in β, which remains unchanged on going to other chalcogens (Se or Te).



322

X = O, S, Se;
Y = CHO, NO_2;
R = H, Me.

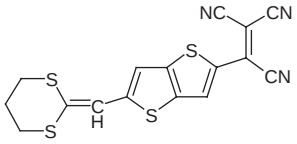


323

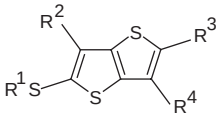
X = O, S, Se, Te.

2-(l,3-Dithian-2-ylidenemethyl)-5-(tricyanovinyl)thieno[3,2-*b*]thiophene (**324**) was used to prepare nonlinear optical polymers (95CAP2104038).

Substituted thioethers of thieno[3,2-*b*]thiophenes **325** possess analogous optical properties. The procedure for their preparation was patented (94GEP4 234230).



324



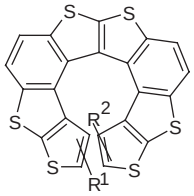
325

R^1 = C_1 –C_{22}-Alk, CH = $C(CN)_2$; R^2, R^3, R^4 = H, Me; R^2 = H, R^3 = NO_2, R^4 = CN, NO_2.

Thienothiophene-containing chromophores bearing the TCNQ group as an acceptor are as thermally stable as analogous chromophores containing the strong tricyanovinyl substituent but they are characterized by a substantially larger second-order optical nonlinearity (96CC(C)793).

Many thieno[3,2-*b*]thiophene derivatives are important synthons for the design of new functional materials possessing chromophoric, conducting or nonlinear optical properties (90AG(E)204, 91CL1117, 94CM2210, 94GEP4234230, 95GEP4339712, 95MI2, 96H1927).

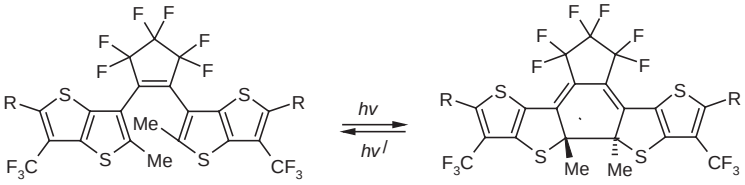
Materials containing hexathiaoctahelicene derivatives **326**, which show high third-harmonic generation and are resistant to thermal and optical laser action, were constructed (94JAP05273613).



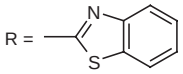
326

R^1, R^2 = H, C_1-C_6-Alk, C_1-C_6-OAlk, OH, NO_2, CN, CHO, Hal.

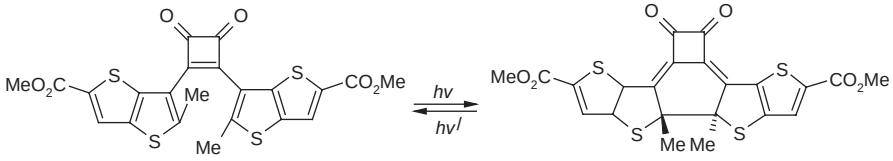
Photochromic compounds **181** were synthesized on the basis of benzothiazole derivatives of thieno[3,2-*b*]thiophene (see Section III.2). Their open (colourless, **181a**) and cyclic (coloured, **181b**) forms have high thermal stability, which makes it possible to perform repeated direct and reverse photo-induced transitions **181a** ⇄ **181b** with retention of the structure (2000MI1, 2001IZV107, 2005KGS360).



181a **181b**

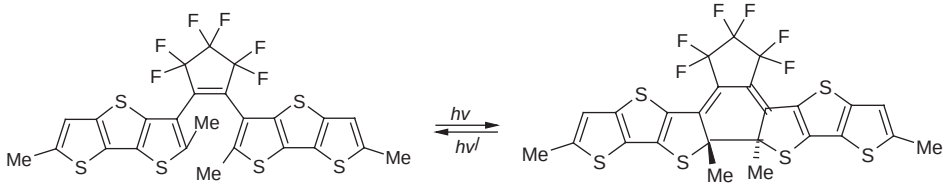


Analogous cyclobutenedione derivatives of thieno[3,2-*b*]thiophene **327** were synthesized in continuing studies of the use of thienothiophenes for the design of new photo-chromic materials (2002IZV1396, 2002MC141). Under UV irradiation ($\lambda = 313$ nm), compound **327** forms thermally stable (in the dark) cyclic form **327b**, which is again transformed into open form **327a** under irradiation with visible light ($\lambda = 578$ nm).



327a **327b**

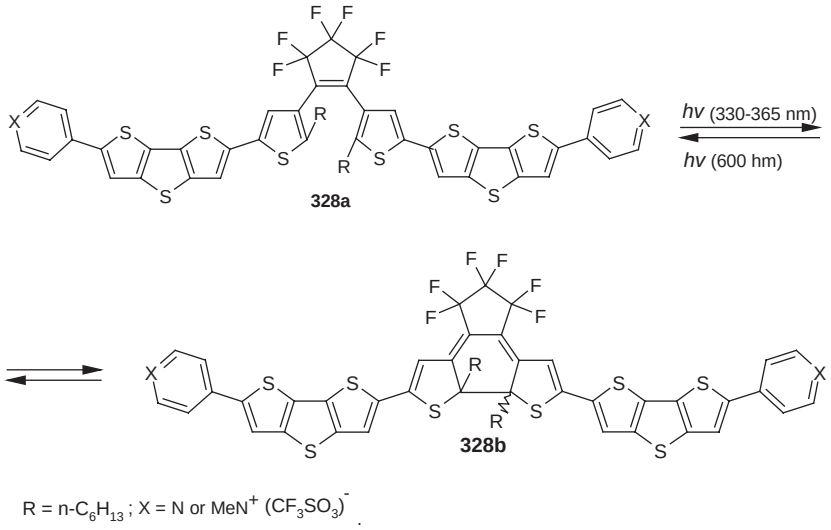
The photochromic characteristics of 1,2-bis(2,6-dimethyldithieno[3,2-*b*:2′,3′-*d*]thiophen-3-yl)hexafluorocyclopent-1-ene (**188**) were studied in an acetonitrile solution (2002IZV1942). The photocyclization **188a** → **188b** was carried out under UV irradiation at 313 nm, and the reverse reaction was performed under irradiation at 578 nm. The long-wavelength absorption maxima for open form **188a** and cyclic form **188b** are 290 and 612 nm, respectively, which are comparable with the corresponding characteristics of benzothiazole derivatives (2000MI1, 2001IZV107).



188a **188b**

Compounds **328a, b**, which have an extensive conjugation between two fused dithienothiophene fragments, were synthesized in the study (94CM2210). High

thermal stability, fatigue strength, sensitivity to the diode laser wavelength, nearly quantitatively reversible interconversion and, particularly, ability to perform nondestructive data reading make it possible to use these compounds as photoswitching elements in practice.



New quadrupolar photophores **189** and **190** containing fragments exhibiting very high two-photon absorption and simultaneously have high quantum yield were synthesized (99CC(C)2055). Other dithienothiophene-containing nonlinear-optical chromophores were also prepared and have found use as optical relays of a new type (99MI1).

Benzo[*b*]annulated thieno[3,2-*b*]thiophenes were patented as organic photoconductors (85JAP58145950) and fluorescent bleaching agents (84GEP3311092).

4. *Conjugated Polymers*

In recent years, the number of publications on photochemical and electrochemical polymerization of thienothiophenes and their polyannulated analogues has increased sharply. These compounds form conjugated polymers possessing unique properties. Since this field of thienothiophene chemistry is beyond the scope of the present review, only the references to such studies are given (82MAC2747, 82MAC2771, 8289TL3315, 83JCP5656, 85MCL241, 86CC1663, 86SM53, 86SM45, 86SM325, 87SM185, 88CC215, 88CC246, 89PS781, 89SM507, 89SM515, 90MI3, 93EUP535490, 93SM217, 94CC1911, 95AM48, 95H2691, 96CL285, 96T471, 97JEC23, 98MCL185, 99MI2, 99SM987).

Studies of copolymerization of a new class of highly efficient optical chromophores with thieno- and dithienothiophenes as linking units led to the design of conducting polymers (94MI3, 95EUP602654, 95GEP4339712, 95MI3, 96CL285, 96SM169, 97GEP19525304, 98MI1, 98MI2, 98MI3, 2000M(EP)555, 2002PMC40,

2002PMC195, 2002PP568, 2002PP584, 2002PP904, 2003PP398, 2004CM5644, 2004PP289). Poly(thieno[3,4-*b*]thiophenes), which are stable conducting polymers, have attracted particular attention. These compounds were prepared by electrochemical polymerization of thieno[3,4-*b*]thiophene and its derivatives. They hold promise, in particular, as new materials for electrochromic devices (2000MI2, 2001MI5, 2001MM1817, 2001MM5746, 2001MI2, 2001MI4, 2002MI2, 2002MI3, 2002MI4, 2002MM7281, 2002PMC40, 2002PMC195, 2002PP568, 2002PP584, 2002PP904, 2003PMC268, 2003PMC292, 2003PMC300).

A new class of silicon-containing copolymers was synthesized by the Heck reaction of distyrylsilane monomers with thiophene and thieno[3,2-*b*]thiophene derivatives, their luminescence properties were studied, and these polymers were demonstrated to be promising electroluminescent materials (2001SM1743, 2002MI5).

A series of alkyl-substituted poly(thieno[3,2-*b*]thiophenes) was synthesized by cross-coupling and oxidative coupling reactions (2004MM6306). Their electronic properties were studied by UV–Vis absorption and fluorescence spectroscopies.

A new method was developed for the preparation of poly(thienothiophenes) with amide bridges involving the formation of thiophene fragments by transformations analogous to those which are applied in the course of polymer synthesis (2004VMS1674).

Poly(thienothiophenes), low band-gap conjugated polymers with a polythiophene-like chain where an aromatic thienothiophene moiety is fused to each thiophene ring, were studied using Raman spectroscopy and photoinduced IR adsorbtion (2002JPC(B)3583).

The electropolymerization kinetics of 3,6-dimethylthieno[3,2-*b*]thiophene was studied by cyclic voltammetry, chronoamperometry and chronopotentiometry on glassy carbon in the presence of a 0.1 M $LiClO_4$ solution (2001JAE839).

C. Dyes

A few publications were devoted to the use of thienothiophene derivatives for the design of new dying materials. For example, diazotization of aminothienothiophene derivatives afforded disperse azo dyes for colouring synthetic or polyester fibres (78SWP603750, 88GEP3622136, 2000MI3, 2001MI6). Thieno[3,2-*b*]thienylidenebis-(benzoquinones) were patented as dyes for optical recording devices (91JAP03048686).

New electro- and photoactive multifunctional dyes were designed on the basis of dithienothiophenes (2000MI4, 2000PP795, 2000PP800). The pigment properties of 2,2,5,5-tetramethyl-2,3,5,6-tetrahydrothieno[3,2-*b*]thiophene (**127**) were compared with those of analogous compounds containing the thioindigoid fragment, and thienothiophene **127** was demonstrated to belong to indigoid dyes (78CB3233, 90T5759).

Compounds of the thieno[2,3-*b*]thiophene (**142**), thieno[3,2-*b*]thiophene (**145**), dithieno[3,2-*b*:2′,3′-*d*]thiophene (**108a**) and thieno[2′,3′: 4 ,5]thieno[2′,3′-*d*]thieno[3,2-*b*]thiophene (**6**) series were also patented as components (in amounts of 0.01–0.8%) for the preparation of nonaqueous electrolyte solutions (2002JAP2002124298).

VI. Conclusion

Analysis of the data published in the literature in the last 25 years demonstrates that the theoretical, synthetic, physicochemical and, particularly, practical aspects of the chemistry of thienothiophenes and their analogues attract growing attention of researchers working in different fields.

The range of practical applications of isomeric thienothiophene derivatives and their O-, N-, S-, Se-, Te-containing and fused analogues is very wide, from real prospects for the design of new medicines (due to a wide spectrum of pharmacological activities) to the design of the previously unknown liquid and clathrate crystals, charge-transfer complexes (organic conductors, magnetic and photosensitive receptors), electroconducting polymers, new nonlinear optical materials necessary for informational technologies, dyes, etc. (2003MI2).

The further development of the chemistry of fused chalcogen-containing heterocycles will be associated with the introduction of various pharmacophoric groups at different positions of the molecules with the aim of preparing new efficient medicines and also with the use of these heterocycles as building blocks for the design of new highly conjugated heterocyclic systems as promising technological materials of the 21st century.

References

16CB277 W. Friedmann, *Chem. Ber.*, **49**, 277 (1916).
16CB1344 W. Friedmann, *Chem. Ber.*, **49**, 1344 (1916).
16CB1352 W. Friedmann, *Chem. Ber.*, **49**, 1352 (1916).
16CB1551 W. Friedmann, *Chem. Ber.*, **49**, 1551 (1916).
1886CB2444 A. Biederman and P. Jacobson, *Chem. Ber.*, **19**, 2444 (1886).
56JA4765 M. S. Newman and D. Lednicer, *J. Am. Chem. Soc.*, **78**, 4765 (1956).
56MI1 M. R. Padhye and J. C. Patel, *J. Sci. Ind. Res.*, **B15**, 49 (1956).
65KGS619 V. G. Zhiryakov and P. I. Abramenko, *Khim. Geterotsikl. Soedin.*, 619 (1965).
65TL2393 M. Martin-Smith, S. T. Reid, and S. Sternhell, *Tetrahedron Lett.*, 2393 (1965).
65ZOR1282 F. M. Stoyanovich and B. P. Fedorov, *Zh. Org. Khim.*, **1**, 1282 (1965).
66JCP1126 O. E. Weigang, J. A. Turner, and P. A. Trouard, *J. Chem. Phys.*, **45**, 1126 (1966).
66KGS529 M. G. Voronkov and V. E. Udre, *Khim. Geterotsikl. Soedin.*, 529 (1966).
67CCA119 N. Trinajstic and A. Hinchliffe, *Croat. Chem. Acta.*, **39**, 119 (1967).
67JA3639 M. P. Cava and N. M. Pollack, *J. Am. Chem. Soc.*, **89**, 3639 (1967).
67TL2889 D. T. Clark, *Tetrahedron Lett.*, **8**, 2889 (1967).
67TL5257 D. T. Clark, *Tetrahedron Lett.*, **8**, 5257 (1967).
67USP3278552 US Pat. 3278552, *Chem. Abstr.*, **66**, 10920 (1967).
67ZN1475 N. Trinajstic and Z. Majerski, *Z. Naturforsch.*, **22A**, 1475 (1967).
67ZOB2220 Ya. L. Gol'dfarb, S. A. Ozolin', and V. P. Litvinov, *Zh. Obshch. Khim.*, **37**, 2220 (1967).
68ACS63 A. Bugge, *Acta Chem. Scand.*, **22**, 63 (1968).
68IZV1419 Ya. L. Gol'dfarb, V. P. Litvinov, and S. A. Ozolin', *Isv. Akad. Nauk SSSR Ser. Khim.*, 11419 (1968)

68IZV1828 V. P. Litvinov and G. Frenkl, *Isv. Akad. Nauk SSSR Ser. Khim.*, 1828 (1968).

68JMS181 D. T. Clark, *J. Mol. Spectrosc.*, **26**, 181 (1968).

68T2567 D. T. Clark, *Tetrahedron*, **24**, 2567 (1968).

68TCA247 J. Fabian, A. Mehlhorn, and R. Zahradnik, *Theor. Chim. Acta*, **12**, 247 (1968).

69ACS2704 A. Bugge, *Acta Chem. Scand.*, **23**, 2704 (1969).

69JCP2657 W. J. Hehre, R. F. Stewart, and J. A. Pople, *J. Chem. Phys.*, **51**, 2657 (1969).

69TL239 J. Fabian and H. Hartmann, *Tetrahedron Lett.*, **10**, 239 (1969).

69USP3433874 Pat.USA 3433874 CIIIA, *Chem. Abstr.*, **71**, 38940 (1969).

70ACS105 A. Bugge, B. Gestblom, and O. Hartmann, *Acta Chem. Scand.*, **24**, 105 (1970).

70JA1453 M. J. S. Dewar and N. Trinajstic, *J. Am. Chem. Soc.*, **92**, 1453 (1970).

70JCS243 N. B. Chapman, C. G. Hughes, and R. M. Scrowston, *J. Chem. Soc. C*, 243 (1970).

70KGS457 M. G. Voronkov and V. E. Udre, *Khim. Geeterotsikl. Soedin.*, 457 (1970).

70MI1 Ya. M. Kimel'fel'd, M. A. Moskaleva, G. N. Zhizhin, V. P. Litvinov, S. A. Ozolin', and Ya. L. Gol'dfarb, *Opt. I Spektrosk.*, **28**, 599 (1970).

70RTC77 H. Wynberg and J. Feijen, *Rec. Trav. Chim. Pays.- Bas.*, **89**, 77 (1970).

71ACS27 A. Bugge, *Acta Chem. Scand.*, **25**, 27 (1971).

71G774 A. Ricci, D. Balucani, and M. Betteli, *Gaz. Chim. Ital.*, **101**, 774 (1971).

71JA2968 M. B. Groen and H. Wynberg, *J. Am. Chem. Soc.*, **93**, 2968 (1971).

71JCS463 N. B. Chapman, C. G. Hughes, and R. M. Scrowston, *J. Chem. Soc. C*, 463 (1971).

71JCS1308 N. B. Chapman, C. G. Hughes, and R. M. Scrowston, *J. Chem. Soc. C*, 1308 (1971).

71JOC1645 F. de Jong and M. J. Janssen, *J. Org. Chem.*, **36**, 1645 (1971).

71MI1 G. N. Zhizhin, M. A. Moskaleva, and E. B. Perfimov, *Opt. I Spektrosk.*, **30**, 562 (1971).

71T5055 J. Kuszman, P. Sohar, and G. Horvath, *Tetrahedron*, **27**, 5055 (1971).

71TL4993 A. Schönberg and M. Mamluk, *Tetrahedron Lett.*, **12**, 4993 (1971).

71ZOR1257 V. S. Bogdanov, V. P. Litvinov, A. N. Sukiasyan, and Ya. L. Gol'dfarb, *Zh. Org. Khim.*, **7**, 1257 (1971).

72ACS2982 S. Gronowitz and B. Maltesson, *Acta Chem. Scand.*, **26**, 2982 (1972).

72AX(B)1336 M. D. Glick and R. E. Cook, *Acta Crystallogr.*, **28B**, 1336 (1972).

72CS137 A. Bugge, *Chem. Scr.*, **2**, 137 (1972).

72JHC879 W. D. Wright Jr., *J. Heterocycl. Chem.*, **9**, 879 (1972).

72KGS427 V. I. Shvedov, V. K. Vasiljeva, and A. N. Grinev, *Khim. Geterotsikl. Soedin.*, 427 (1972).

73CR365 Y. Gozien and P. Savmagne, *Compt. Rend.*, **B276**, 365 (1973).

73CS190 A. Bugge, *Chem. Scr.*, **3**, 190 (1973).

73JA2558 M. P. Cava, N. M. Pollack, and G. A. Dieterle, *J. Am. Chem. Soc.*, **95**, 2558 (1973).

73JA2561 M. P. Cava, M. Behforouz, G. E. Husbans, and M. Srinivasan, *J. Am. Chem. Soc.*, **95**, 2561 (1973).

73JA3692 J. H. Dopper, D. Oudman, and H. Wynberg, *J. Am. Chem. Soc.*, **95**, 3692 (1973).

73JPR850 V. P. Litvinov, Ja. L. Gol'dfarb, V. S. Bogdanov, I. P. Konjaeva, and A. N. Sukiasian, *J. Prakt. Chem.*, **315**, 850 (1973).

73T3085	P. A. Clark, R. Gleiter, and E. Heilbronner, *Tetrahedron*, **29**, 3085 (1973).
73USP3733322	U.S. Pat. 3733322, *Chem. Abstr.*, **79**, 18688 (1973).
74CS49	Ya. L. Gol'dfarb, V. P. Litvinov, G. M. Zhidomirov, I. A. Abronin, and R. Z. Zakharyan, *Chem. Scr.*, **5**, 49 (1974).
74CS236	S. Gronowitz, T. Frejd, and A. -B. Hörnfeldt, *Chem. Scripta*, **5**, 236 (1974).
74IZV1570	Ya. L. Goldfarb, I. P. Konjaeva, and V. P. Litvinov, *Isv. Akad. Nauk SSSR Ser. Khim.*, 1570 (1974).
74IZV1575	V. P. Litvinov, I. P. Konjaeva, and Ya. L. Goldfarb, *Isv. Akad. Nauk SSSR Ser. Khim.*, 1575 (1974).
74JA1817	M. P. Cava, M. A. Sprecker, and W. R. Hall, *J. Am. Chem. Soc.*, **96**, 1817 (1974).
74SC29	S. W. Schneller and J. D. Petru, *Synth. Commun.*, **4**, 29 (1974).
74T93	L. Dalgaard, L. Jensen, and S. -O. Lawesson, *Tetrahedron*, **30**, 93 (1974).
74ZOR811	M. G. Voronkov and L. N. Chochlova, *Zh. Org. Khim.*, **10**, 811 (1974).
75BSF2575	B. Capron, C. Paulmier, and P. Pastour, *Bull. Soc. Chim. Fr.*, 2575 (1975).
75JOC3384	G. Martelli, L. Testaferri, and P. Zanitaro, *J. Org. Chem.*, **40**, 3384 (1975).
75JOC3392	L. Tastaferri, M. Tiecco, and P. Zanirato, *J. Org. Chem.*, **40**, 3392 (1975).
75KGS492	V. P. Litvinov, T. V. Tschedrinskaya, P. A. Konstantinov, and Ya. L. Gol'dfarb, *Khim. Geterotsikl. Soedin.*, 199 (1980).
75MI1	V. P. Litvinov, Doctoral Thesis in Chemical Sciences, Institute of Organic Chemistry, Academy of Sciences of the USSR, Moscow (1975).
75MI2	I. P. Konjaeva, Candidate Thesis in Chemical Sciences, Institute of Organic Chemistry, Academy of Sciencts of the USSR, Moscow (1975).
75MI3	Ya. M. Kimel'fel'd, M. A. Moskaleva, L. N. Mostavaya, G. N. Zhizhin, V. P. Litvinov, and I. P. Konyaeva, *Opt. I Spektrosk.*, **39**, 493 (1975).
76AHC123	V. P. Litvinov and Ya. L. Goldfarb, *Adv. Heterocycl. Chem.*, **19**, 123 (1976).
76CP297	A. Brillante and L. A. Dissado, *Chem. Phys.*, **12**, 297 (1976).
76CS159	S. Gronowitz, A. Konar, and A. -B. Hörnfeldt, *Chem. Scripta*, **10**, 159 (1976).
76JA7187	C. Muller, A. Schweig, M. P. Cava, and M. V. Lakshmikanthan, *J. Am. Chem. Soc.*, **98**, 7187 (1976).
76KGS1039	P. I. Abramenko, *Khim. Geterotsikl. Soedin.*, 1039 (1976).
76MI1	V. P. Litvinov, in *"New Directions in the Chemistry of Thiophene"* (Ya. L. Gol'dfarb ed.), p. 190, Nauka, Moscow (1976).
76T3055	M. Augustin, W. -D. Rudorf, and U. Schmidt, *Tetrahedron*, **32**, 3055 (1976).
76TL2581	C. J. Horner, L. E. Saris, M. V. Lakshmikantham, and M. P. Cava, *Tetrahedron Lett.*, 2581 (1976).
76ZOR1574	I. Ya. Kvitko, N. B. Sokolova, S. P. Fradkina, and A. V. Eltzov, *Zh. Org. Khim.*, **12**, 1574 (1976).
77CB1421	U. Luchmann, F. G. Wentz, and W. Luttke, *Chem. Ber.*, **110**, 1421 (1977).
77CCA107	M. Milun and N. Trinajstic, *Croat. Chem. Acta*, **49**, 107 (1977).

77GEP2703624 Ger. Pat. 2703624, *Chem. Abstr.*, **87**, 168000 (1977).
77JA1692 I. Gutman, M. Milun, and N. Trinajstic, *J. Am. Chem. Soc.*, **99**, 1692 (1977).
77JCP51 F. Bartinelli, A. Brillante, P. Palmieri, and C. Taliani, *J. Chem. Phys.*, **66**, 51 (1977).
77JCS(P2)1327 G. F. Pedulli, A. Alberti, and M. Guerra, *J. Chem. Soc. Perkin Trans. 2*, 1327 (1977).
77JOC2230 R. Gleiter, M. Kobayashi, J. Spanget-Larsen, S. Gronowitz, A. Konar, and M. Farnier, *J. Org. Chem.*, **42**, 2230 (1977).
77MI1 P. Cagniant, M. -M. Briola, and G. Kirsh, *C. R. Seances Acad. Sci. Ser. C*, **285**, 21 (1977).
77ZOB1623 S. P. Fradkina, N. B. Sokolova, I. Ya. Kvitko, V. M. Grebenkina, and A. V. Eltzov, *Zh. Obshch. Khim.*, **47**, 1623 (1977).
77ZOR2624 A. V. Anisimov, V. F. Ionova, and E. A. Viktorova, *Zh. Org. Khim.*, **13**, 2624 (1977).
78APS368 S. Gronowitz, M. Herslof, and R. Svenson, *Acta Pharm. Soc.*, **15**, 368 (1978).
78CB3233 U. Luhman, F. G. Wentz, B. Knieriem, and W. Luttke, *Chem. Ber.*, **111**, 3233 (1978).
78JA3893 R. Gleiter, R. Bartetzko, G. Brachler, and H. Bock, *J. Am. Chem. Soc.*, **43**, 3893 (1978).
78JCS(P2)212 G. F. Pedulli, M. Tiecco, M. Guerra, G. Martelli, and P. Zanirato, *J. Chem. Soc. Perkin Trans. 2*, 212 (1978).
78JOC2197 L. Testaferri, M. Tiecco, P. Zanitaro, and G. Martelli, *J. Org. Chem.*, **40**, 2197 (1978).
78MI1 V. P. Litvinov, in *"Topics in Organic Sulfur Chemistry"* (M. Tishler ed.), p. 157, University Press, Ljubljana (1978).
78SWP603750 Swiss Pat. 603750, *Chem. Abstr.*, **89**, 199082 (1978).
79BSB325 P. Meunier, *Bull. Soc. Chim. Belg.*, **88**, 325 (1979).
79FRP2378783 Fr. Pat. 2378783, *Chem. Abstr.*, **90**, 121569 (1979).
79G395 A. Alberti and G. F. Pedulli, *Gaz. Chim. Ital.*, **109**, 395 (1979).
79JCS(P2)1568 A. Alberti, M. Guerra, and G. F. Pedulli, *J. Chem. Soc. Perkin Trans. 2*, 1568 (1979).
79KGS1062 A. V. Anisimov, V. F. Ionova, V. S. Babayzev, V. K. Govorek, and E. A. Viktorova, *Khim. Geterotsikl. Soedin.*, 1062 (1979).
79KGS1424 N. N. Alekseev and S. V. Tolkunov, *Khim. Geterotsikl. Soedin.*, 1424 (1979).
79MI1 A. V Anisimov, V. A. Kulikov, and E. A. Viktorova, *Vestnik Moscow. Univ. Ser. 2 Khim.*, **20**, 376 (1979).
80CS206 S. Gronowitz, A. Konar, and V. P. Litvinov, *Chem. Scr.*, **15**, 206 (1980).
80JMC878 J. K. Chakrabarti, L. Horsman, T. M. Hotten, I. A. Pullar, D. E. Tupper, and F. G. Wright, *J. Med. Chem.*, **23**, 878 (1980).
80JOM145 A. Alberti, A. Hudson, G. F. Pedully, and P. Zanirato, *J. Organomet. Chem.*, **198**, 145 (1980).
80KGS199 I. A. Abronin, V. P. Litvinov, G. M. Zhidomirov, A. Z. Dzhumanazarova, and Ya. L. Gol'dfarb, *Khim. Geterotsikl. Soedin.*, 199 (1980).
80T2711 N. K. DasGupta and F. W. Birss, *Tetrahedron*, **36**, 2711 (1980).
80T3317 A. Konar and S. Gronowitz, *Tetrahedron*, **36**, 3317 (1980).
80TL3617 S. Braverman, M. Freud, and I. Goldberg, *Tetrahedron Lett.*, **21**, 3617 (1980).
80ZC96 M. Augustin and S. Bielka, *Z. Chem.*, **20**, 96 (1980).
80ZOR399 V. I. Perevalova, O. B. Bannikova, E. N. Deryagina, and M. G. Voronkov, *Zh. Org. Khim.*, **16**, 399 (1980).

80ZOR425 S. Yu. Zherdeva, A. Ya. Zheltov, T. A. Kosik, and B. I. Stepanov, *Zh. Org. Khim.*, **16**, 425 (1980).
80ZOR430 S. Yu. Zherdeva, A. Barudi, A. Ya. Zheltov, and B. I. Stepanov, *Zh. Org. Khim.*, **16**, 430 (1980).
80ZOR438 A. Braudi, A. V. Kudryavzev, A. Ya. Zheltov, and B. I. Stepanov, *Zh. Org. Khim.*, **16**, 438 (1980).
81IZV1285 S. Gronowitz, A. Konar, I. A. Abronin, and V. P. Litvinov, *Izv. Akad. Nauk SSSR Ser. Khim.*, 1285 (1981).
81JCS(P1)1078 A. W. Faull and R. Hull, *J. Chem. Soc. Perkin Trans. 1*, 1078 (1981).
81JHC1277 V. J. Ram, H. K. Pandey, and A. J. Vlientick, *J. Heterocycl. Chem.*, **18**, 1277 (1981).
81LA1729 H. Behringer and E. Meinetsberger, *Liebigs Ann. Chem.*, 1729 (1981).
81LA1928 H. Behringer and E. Meinetsberger, *Liebigs Ann. Chem.*, 1928 (1981).
81MI1 R. L. P de Jong, H. D. Verkruijsse, and L. Brandsma, in *"Perspectives in the Organic Chemistry of Sulfur"* (B. Zwanen burg and A. Z. H. Klunder, eds.), p. 105, Elsevier, Amsterdam (1981).
81MI2 S. Yu. Zherdeva, A. Ya. Zheltov, and B. I. Stepanov, *Isv. Vuzov. Khim. Khim. Technol.*, **24**, 246 (1981).
81MI3 Yu. Vysotzkaya, B. P. Zemskij, E. A. Zemskaya, and N. N. Alekseev, *Zh. Strukt. Khim.*, **22**, 3 (1981).
81USSR755785 USSR Pat. 755785, *Chem. Abstr.*, **94**, 47308 (1981).
81USSR767108 USSR Pat. 767108, *Chem. Abstr.*, **94**, 121500 (1981).
81ZOR1103 M. G. Voronkov, E. N. Deryagina, V. I. Perevalova, and O. B. Bannikova, *Zh. Org. Khim.*, **17**, 1103 (1981).
82BSF342 J. -M. Catel and Y. Mollier, *Bull. Soc. Chim. Fr.*, 342 (1982).
82CS75 I. A. Abronin, A. Z. Djumanazarova, and V. P. Litvinov, *Chem. Scripta*, **19**, 75 (1982).
82CS214 A. Z. Djumanazarova, V. P. Litvinov, and A. Konar, *Chem. Scripta*, **20**, 214 (1982).
82DOK97 A. V. Anisimov, S. M. Panov, and E. A. Viktorova, *Dokl. Akad. Nauk SSSR*, **267**, 97 (1982).
82JCS(P2)295 W. J. Archer and R. Taylor, *J. Chem. Soc. Perkin Trans. 2*, 295 (1982).
82JCS(P2)301 W. J. Archer and R. Taylor, *J. Chem. Soc. Perkin Trans. 2*, 301 (1982).
82JCS(P2)447 B. Samori, P. Mariani, and G. P. Spada, *J. Chem. Soc. Perkin Trans. 2*, 447 (1982).
82JOC977 R. H. Hall, H. J. den Hertog, D. N. Reinhoudt, S. Harkema, C. J. van Hummel, and J. W. H. M. Uiterwijk, *J. Org. Chem.*, **47**, 977 (1982).
82JOC3550 S. Singh, M. M. Bhadhade, K. Venkatesan, and V. Ramamurthy, *J. Org. Chem.*, **47**, 3550 (1982).
82LA315 H. Behringer and E. Meinetsberger, *Liebigs Ann. Chem.*, 315 (1982).
82MAC2747 G. Kossmehl, P. Beimling, and G. Manecke, *Makromol. Chem.*, **183**, 2747 (1982).
82MAC2771 G. Kossmehl, P. Beimling, and G. Menecke, *Makromol. Chem.*, **183**, 2771 (1982).
82MI1 A. Z. Sadybakasova, Candidate Thesis in Chemical Sciences, Institute of Organic Chemistry, Academy of Sciencts of the USSR, Moscow (1982).
82MI2 R. P. Shibaeva, in "*Extended Linear Chain Compounds*" (J. C. Miller, ed.), Vol. 2, pp. 435–467, Plenum, New York (1982).

83CC1056 R. L. P de Jong and L. Brandsma, *J. Chem. Soc. Chem. Commun.*, 1056 (1983).

83CS22 A. Konar and V. P. Litvinov, *Chem. Scripta*, **22**, 22 (1983).

83JA1705 K. J. Miller, K. F. Moshner, and K. T. Potts, *J. Am. Chem. Soc.*, **105**, 1705 (1983).

83JA1979 B. M. Gimarc, *J. Am. Chem. Soc.*, **105**, 1979 (1983).

83KGS37 V. I. Dulenko, S. V. Tolkunov, and N. N. Alekseev, *Khim. Geterotsikl. Soedin.*, 37 (1983).

83ZOR1079 M. G. Voronkov, E. N. Deryagina, L. G. Shagun, and V. Yu. Vitkovskii, *Zh. Org. Khim.*, **19**, 1079 (1983).

84GEP3311092 Ger. Pat. 3311092, *Chem. Abstr.*, **100**, 122770 (1984).

84JMS345 J. P. Jacobson and C. H. Hansen, *J. Mol. Struct.*, **118**, 345 (1984).

84MI1 R.B. Mallory, C.W. Mallory, "*Photocyclization of Stilbenes and Related Molecule. Organic Reactions*" Vol. 30, Wiley, New York (1984).

84P4 R. Pech and R. Bohm, *Pharmazie*, **39**, 4 (1984).

85CJC917 A. Alberti, A. Hudson, C. F. Oedully, W. G. McGimpsey, and J. K. S. Wan, *Can. J. Chem.*, **63**, 917 (1985).

85EUP146263 Eur. Pat. 146263, *Chem. Abstr.*, **103**, 215315 (1985).

85GEP3342631 Ger. Pat. 3342631, *Chem. Abstr.*, **103**, 186953 (1985).

85JA5801 S. Yoneda, K. Ozaki, A. Tsubouchi, H. Kojima, K. Yanagi, and M. Minobe, *J. Am. Chem. Soc.*, **107**, 5801 (1985).

85JAP58145950 Jpn. Pat. 58145950, *Chem. Abstr.*, **102**, 157942 (1985).

85JMC1896 S. Kukolja, S. E. Draheim, B. J. Graves, D. C. Hunden, J. L. Pfeil, R. D. G. Cooper, J. L. Ott, and F. T. Counter, *J. Med. Chem.*, **28**, 1896 (1985).

85JOC3732 S. Singh and V. Ramamurthy, *J. Org. Chem.*, **50**, 3732 (1985).

85KGS1134 M. G. Voronkov, E. N. Deryagina, E. N. Suchomazova, N. A. Korchevin, L. V. Klyba, and M. V. Sigalov, *Khim. Getervotsikl. Soedin.*, 1134 (1985).

85MCL241 P. Di Marco, M. Mastragostino, and C. Taliani, *Mol. Cryst. Liq. Cryst.*, **118**, 241 (1985).

85TL1983 J. Nakayama, M. Machida, R. Saito, and M. Hoshino, *Tetrahedron Lett.*, **26**, 1983 (1985).

85ZN1199 G. Kossmehl and D. Budwill, *Z. Naturforsch. B*, **40**, 1199 (1985).

86CC1663 A. Berlin, G. A. Pagani, and F. Sannicolo, *J. Chem. Soc. Chem. Commun.*, 1663 (1986).

86JA4303 J. J. Ott and B. M. Gimarc, *J. Am. Chem. Soc.*, **108**, 4303 (1986).

86JA4993 A. Alberti, C. Chatgilialoglu, and G. F. Pedulli, *J. Am. Chem. Soc.*, **108**, 4993 (1986).

86KGS1614 M. G. Voronkov, E. N. Deryagina, L. K. Papernaya, E. N. Suchomazova, N. A. Korchevin, and G. G. Efremova, *Khim. Geterotsikl. Soedin.*, 1614 (1986).

86MI1 T. Fuchigami, Z. E. Kandeel, T. Nonaka, and H. J. Tien, *J. Chin. Chem., Soc. (Taipei),* **33**, 241 (1986); *Chem. Abstr.*, **107**, 175909 (1987).

86MI2 G.A. Kossmehl, in "*Handbook of Conductive Polymers, Pt. 1*" (T.A. Skotheim, ed.), pp. 364–397, Dekker, New York (1986).

86SM45 N. Colaneri, M. Kobayashi, A. J. Heeger, and F. Wudl, *Synth. Met.*, **14**, 45 (1986).

86SM53 T. R. Jow, K. Y. Jen, R. L. Elsenbaumer, L. W. Schacklette, M. Angelopouls, and M. P. Cava, *Synth. Met.*, **14**, 53 (1986).

86SM325 R. Danieli, C. Taliani, R. Zamboni, G. Giro, M. Biserni, M. Mastragostino, and A. Testoni, *Synth. Met.*, **13**, 325 (1986).

86USP4581352 US Pat. 4581352, *Chem. Abstr.*, **105**, 133654 (1986).
86ZOB2087 N. A. Korchevin, L. K. Papernaya, L. A. Ostrouchova, E. N. Suchomazova, G. G. Efremova, E. N. Deryagina, and M. G. Voronkov, *Zh. Obshch. Khim.*, **56**, 2087 (1986).
87MI1 J. P. Ferraro and J. M. Williams (eds.), *"Introduction to Synthetic Electrical Conductors"*, Academic Press, New York (1987).
87SM185 R. Lazzaroni, A. De Pryck, C. Debaisieux, J. Riga, J. Verbist, J. L. Bredas, J. Delhalle, and J. M. Andre, *Synth. Met.*, **21**, 185 (1987).
88AG597 T. Sugimoto, T. Nagatomi, H. Ando, and Z. Yoshida, *Angew. Chem.*, **100**, 597 (1988).
88CC215 K. -Y. Jen, H. Eckhardt, T. R. Low, L. W. Shackletce, and R. L. Elsenbauner, *J. Chem. Soc. Chem. Commun.*, 215 (1988).
88CC246 A. Bolognesi, S. Catellani, S. Destri, R. Zamboni, and C. Taliani, *J. Chem. Soc. Chem. Commun.*, 247 (1988).
88CC959 J. Nakayama, A. Ishii, Y. Kobayashi, and M. Hoshino, *J. Chem. Soc. Chem. Commun.*, 959 (1988).
88CRV201 J. Miller, A. J. Epstein, and W. M. Reiff, *Chem. Rev.*, **88**, 201 (1988).
88GEP3622136 Ger. Pat. 3622136, *Chem. Abstr.*, **108**, 169159 (1988).
88JA1793 T. Kobayashi, K. Ozaki, and S. Yoneda, *J. Am. Chem. Soc.*, **110**, 1793 (1988).
88JHC559 S. Yoneda, K. Ozaki, A. Tsubouchi, H. Kojima, and K. Yanagi, *J. Heterocycl. Chem.*, **25**, 559 (1988).
88JHC1363 S. L. Castle, J. -K. Luo, H. Kudo, R. N. Castle, and M. L. Lee, *J. Heterocycl. Chem.*, **25**, 1363 (1988).
88KGS1041 N. A. Korchevin, E. N. Suchomazova, N. V. Russavskaya, L. P. Turchaninova, G. G. Efremova, N. A. Kalinina, E. N. Deryagina, and M. G. Voronkov, *Khim. Geterotsikl. Soedin.*, 1041 (1988).
88MI1 E. Lam, H. Breteler, T. Arnason and L. Hansen (eds.), *"Chemistry and Biology of Naturally Occuring Acetylenes and Related Compounds"*, Elsevier, Amsterdam (1988).
88USP4720503 US Pat. 4720503, *Chem. Abstr.*, **108**, 94535 (1988).
89AG1254 Y. Kono, H. Miyamoto, Y. Aso, T. Otsubo, F. Ogura, T. Tanaka, and M. Sawada, *Angew. Chem.*, **101**, 1254 (1989).
89BCJ1547 K. Yui, H. Ishida, Y. Aso, T. Otsubo, F. Ogura, A. Kawamoto, and Y. Tanaka, *Bull. Chem. Soc. Jpn.*, **62**, 1547 (1989).
89CC223 A. Tsubouchi, N. Matsumura, H. Inoue, N. Hamasaki, S. Yvoneda, and K. Yanagi, *J. Chem. Soc. Chem. Commun.*, 223 (1989).
89KGS1565 N. V. Russavskaya, N. A. Korchevin, E. N. Suchomazova, E. N. Deryagina, and M. G. Voronkov, *Khim. Geterotsikl. Soedin.*, 1565 (1989).
89MI1 N. A. Sluzkaya, A. Barudi, A. Yf/Zheltov, and B. I. Stepanov, *Izv. Vuzov Khim. Khim. Tekhnol.*, **32**, 32 (1989).
89MI2 M. Negwer, Organische-Chemische Arzneimittel and ihre Synonima, 6, Anflage, Akademie-Verlag, Berlin (1989).
89MI3 K. Kobayashi, in *"Developments in the Organic Chemistry of Sulfur"* (C. T. Pedersen and J. Becher, eds.), Gordon and Breach, New York (1989).
89PS781 C. Taliani, R. Zamboni, R. Danieli, P. Ostoja, W. Porzio, R. Lazzaroni, and J. Bredas, *Phys. Scr.*, **40**, 781 (1989).
89PS187 O. Kobayashi, *Phosphorus, Sulfur, Silicon Relat. Elemn.*, **43**, 187 (1989).
89SM507 C. Taliani, G. Ruani, and R. Zamboni, *Synth. Met.*, **28**, C507 (1989).
89SM515 L. Lazzaroni, C. Taliani, R. Zamboni, R. Danieli, P. Ostoja, W. Porzio, and J. Bredas, *Synth. Met.*, **28**, 515 (1989).

89TL3315 Y. Mazaki and K. Kobayashi, *Tetrahedron Lett.*, **30**, 3315 (1989).
89USP4806592 US Pat. 4806592, *Chem. Abstr.*, **111**, 97215 (1989).
89ZOR2382 K. Pzhewozki, M. G. Voronkov, and L. Pzhewozki, *Zh. Org. Khim.*, **25**, 2382 (1989).
89ZOR2588 M. G. Voronkov, E. N. Deryagina, L. A. Ostrouchova, N. A. Korchevin, E. N. Suchomazova, A. P. Zhnikin, and L. P. Turchaninova, *Zh. Org. Khim.*, **25**, 2588 (1989).
90AG(E)204 E. Guther, S. Hunig, K. Peters, H. G. von Schnering, J. -U. von Schutz, S. Soderholm, H. -P. Werner, and H. C. Wolf, *Angew. Chem. Int. Ed. Engl.*, **29**, 204 (1990).
90CC1196 K. Takahashi and M. Ogiyama, *J. Chem. Soc. Chem. Commun.*, 1196 (1990).
90JHC2165 D. Peters, A. -B. Hörnfeldt, and S. Gronowitz, *J. Heterocycl. Chem.*, **27**, 2165 (1990).
90LA115 D. Wobig, *Liebigs Ann. Chem.*, 115 (1990).
90MI2 G. Bocceli, L. Gardellini, G. De Meo, A. Ricci, C. Rizzoli, and G. Tosi, *J. Crystallogr. Spectrosc. Res.*, **20**, 561 (1990).
90MI3 D. R. Rutherford, J. K. Stille, and C. M. Elliot, *Polym. Prep.*, **31**, 643 (1990); *Chem. Abstr.*, **114**, 207942 (1991).
90P895 D. Briel, *Pharmazie*, **45**, 895 (1990).
90PCT8912061 Pat. WO PCT Int. Appl. 8912061, *Chem. Abstr.*, **112**, 235778 (1990).
90T5759 S. Braverman and M. Freud, *Tetrahedron*, **46**, 5759 (1990).
90USP4894390 US Pat. 4894390, *Chem. Abstr.*, **113**, 191322 (1990).
90USP4929549 US Pat. 4929549, *Chem. Abstr.*, **113**, 172000 (1990).
91CC1268 J. P. Ferraris and T. L. Lambert, *J. Chem. Soc. Chem. Commun.*, 1268 (1991)
91CL1117 Y. Mazaki, N. Takiguchi, and K. Kobayashi, *Chemv. Lett.*, 1117 (1991).
91H2323 G. Karminski-Zamola, D. Pavličić, M. Bajić, and N. Blazević, *Heterocycles*, **32**, 2323 (1991).
91JA2764 D. A. Kaisaki, W. Chang, and D. A. Dougherty, *J. Am. Chem. Soc.*, **113**, 2764 (1991).
91JA7064 J. M. Tour, R. Wu, and J. S. Schum, *J. Am. Chem. Soc.*, **113**, 7064 (1991).
91JAP03038588 Jap. Pat. 03038588, *Chem. Abstr.*, **115**, 159122 (1991).
91JAP03048686 Jpn. Pat. 03048686, *Chem. Abstr.*, **115**, 92058 (1991).
91JHC13 T. M. Williams, R. J. Hudcosky, C. A. Hunt, and K. L. Shepard, *J. Heterocycl.*, **28**, 13 (1991).
91JHC109 J. L. Jackson, *J. Heterocycl. Chem.*, **28**, 109 (1991).
91JHC737 J. -K. Luo, A. S. Zektzer, and R. N. Castle, *J. Heterocycl. Chem.*, **28**, 737 (1991).
91JHC1623 D. Peters, A. -B. Hörnfeldt, and S. Gronowitz, *J. Heterocycl. Chem.*, **28**, 1623 (1991).
91JMC1805 J. D. Prugh, G. D. Hartman, P. J. Mallorga, B. M. McKeever, S. R. Michelson, M. A. Murcko, H. Schwam, R. L. Smith, J. M. Sondey, J. P. Springer, and F. M. Sugure, *J. Med. Chem.*, **34**, 1805 (1991).
91JOC78 A. Ishii, J. Nakayama, J. Kazami, Y. Ida, T. Nakamura, and M. Hoshino, *J. Org. Chem.*, **56**, 78 (1991).
91KGS1312 N. A. Korchevin, E. N. Suchomazova, N. V. Russavakaya, L. P. Turchaninova, M. V. Sigalov, L. V. Klyba, E. N. Deryagina, and M. G. Voronkov, *Khim. Geterotsikl. Soedin.*, 1312 (1991).
91MI1 R. A. Ham and D. Bloor (eds.), "*Organic Materials for Non-linear Optics*" The Royal Society of Chemistry, Cambridge, Special Publication No. 91 (1991).

91MI2 J. E. Sohn, E. D. Stucky, and S. Marder (eds.), "*Materials for Nonlinear Optics. Chemical Perspective*" ACS Symposium Sweries 455, American Chemical Society, Washington, DC (1991).
91MI3 D. A. Dougherty, R. H. Grubbs, D. A. Kaisaki, W. Chang, S. J. Jacobs, D. A. Shultz, K. K. Anderson, R. Jain, P. T. Ho, and E. G. Stewart, in, "*Magnetic Molecular Materials*" (D. Gatteschi, O. Kahn, J. C. Miller, and F. Palacio, eds.), pp. 105–120, Kulwer, Dordrecht (1991).
91SC145 R. L. P de Jong and L. Brandsma, *Synth. Commun.*, **21**, 145 (1991).
91SM403 S. Martina, V. Enkelmann, A. -D. Schluter, and G. Wegner, *Synth. Met.*, **41–43**, 403 (1991).
91SM3287 G. Heckmann, R. Johnan, G. Kraft, and G. Wolmershauser, *Synth. Met.*, **41–43**, 3287 (1991).
91TL4367 Y. Mazaki, S. Murta, and K. Kobayashi, *Tetrahedron Lett.*, **32**, 4367 (1991).
91ZOR354 L. A. Ostrouchova, E. N. Deryagina, N. A. Korchevin, G. K. Musorin, S. V. Amosova, and M. G. Voronkov, *Zh. Org. Khim.*, **27**, 354 (1991).
92BCJ1855 K. Takahashi and T. Nihira, *Bull. Chem. Soc. Jpn.*, **65**, 1855 (1992).
92CC1381 Y. Mazaki, N. Hayashi, and K. Kobayashi, *J. Chem. Soc. Chem. Commun.*, 1381 (1992).
92CC1661 Y. Mazaki, K. Awaga, and K. Kobayashi, *J. Chem. Soc. Chem. Commun.*, 1661 (1992).
92CL1689 N. Hayashi, Y. Mazaki, and K. Kobayashi, *Chem. Lett.*, 1689 (1992).
92EUP480692 Eur. Pat. 480692, *Chem. Abstr.*, **117**, 485351 (1992).
92EUP480745 Eur. Pat. 480745, *Chem. Abstr.*, **117**, 69850 (1992).
92EUP483647 Eur. Pat. 483647, *Chem. Abstr.*, **117**, 69722 (1992).
92JCS(P1)761 Y. Mazaki and K. Kobayashi, *J. Chem. Soc. Perkin Trans. 2*, 761 (1992).
92JCS(P1)973 S. Athmani, M. F. Farhat, and B. Iddon, *J. Chem. Soc. Perkin Trans. 1*, 973 (1992).
92JCS(P2)765 N. Sato, Y. Mazaki, K. Kobayashi, and T. Kobayashi, *J. Chem. Soc. Perkin Trans. 2*, 765 (1992).
92LA387 W. D. Rudorf, J. Koditz, A. Tersakian, and S. K. Chatterjee, *Liebigs Ann. Chem.*, 387 (1992).
92MCL75 Y. Mazaki, N. Hayashi, and K. Kobayashi, *Mol. Cryst. Liq. Cryst.*, **219**, 75 (1992).
92MM2294 D. R. Rutherford, J. K. Stille, C. M. Elliot, and V. R. Reichert, *Macromolecules*, **25**, 2294 (1992).
92PS15 A. K. El-Shafei, A. H. Abdel-Ghany, A. A. Sultan, and M. M. El-Saghier, *Phosphorus Sulfur Silicon Relat. Elem.*, **73**, 15 (1992).
92PS73 A. K. El-Shafei, M. M. El-Saghier, A. A. Sultan, and A. M. Soliman, *Phosphorus Sulfur Silicon Relat. Elem.*, **73**, 73 (1992).
92SL137 E. N. Deryagina, N. V. Russavskaya, E. N. Suchomazova, and N. A. Korchevin, *Sulfur Lett.*, **14**, 137 (1992).
93BCJ2011 A. M. M. El-Saghier, *Bull. Chem. Soc. Jpn.*, **66**, 2011 (1993).
93BCJ2033 T. Otsubo, Y. Kono, N. Hozo, H. Miyamoto, Y. Aso, F. Ogura, T. Tanaka, and M. Sawada, *Bull. Chem. Soc. Jpn.*, **66**, 2033 (1993).
93CC345 D. Lorcy, K. D. Robinson, Y. Okuda, J. L. Atwood, and M. P. Cava, *J. Chem. Soc. Chem. Commun.*, 345 (1993).
93EUP535490 Eur. Pat. 535490, *Chem. Abstr.*, **119**, 162372 (1993).
93JAP04338761 Jap. Pat. 04338761, *Chem. Abstr.*, **118**, 263832 (1993).
93JOC5209 P. Kaszynski and D. A. Dougherty, *J. Org. Chem.*, **58**, 5209 (1993).
93PAC127 K. Takahasi, *Pure Appl. Chem.*, 127 (1993).

93SM217 M. Sickerski, J. Przyluski, and J. Plocharski, *Synth. Met.*, **61**, 217 (1993).

93TL5653 D. C. Harrowen, *Tetrahedron Lett.*, **34**, 5653 (1983).

93USP5143914 US Pat. 5143914, *Chem. Abstr.*, **118**, 101708 (1993).

93ZN1621 R. Gomper, R. Knieler, and K. Polborn, *Z. Naturforsch.*, **48B**, 1621 (1993).

93ZOR2246 E. N. Deryagina, N. A. Korthevin, E. N. Suchomazova, N. V. Russavskaya, and M. G. Voronkov, *Zh. Org. Khim.*, **29**, 2246 (1993).

94AG(E)739 W. Schroth, E. Hintzsche, M. Felicetti, R. Spitzner, J. Sieler, and R. Kempe, *Angew. Chem. Int. Ed. Engl.*, **33**, 739 (1994).

94AM654 N. Hayashi, Y. Mazaki, and K. Kobayashi, *Adv. Mater.*, **6**, 654 (1994).

94BMC2769 F. D. Dorsey, S. L. McDaniel, R. B. Levin, J. P. Vacca, P. L. Darke, J. A. Zugay, E. A. Emini, W. A. Schlef, J. H. Lin, I. W. Chen, M. K. Holloway, P. S. Anderson, and J. R. Huff, *Bioorg. Med. Chem. Lett.*, **4**, 2769 (1994).

94CB401 W. Schroth, E. Hintzsche, H. Viola, R. Winkler, H. Klose, R. Boese, R. Kempe, and J. Sieler, *Chem. Ber.*, **127**, 401 (1994).

94CC1765 H. Brisset, C. Thobie-Gantier, M. Jubault, A. Gorgnes, and J. Roncali, *J. Chem. Soc. Chem. Commun.*, 1765 (1994).

94CC1911 M. Catellani, T. Caronna, and S. V. Meille, *J. Chem. Soc. Chem. Commun.*, 1911 (1994).

94CC2351 N. Hayashi, Y. Mazaki, and K. Kobayashi, *J. Chem. Soc. Chem. Commun.*, 2351 (1994).

94CM2210 V. P. Rao, K. Y. Wong, A. -K. Y. Jen, and K. J. Drost, *Chem. Mater.*, **6**, 2210 (1994).

94EUP568289 Eur. Pat. Appl. 568289, *Chem. Abstr.*, **120**, 298461 (1994).

94GEP4234230 Ger. Pat. 4234230, *Chem. Abstr.*, **121**, 83320 (1994).

94H143 K. S. Choi, K. Sawada, H. Dong, M. Hoshino, and J. Nakayama, *Heterocycles*, **38**, 143 (1994).

94JAP05273613 Jpn. Pat. 05273613, *Chem. Abstr.*, **120**, 148329 (1994).

94JCS(P1)2603 D. Prim and G. Kirsh, *J. Chem. Soc. Perkin Trans. 1*, 2603 (1994).

94JCS(P1)2735 D. W. Hawkins, B. Iddon, D. S. Longthorne, and P. J. Rosyk, *J. Chem. Soc. Perkin Trans. 1*, 2735 (1994).

94JOC2223 N. Beye and M. P. Cava, *J. Org. Chem.*, **59**, 2223 (1994).

94MI1 P. Boldt, M. Blenkle, I. Cabrera, D. Lupo, and W. Hickel, *Nonlinear Opt.*, **8**, 137 (1994); *Chem. Abstr.,* **123**, 285862 (1995).

94MI2 H. Tsuzuki, M. Mukomoto, T. Tsukinoki, S. Mataka, M. Tashiro, T. Yonemitsu, and Y. Negano, *J. Label. Compd. Radiopharm.*, **34**, 1087 (1994); *Chem. Abstr.*, **122**, 132545 (1995).

94MI3 A. -K. Y. Jen, V. P. Rao, K. J. Drost, Y. Cai, R. M. Mininni, J. T. Kanney, E. S. Binkley, and L. R. Dalton, *Proc. SPIE-Int. Soc. Opt. Eng.*, **2285**, 49 (1994); *Chem. Abstr.*, **123**, 84708 (1995).

94MCL81 N. Hayashi, Y. Mazaki, and K. Kobayashi, *Mol. Cryst. Liq. Cryst.*, **248**, 81 (1994).

94S521 G. Capozzi, F. De Sio, S. Menichetti, C. Nativi, and P. L. Pacini, *Synthesis*, 521 (1994).

94TL5883 N. Hayashi, Y. Mazaki, and K. Kobayashi, *Tetrahedron Lett.*, **35**, 5883 (1994).

94TL7589 D. A. Torres and J. P. Ferraris, *Tetrahedron Lett.*, **35**, 7589 (1994).

95AG(E)1119 G. M. Tsivgoulis and J. -M. Lehn, *Angew. Chem. Int. Ed. Engl.*, **34**, 1119 (1995).

95AM48 G. Zotti, A. Berlin, G. Pagani, G. Schiavon, and S. Zecchin, *Adv. Mater.*, **7**, 48 (1995).

95BCJ1193 M. Tanaka, T. Ishida, T. Nogami, H. Yoshikawa, M. Yasui, and F. Iwasaki, *Bull. Chem. Soc. Jpn.*, **68**, 1193 (1995).
95BMC185 B. M. Kim, J. P. Guare, J. P. Vacca, S. R. Michelson, P. L. Darke, J. A. Zugay, E. A. Emini, W. Schleif, J. H. Lin, I. W. Chen, K. Vastang, P. S. Anderson, and J. R. Huff, *Bioorg. Med. Chem. Lett.*, **5**, 185 (1995).
95CCC1578 R. M. Mohareb, S. M. Sherif, A. Habashi, N. I. Abdel-Sayed, and S. S. Osman, *Collect. Czech. Chem. Commun.*, **60**, 1578 (1995).
95CAP2104038 Can. Pat. 2104038, *Chem. Abstr.*, **122**, 214800 (1995).
95EUP602654 Eur. Pat. 602654, *Chem. Abstr.*, **122**, 67889 (1995).
95GEP4339712 Ger. Pat. 4339712, *Chem. Abstr.*, **123**, 172626 (1995).
95H1659 J. Dogan, G. Karminski-Zamola, and D. W. Boykin, *Heterocycles*, **41**, 1659 (1995).
95H2691 M. Malesevic, G. Karminski-Zamola, M. Bajic, and D. W. Boykin, *Heterocycles*, **41**, 2691 (1995).
95JHC317 J. -K. Luo, H. Kudo, R. F. Federspiel, and R. N. Castle, *J. Heterocycl. Chem.*, **32**, 317 (1995).
95JHC659 J. -K. Luo, R. F. Federspiel, and R. N. Castle, *J. Heterocycl. Chem.*, **32**, 659 (1995).
95JOC2092 T. Akita, Y. Mazaki, K. Kobayashi, N. Koga, and H. Iwamura, *J. Org. Chem.*, **60**, 2092 (1995).
95JOC6342 N. Hayashi, Y. Mazaki, and K. Kobayashi, *J. Org. Chem.*, **60**, 6342 (1995).
95MI1 E. N. Deryagina, N. A. Korchevin, E. N. Suchomazova, N. V. Russavskaya, and E. P. Levanova, *Neftekhimiya*, **35**, 472 (1995).
95MI2 P. Boldt, M. Blenkle, I. Cabrera, D. Lupo, and W. Hickel, *Nonlinear Opt.*, **8**, 173 (1994).
95MI3 M. Doerr, R. Zentel, P. Boldt, J. Wichern, M. Eich, M. Sprave, and J. Vydra, *Proc. SPIE-Int. Soc. Opt. Eng.*, **2527**, 105 (1995); *Chem. Abstr.*, **124**, 177566 (1996).
95PCT9504531 Pat. WO PCT Int. Appl. 9504531, *Chem. Abstr.*, **123**, 228162 (1995).
95SL53 R. A. Aitken, C. K. Bradbury, G. Burns, and J. J. Morrison, *Synlett*, 53 (1995).
95SM309 M. Fujitsuka, T. Sato, and H. Segawa, *Synth. Met.*, **69**, 309 (1995).
95TL5543 T. Akita, Y. Mazaki, K. Kobayashi, and K. Ushida, *Tetrahedron Lett.*, **36**, 5543 (1995).
95ZOR127 V. A. Artyomov, A. M. Shestopalov, and V. P. Litvinov, *Zh. Org. Khim.*, **31**, 127 (1995).
95ZOR925 E. N. Deryagina, E. N. Suchomazova, E. P. Levanova, and M. G. Voronkov, *Zh. Org. Khim.*, **31**, 925 (1995).
96CC(C)793 P. Boldt, G. Bourhill, C. Braenchle, Y. Yim, R. Kammler, J. Rase, and J. Wichern, *Chem. Commun. (Cambridge)*, 793 (1996).
96CL285 M. Fujitsuka, T. Sato, A. Watanabe, O. Ito, and T. Shimidzu, *Chem. Lett.*, 285 (1996).
96CL421 N. Matsumura, Y. Yagyu, H. Tanaka, H. Inoue, K. Takada, M. Yasui, and F. Iwasaki, *Chem. Lett.*, 421 (1996).
96GEP4422488 Ger. Pat. 4422488, *Chem. Abstr.*, **124**, 161203 (1996).
96H1927 K. Takahashi and S. Tarutani, *Heterocycles*, **43**, 1927 (1996).
96JCS(P2)1377 M. Blenkle, P. Bold, C. Brauchle, W. Grahn, I. Ledoux, H. Nerenz, S. Stadler, J. Wichern, and J. Zyss, *J. Chem. Soc. Perkin Trans. 2*, 1377 (1996).
96JHC119 A. P. Halverson, R. N. Castle, and L. W. Castle, *J. Heterocycl. Chem.*, **33**, 119 (1996).

96JHC185 J. K. Luo, R. F. Federspiel, R. N. Castle, and L. W. Castle, *J. Heterocycl. Chem.*, **33**, 185 (1996).

96JPR403 W. Kantlehner, M. Hauber, and M. Vettel, *J. Prakt. Chem. -Chem. -Ztg.*, **338**, 403 (1996).

96MCL159 N. Hayashi and K. Kobayashi, *Mol. Cryst. Liq. Cryst.*, **276**, 159 (1996).

96SM169 R. Cervini, A. B. Holmes, S. C. Moratti, A. Koehler, and R. H. Friend, *Synth. Met.*, **76**, 169 (1996).

96T471 J. Nakayama, H. Dong, K. Sawada, A. Ishii, and S. Kumakura, *Tetrahedron*, **52**, 471 (1996).

96T1011 V. A. Artyomov, L. A. Rodinovskaya, A. M. Shestopalov, and V. P. Litvinov, *Tetrahedron*, **52**, 1011 (1996).

96T6893 T. Akita and K. Kobayashi, *Tetrahedron*, **52**, 6893 (1996).

96TL1003 A. L. Marzinzik and E. R. Felder, *Tetrahedron Lett.*, **37**, 1003 (1996).

97CC(C)2355 S. L. Fuller, B. Iddon, and K. A. Smith, *Chem. Commun. (Cambridge)*, 2355 (1997).

97GEP19525304 Ger. Pat. 19525304, *Chem. Abstr.*, **126**, 173016 (1997).

97JCS(P1)3465 S. L. Fuller, B. Iddon, and K.A. Smith, *J. Chem. Soc. Perkin Trans. 1*, 3465 (1997).

97JEC23 C. Arbizzani, M. Catellani, M. Mastragostino, and M. G. Cerroni, *J. Electroanal. Chem.*, **423**, 23 (1997).

97SM1851 T. Remonen, J. Hellberg, and J. -U. Schutz, *Synth. Met.*, **86**, 1851 (1997).

97T7509 W. Schroth, E. Hintzsche, H. Jordan, T. Jende, R. Spitzner, and I. Thondorf, *Tetrahedron*, **53**, 7509 (1997).

97TL4581 M. Iyoda, M. Miura, S. Sasaki, S. M. H. Kabir, Y. Kuwatani, and M. Yoshida, *Tetrahedron Lett.*, **38**, 4581 (1997).

98CC(C)1965 M. Tanaka and K. Kobayashy, *Chem. Commun. (Cambridge)*, 1965 (1998).

98HEC227 N. Jarkas, G. Kiesh, and P. Seck, *Heterocycl. Commun.*, **4**, 227 (1998).

98JCS(P1)3973 R. A. Aitken, G. Burns, and J. J. Morrison, *J. Chem. Soc. Perkin Trans. 1*, 3973 (1998).

98JHC725 H. Sashida and S. Yasuike, *J. Heterocycl. Chem.*, **35**, 725 (1998).

98JHC1441 J. K. Luo, R. F. Federspiel, and R. N. Castle, *J. Heterocycl. Chem.*, **35**, 1441 (1998).

98JOC163 N. Matsumura, H. Tanaka, Y. Yagyu, K. Mizuno, H. Inoue, K. Takada, M. Yasui, and F. Iwasaki, *J. Org. Chem.*, **63**, 163 (1998).

98MCL185 K. Kuruma, N. Hayashi, Y. Mazaki, T. Imakubo, and K. Kobayashi, *Mol. Cryst. Liq. Cryst. A*, **313**, 185 (1998).

98MI1 C. Arbizzani, M. Catellani, S. Luzzati, and M. Mastragostino, *Mater. Res. Soc. Symp. Proc.*, 488 (1998); *Chem. Abstr.*, **129**, 88498 (1998).

98MI2 A. B. Holmes, B. S. Chuah, X. -C. Li, F. Cacialli, J. Morgado, H. Sirringhaus, D. A. Dos Santos, S. S. Moratti, J. -L. Breads, R. H. Friend, and F. Garnier, *Proc. SPIE-Int. Soc. Opt. Eng.*, **3476**, 24 (1998); *Chem. Abstr.*,**130**, 344748 (1999).

98MI3 B. S. Chuah, X. -C. Li, F. Cacialli, J. E. Davies, C. N. Feeder, R. H. Friend, F. Carnier, A. B. Holmes, S. C. Moratti, and H. Sirringhaus, *Ann. Tech. Conf. -Soc. Plast. Eng.*, *56th*, **2**, 1321 (1998); *Chem. Abstr.*, **130**, 73545 (1999).

98NJC771 H. -H. Tso, J. -S. Wang, C. -Y. Wu, and H. -C. Lin, *New. J. Chem.*, **22**, 771 (1998).

98PCT9822494 Pat. WO PCT Int. Appl. 9822494, *Chem. Abstr.*, **129,** 41414 (1998).

99CC(C)2055 L. Ventelon, L. Moreaux, J. Mertz, and M. Blanchard-Desce, *Chem. Commun. (Cambridge)*, 2055 (1999).

99CP51 V. Alain, S. Rodolgia, M. Blanchard-Desce, S. Lebous, K. Lukaszuk, R. Wortmann, U. Gubler, C. Bosshard, and P. Gunter, *Chem. Phys.*, **245**, 51 (1999).

99CSJ1395 K. Kuruma, H. Nakagawa, T. Imakubo, and K. Kobayashi, *Chem. Soc. Jpn.*, **72**, 1395 (1999).

99JAP11199582 Jpn. Pat. 11199582, *Chem. Abstr.*, **131**, 97622 (1999).

99JCS(P1)1273 S. L. Fuller, B. Iddon, and K. A. Smith, *J. Chem. Soc. Perkin Trans. 1*, 1273 (1999).

99JHC249 H. -H. Chen, J. A. May, and V. M. Lynch, *J. Heterocycl. Chem.*, **36**, 249 (1999).

99JMC2409 M. S. Egberston, J. J. Cook, B. Bednar, J. D. Prugh, R. A. Bednar, S. L. Gaul, R. J. Gould, G. D. Hartman, C. F. Homnick, M. A. Holahan, L. A. Libby, G. R. Sitko, M. T. Stranieri, L. M. Vassalo, J. J. Lynch, and R. J. Lynch, *J. Med. Chem.*, **42**, 2409 (1999).

99MI1 O. -K. Kim, A. Fort, M. Barzoukas, M. Blanchard-Desce, and J. -M. Lehn, *J. Mater. Chem.*, **9**, 2227 (1999).

99MI2 T. Itoh, T. Nakamura, and M. Kubo, *Polym. Chem.*, **37**, 3027 (1999); *Chem. Abstr.*, **131**, 257914 (1999).

99PCT9912989 Pat. WO PCT Int. Appl. 9912989, *Chem. Abstr.*, **130**, 252238 (1999).

99S2030 S. H. Mashraqui, H. Hariharasubrahmanin, and S. Kumar, *Synthesis*, 2030 (1999).

99SM987 J. J. Morrison, M. M. Murray, X. C. Li, A. B. Holmes, S. C. Morratti, R. H. Fried, and R. Sirringhaus, *Synth. Met.*, **102**, 987 (1999).

2000H761 S. M. H. Kabir, M. Miura, S. Sasaki, G. Harada, Y. Kuwatani, M. Yoshida, and M. Iyoda, *Heterocycles*, **52**, 761 (2000).

2000JA1082 R. Sekiya, K. Kiyo-oka, T. Imakubo, and K. Kobayasi, *J. Am. Chem. Soc.*, **122**, 1082 (2000).

2000LC321 D. Haristoy, S. Mery, B. Heinrich, L. Mager, J. F. Nicoud, and D. Guillon, *Liq. Cryst.*, **27**, 321 (2000); *Chem. Abstr.*, **133**, 97114 (2000).

2000M(EP)555 A. S. Diez, S. Saidman, and R. O. Garay, *Molecules (Electronic Publication)*, **5**, 555 (2000).

2000MI1 O. Yu. Zolotarskaya, Candidate Thesis in Chemical Sciences, Institute of Organic Chemistry, Russian Academy of Sciencts, Moscow (1975).

2000MI2 X. Zhang, *(Univ. Texas)*, *Diss. Abstr. Int.*, *B2001*, **61**, 5899 (2000); *Chem. Abstr.*, **136**, 135120 (2002).

2000MI3 D. W. Rangnehar and V. R. Telange, *J. Ind. Counc. Chem.*, **17**, 11 (2000); *Chem. Abstr.*, **134**, 327869 (2001).

2000MI4 O. -K. Kim, H. Woo, J. K. Kim, and Z. Huang, *Proc. SPIE-Int. Soc. Opt. Eng.*, 3955 (2000); *Chem. Abstr.*, **133**, 81276 (2000).

2000PP795 O. -K. Kim, H. Y. Woo, W. B. Heuer, K. -S. Kim, and K. -S. Lee, *Polym. Prep.*, **41**, 795 (2000); *Chem. Abstr.*, **132**, 285675 (2000).

2000PP800 O. -K. Kim, J. K. Kim, D. J. Kim, and C. Y. Kim, *Polym. Prep.*, **41**, 800 (2000); *Chem. Abstr.*, **132**, 286080 (2000).

2000PS45 H. Abdel-Ghany and A. Khodary, *Phosphorus Sulfur Silicon Relat. Elem.*, **166**, 45 (2000); *Chem. Abstr.*, **135**, 61252 (2001).

2000PS57 Z. H. Khalil, A. S. Yanni, A. M. Gaber, and Sh. A. Abdel-Mohsen, *Phosphorus Sulfur Silicon Relat. Elem.*, **166**, 57 (2000); *Chem. Abstr.*, **135**, 61253 (2001).

2000PS259 A. Khodary and H. Abdel-Ghany, *Phosphorus Sulfur Silicon Relat. Elem.*, **162**, 259 (2000).

2000SC1695 S. H. Mashraqui and H. Hariharasubrahmanian, *Synth. Commun.*, **30**, 1695 (2000).

2000SL215 L. Brandsma, E. H. Morkved, O. Bjorlo, V. A. Potapov, and S. V. Amosova, *Sulfur Lett.*, **23**, 215 (2000).

2000TL3607 J. -P. Tranchier, R. Chavignon, D. Prim, A. Auffrant, Z. F. Plyta, F. Rose-Munch, and E. Rose, *Tetrahedron Lett.*, **41**, 3607 (2000).

2000TL8843 R. R. Amaresh, M. L. Lakshmikantham, R. Geng, and M. P. Cava, *Tetrahedron Lett.*, **41**, 8843 (2000).

2001IC(E)233 M. Landman, H. Goerls, and S. Lotz, *Eur. J. Inorg. Chem.*, 233 (2001).

2001IZV107 M. M. Krayushkin, F. M. Stoyanovich, O. Yu. Zolotarskaya, I. V. Muravjev, A. Yu. Martynkin, L. G. Vorontzova, Z. A. Starikova, V. L. Ivanov, and B. MUzhinov, *Isv. Akad. Nauk Ser. Khim.*, 107 (2001).

2001JAE839 S. B. Saidman, R. O. Garay, and J. B. Bessone, *J. Appl. Electrochim.*, **31**, 839 (2001); *Chem. Abstr.*, **136**, 11841 (2002).

2001JHC1167 A. Comel and G. Kirsch, *J. Heterocycl. Chem.*, **38**, 1167 (2001).

2001JOC803 M. Tanaka, N. Tanifuji, S. Hatada, and K. Kobayashi, *J. Org. Chem.*, **66**, 803 (2001).

2001JOC2470 S. Ito, S. Kikuchi, T. Okujima, N. Morita, and T. Asao, *J. Org. Chem.*, **66**, 2470 (2001).

2001KGS850 S. V. Tolkunov and V. I. Dulenko, *Khim. Geterotsikl. Soedin.*, 850 (2001).

2001MI1 S. Kobata and M. Irie, *Kagaku (Kyoto, Japan)*, **56**, 19 (2001); *Chem. Abstr.*, **136**, 239250 (2003).

2001MI2 A. -M. Ren, J. -K. Feng, J. -F. Guo, S. -Q. Zhang, and H. Cheng, *Huaxue Xuebao*, **59**, 2126 (2001); *Chem. Abstr.*, **136**, 247298 (2003).

2001MI3 F. B. Whitfield and D. S. Mottram, *J. Agricult. Food. Chem.*, **49**, 816 (2001); *Chem. Abstr.*, **134**, 265343 (2001).

2001MI4 K. Lee and G. A. Sotzing, *Polym. Prep. (Am. Chem. Soc., Div. Polym. Chem.)*, **42**, 413 (2001); *Chem. Abstr.*, **135**, 358490 (2001).

2001MI5 G. A. Sotzing and K. Lee, *Polym. Mat. Sci. Eng.*, **85**, 284 (2001); *Chem. Abstr.*, **135**, 273491 (2001).

2001MI6 D. W. Rangnehar and V. R. Telange, *J. Ind. Counc. Chem.*, **17**, 11 (2000); *Chem. Abstr.*, **134**, 327869 (2001).

2001MM1817 M. Pomerantz, X. Gu, and S. X. Zhang, *Macromolecules*, **34**, 1817 (2001).

2001MM5746 K. Lee and G. A. Sotzing, *Macromolecules*, **34**, 5746 (2001).

2001PCT0134153 Pat. WO PCT Int. Appl. 0134153, *Chem. Abstr.*, **134**, 353541 (2001).

2001PCT0134154 Pat. WO PCT Int. Appl. 0134154, *Chem. Abstr.*, **135**, 353542 (2001).

2001PCT0134159 Pat. WO PCT Int. Appl. 0134159, *Chem. Abstr.*, **134**, 353547 (2001).

2001PCT0134565 Pat. WO PCT Int. Appl. 0134565, *Chem. Abstr.*, **134**, 353549 (2001).

2001SM1743 N. S. Beak, S. -H. Jung, D. J. Oh, H. K. Kim, G. T. Hwang, and B. H. Kim, *Synth. Met.*, **121**, 1743 (2001).

2002CPB656 J. Dogan-Koruznjak, N. Slade, B. Zamola, K. Pavelič, and G. Karminski-Zamola, *Chem. Pharm. Bull.*, **50**, 656 (2002).

2002IZV1396 M. M. Krayushkin, V. Z. Shirinyan, L. I. Belen'kii, and A. Yu. Shadronov, *Izv. Akad. Nauk. Ser. Khim.*, 1396 (2002).

2002IZV1942 M. M. Krayushkin, F. M. Stoyanovich, O. Yu. Zolotarskaya, V. N. Yarovenko, V. N. Bulgakova, I. V. Zavarzin, and A. Yu. Martynkin, *Izv. Akad. Nauk. Ser. Khim.*, 1942 (2002).

2002JAP2002124298 Jpn. Pat. 2002124298, *Chem. Abstr.*, **136**, 343312 (2002).

2002JOC2453 R. R. Amaresh, M. L. Lakshmikantham, J. W. Baldwin, M. P. Cava, R. M. Metzger, and R. D. Rogers, *J. Org. Chem.*, **67**, 2453 (2002).

2002JOM56 M. Sato, A. Asami, G. Maruyama, M. Kosuge, J. Nakayama, S. Kumakura, and T. Fujihara, *J. Organomettal. Chem.*, **654**, 56 (2002).

2002JPC(B)3583 A. Cravino, H. Neugebauer, S. Luzzati, M. Catellani, A. Petr, L. Dunsch, and N. S. Sariciftci, *J. Phys. Chem., B*, **106**, 3583 (2002).

2002MC141 M. M. Krayushkin, V. Z. Shirinian, L. I. Belen'kii, and A. Yu. Shadronov, *Mendeleev Commun.*, 141 (2002).

2002MI1 M. Landham, H. Goerls, and S. Lotz, *Z. Anorg. Allgem. Chem.*, **628**, 2037, (2002).

2002MI2 K. Lee and G. A. Sotzing, *Polym. Preprints* (*Am. Chem. Soc.*, *Div. Polym. Chem.*), **43**, 568 (2002); *Chem. Abstr.*, **137**, 248076 (2002).

2002MI3 V. Seshardi, K. Lee, and G. A. Sotzing, *Polym. Preprints* (*Am. Chem. Soc.*, *Div. Polym. Chem.*), **43**, 584 (2002); *Chem. Abstr.*, **137**, 279570 (2002).

2002MI4 G. A. Sotzing, B. Lee, N. Reyes, and M. B. Smith, *Polym. Preprints* (*Am. Chem. Soc.*, *Div. Polym. Chem.*), **43**, 904 (2002); *Chem. Abstr.*, **137**, 370651 (2002).

2002MI5 K. L. Paik, N. S. Baek, H. K. Kim, Y. Lee, and K. J. Lee, *Thin Solid Films*, **417**, 132 (2002); *Chem. Abstr.*, **138**, 90166 (2003).

2002MM7281 G. A. Sotzing and K. Lee, *Macromolecules*, **35**, 7281 (2002).

2002PMC40 G. A. Sotzing, K. Lee, L. Wu, and M. Marqeuz, *Polym. Mat. Sci. Eng.*, **86**, 40 (2002); *Chem. Abstr.*, **136**, 386772 (2003).

2002PMC195 K. Lee, L. Wu, G. A. Sotzing, and A. Gregory, *Polym. Mat. Sci. Eng.*, **86**, 195 (2002); *Chem. Abstr.*, **136**, 386527 (2002).

2002PP568 B. Lee and G. A. Sotzing, *Poyimer Reprints* (*Am. Chem. Soc.*, *Div. Polym. Chem.*), **43**, 568 (2002); *Chem. Abstr.*, **137**, 248076 (2003).

2002PP584 V. Seshadri, B. Lee, and G. A. Sotzing, *Polymer Reprints* (*Am. Chem. Soc.*, *Div. Polym. Chem.*), **43**, 584 (2002); *Chem. Abstr.*, **137**, 279570 (2003).

2002PP904 G. A. Sotzing, B. Lee, N. Reyes, and M. B. Smith, *Polymer Reprints* (*Am. Chem. Soc. Div. Polym. Chem.*), **43**, 904 (2002); *Chem. Abstr.*, **137**, 370651 (2003).

2002TL9615 M. L. Birsa, M. Cherinsky, and S. Braverman, *Tetrahedron Lett.*, **43**, 9615 (2002).

2003JOM39 J. Chanston, H. Gorls, and S. Lotz, *J. Organometall. Chem.*, **687**, 39 (2003).

2003MI1 S. Kobata and M. Irie, *Kagaku* (*Kyoto*, *Japan*), **56**, 19 (2001); *Chem. Abstr.*, **136**, 239250 (2003).

2003MI2 M. M. Krayushkin, "*The Chemistry and Biological Activity of Oxigen- and Sulfur-Containing Heterocycles*" Vol. 1, p. 289, Proceedings of II International Conference, ISB Press, Moscow (2003).

2003PMC268 G. A. Sotzing, V. Seshardi, K. Lee, B. Lee, and L. Wu, *Polym. Mat. Sci. Eng.*, **88**, 268 (2003); *Chem. Abstr.*, **138**, 354516 (2003).

2003PMC292 V. Seshadri, K. Lee, U. Salzner, and G. A. Sotzing, *Polym. Mat. Sci. Eng.*, **88**, 292 (2003); *Chem. Abstr.*, **138**, 386133 (2003).

2003PMC300 V. Seshardi, L. Wu, and G. A. Sotzing, *Polym. Mat. Sci. Eng.*, **88**, 300 (2003); *Chem. Abstr.*, **138**, 321951 (2003).

2003PP398 V. Seshadri and G. A. Sotzing, *Polymer Reprints* (*Am. Chem. Soc.*, *Div. Polym. Chem.*), **44**, 398 (2003); *Chem. Abstr.*, **140**, 17074 (2004).

2003PS1211 H. M. Moustafa, A. Khodary, and A. M. M. El-Saghier, *Phosphorus Sulfur Silicon Relat Elem.*, **178**, 1211 (2003).

2004AX(C)o1202 M. S. Khan, R. S. Al-Naamani, B. Ahres, and P. R. Raithby, *Acta Crystallogr. Sect. C*, **E60**, o1202 (2004).
2004CM5644 V. Seshadri and G. A. Sotzing, *Chem. Mater.*, **16**, 5644 (2004).
2004JMS107 S. H. Mashraqui, M. Ashraf, H. Hariharasubrahmanin, R. M. Kellog, and A. Meetsma, *J. Molec. Stuct.*, **689**, 107 (2004).
2004MI1 A. Comel, G. Sommen, and G. Kirsch, *Mini-Reviews in Organic Chemistry*, **1**, 367 (2004); *Chem. Abstr.*, **141**, 395447 (2004).
2004MM6306 X. Zhang, M. Koehler, and A. J. Adam, *Macromolecules*, **37**, 6306 (2004).
2004PP289 B. Lee and G. A. Sotzing, *Polymer Reprints* (*Am. Chem. Soc.*, *Div. Polym. Chem.*), **45**, 289 (2004); *Chem. Abstr.*, **141**, 24087 (2004).
2004S451 G. C. A. Sommen and K. G. Alain, *Synthesis*, 451 (2004).
2004VMS1674 E. N. Rodlovskaya, N. G. Frolova, E. D. Savin, and V. I. Nedel'kin, *Vysokomolekulyarnye Soedin.*, **46**, 1674 (2004).
2005KGS360 M. M. Krayushkin, M. A. Kalik, D. V. Kozhinov, A. Yu. Martynkin, Yu. P. Strokach, and V. A. Barchevskii, *Khim. Geterotsikl. Soedin.*, 360 (2005).
2005USC235 V. P. Litvinov, *Usp. Khim.*, **74**, 235 (2005).

Retrosynthetic Approach to the Synthesis of Phenothiazines

Ioan A. Silberg,[a] Gabriela Cormos,[b] and Daniela Carmen Oniciu,[c]

[a]*Department of Organic Chemistry, Babes-Bolyai University, Str. Arany Janos 11, RO-400028, Cluj-Napoca, Romania*
[b]*Victor Papilian Faculty of Medicine, Lucian Blaga University, Str. Pompeiu Onofreiu 2-4, RO-550166, Sibiu, Romania*
[c]*Department of Chemistry, University of Florida, Gainesville, FL 32611, USA*

I. Introduction

The first compound containing a phenothiazine ring, 3,7-diaminophenazathionium chloride, was obtained in 1876 by Lauth (1876CB1035). Bernthsen synthesized the parent phenothiazine in 1883, by heating diphenylamine with sulfur (1883CB2896).

The chemistry of phenothiazine has evolved in several directions since his discovery in the nineteenth century. Initially, the interest in this heterocycle was due to its quinonoid derivatives, widespread as intermediates in sulfur dye chemistry (1876CB1035, 12CB2012). Then followed the discovery of the antihelmintic action of unsubstituted (50MI(1)124) and of some C-substituted (56AJC397) phenothiazines, which made these compounds important adjuvants in the meat industry that increased the availability of animal products. The brightest period started in the 1950s with the introduction of phenothiazine derivatives in medicine. The antihistaminic (46MI363, 48MI197) and neuroleptic (52MI206) action of some N,C-substituted phenothiazines has made them essential chemotherapeutic tools even nowadays. Lately, the research in this class has been focused on the synthesis

ADVANCES IN HETEROCYCLIC CHEMISTRY
VOLUME 90 ISSN: 0065-2725 DOI: 10.1016/S0065-2725(05)90003-2

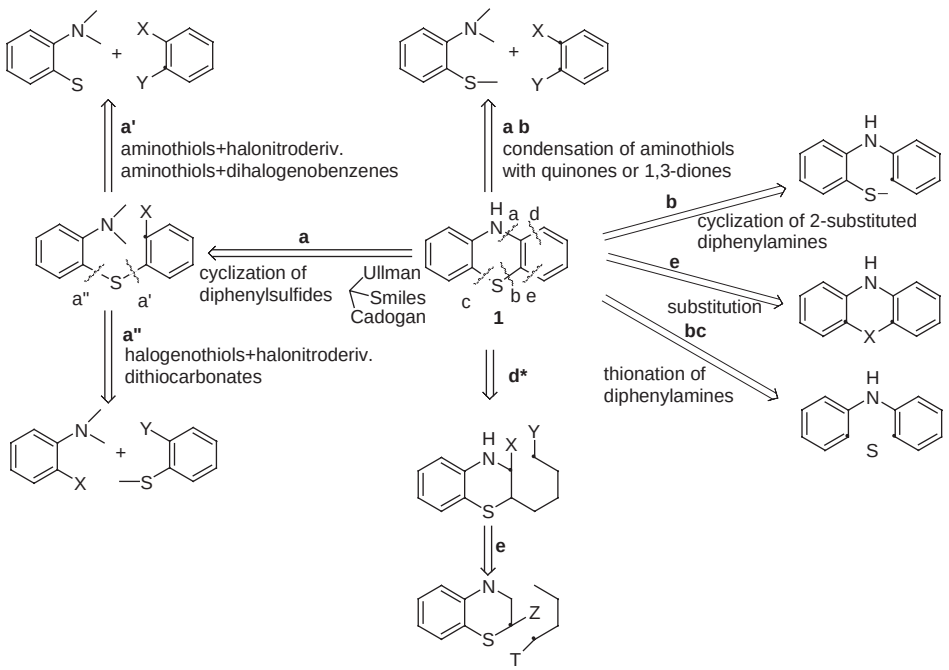
and investigation of the properties of new phenothiazines in the quest for advanced materials with potential use in modern applied physics.

The literature on phenothiazine derivatives was reviewed exhaustively in an earlier monograph edited by R. R. Gupta (88MI1).

In the synthesis of phenothiazines, ring closure successfully rivals with other reactions involving functional group insertion, removal or modification, and the scope of this review is to summarize the cyclization reactions known to produce the phenothiazine ring based on a retrosynthetic analysis scheme. Although we tried to ensure the coverage of all known synthetic pathways, the literature references are, however, limited to the most significant examples (the same procedure, e.g. thionation, has been used without relevant modifications by a spate of authors).

The purpose of the retrosynthetic analysis consists in identifying and disconnecting the strategic chemical bonds in the target molecule, bonds that can be easily reconnected synthetically. Such successive disconnections yield syntons and starting molecules with simple structures (eventually commercial compounds).

According to the accepted rules, in such retrosynthetic analyses, we indicate the bond that will be disconnected in the target molecule and used an arrow $\Rightarrow$ to show the resultant precursors. Under this arrow, we mention the reactions that allow the reconnection of the respective bond. The disconnection possibilities for the phenothiazine molecule are depicted in Scheme 1.



Scheme 1

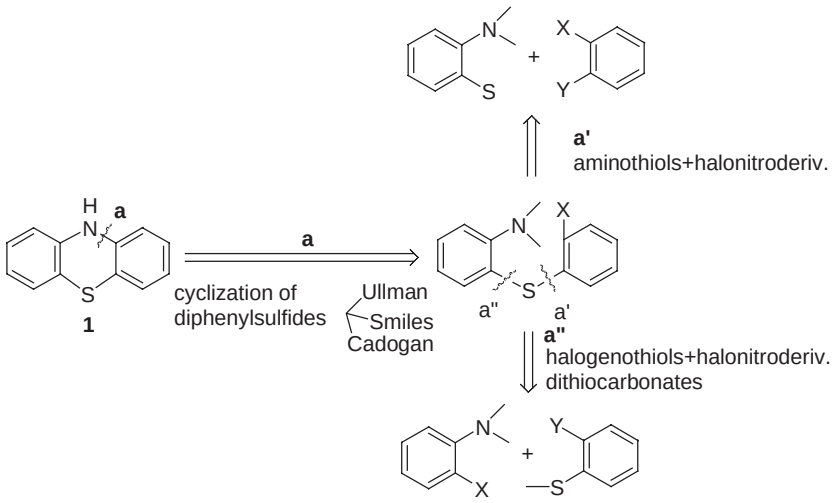
II. Syntheses *via* "a, a′, a″"

A first retrosynthetic approach disconnects the C–N bond yielding a diphenyl sulfide that can remake the initial phenothiazine *via* cyclization (Scheme 2). Sulfides that could produce phenothiazines by cyclization can be prepared as described in Section II.B. This is a relatively general pathway that allows for the synthesis of a large number of phenothiazine derivatives.

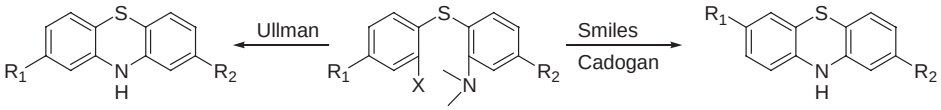
A. Cyclization of Sulfides

The preparation of phenothiazines by the "a" pathway of the retrosynthetic analysis (Schemes 1 and 2) encompasses the cyclization of suitably substituted diphenyl sulfides.

In the left ring of the diphenyl sulfide molecule, there are two reaction centers that may undergo nucleophilic attack by the nitrogen atom of the amino group: the carbon atom to which the sulfur bridge is attached (and in this case the reaction occurs *via* a Smiles rearrangement or a Cadogan mechanism), or the carbon atom carrying the X group (when the reaction occurs *via* an Ullmann cyclization) (Scheme 3).



Scheme 2



Scheme 3

The reaction pathway is determined by the nature and the position of the substituents on the two rings and by the reaction conditions. Usually, when $-N<$ is an amino group and X is a halogen, the reaction occurs *via* an Ullmann cyclization, and when $X = NO_2$, a Smiles rearrangement is preferred.

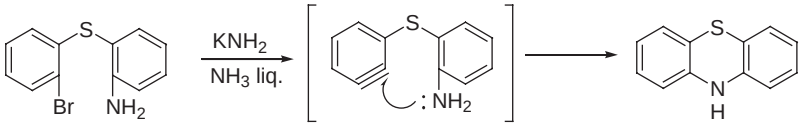
1. *Cyclization of Diphenyl Sulfides*

a. Syntheses via Ullmann-Type Cyclization. Hrutford and Bunnett (58JA2021) obtained phenothiazine (35% yield) by the treatment of *o*-amino-*o'*-bromodiphenyl sulfide **2** with KNH_2 in liquid ammonia. The reaction occurs with a benzyne as intermediate (Scheme 4).

In the same way, 2-bromo-2′-hydrazino-diphenyl sulfide cyclizes to *N*-aminophenothiazine (also through a benzyne intermediate) (78JHC1137). Other syntheses of phenothiazine derivatives by an Ullmann-type cyclization were reported earlier (50JA888, 81JHC759, 57USP2769002).

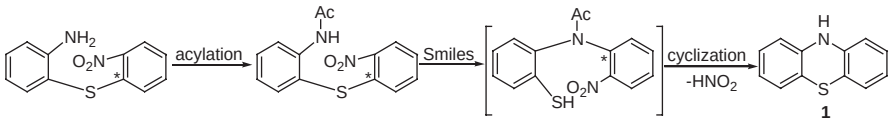
b. Syntheses of Phenothiazines via Smiles Rearrangement. The cyclization *via* the Smiles rearrangement comprises two steps: the actual Smiles rearrangement, followed by a cyclization involving the loss of nitrous acid (Scheme 5).

i. The Smiles Rearrangement. The Smiles rearrangement is an intramolecular nucleophilic aromatic substitution resulting in the migration of an aromatic ring from one heteroatom to another (31JCS3264, 39AR191, 53JCS4198 58QR1, 51CRV362, 35JCS181) (Scheme 6).

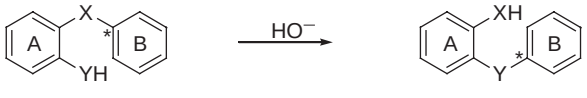


2 **1**

Scheme 4



Scheme 5



3 **4**

Scheme 6

There are two steps in this rearrangement that are governed by similar parameters:

(i) The first step is of the generation of the nucleophilic attacking group, which is usually base catalyzed, and involves the conversion of the $-YH$ moiety to $-Y^-$ by proton removal using sodium or potassium hydroxide, or by other strong base. This first step is affected by some factors:

The alkalinity of the medium: in alcoholic solvents, the rate of the rearrangement increases in the order $NaOH < NaOMe < NaOEt < NaOPr\text{-}i$ that appears to be the order of proton acceptance by the corresponding base (88MI1);

The acidity of the YH function: when $YH = NH_2$ substituents such as NHCHO, $NHCOCH_3$, $NHCOC_6H_4NO_2$-2, $NHCOC_6H_2(NO_2)_3$-2,4,6, $NHSO_2C_6H_5$ enhance the acidity of this group. Diphenyl sulfides with $NHCH_3$ do not rearrange because of the non-acidifying character of the CH_3 group (88MI1).

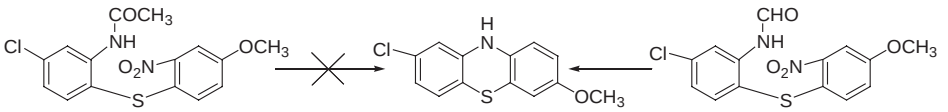
(ii) The second step of the rearrangement encompasses the nucleophilic attack of the Y^- moiety at the carbon atom (*) of the B ring to produce structure **4**. This step is influenced by similar factors:

The nucleophilic character of the Y^- moiety: although the substituents mentioned enhance the acidity of YH function ($YH = NH_2$), they decrease the nucleophilicity of the anion Y^-, therefore the rearrangement appears to be the result of two counterbalancing effects. Diphenyl sulfides with $-NHCHO$, $-NHCOCH_3$, $-NHCOC_6H_4NO_2$-2 as the YH moiety undergo a Smiles rearrangement whereas diphenyl sulfides with $NHCOC_6H_2(NO_2)_3$-2,4,6 or $NHSO_2C_6H_5$ fail to undergo this transformation. Although they are sufficiently acidic to ionize, they are too weakly nucleophilic to perform the second step of the rearrangement (88MI1).

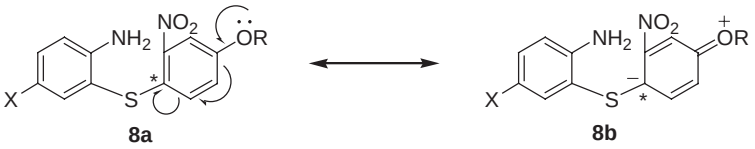
Sometimes acetamides fail to rearrange (56JOC28, 57JA4375, 59JOC968) while formamides undergo rearrangement and cyclization, i.e. 2-acetamido-4-chloro-4′-methoxy-2′-nitrodiphenyl sulfide **5** failed to undergo rearrangement to 2-chloro-7-methoxyphenothiazine **6** whereas the corresponding formyl derivative **7** provided the desired compound **6** (64JOC2453) (Scheme 7).

The electrophilic character of the carbon atom (*) of ring B: This factor is strongly affected by the substituents of the B ring. Usually an *ortho*- or *para*-nitro function is used as an activating group. It is interesting that a single *ortho* group is a stronger activator than a solitary *para*-nitro group (32JCS1488, 35JCS1234).

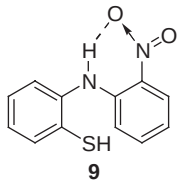
The actions of the substituents and the interactions between them may be illustrated by the following example: 2-amino-4-halo-4′-alkoxy-2′-nitrodiphenyl sulfides such as **8a** do not undergo a Smiles rearrangement (56JOC28) because although the 4-halo-substituent acidifies the NH_2 group, the electron donating effect of an alkoxy group at 4′ position decreases too strongly the electrophilicity of carbon (*) (Scheme 8).



Scheme 7



Scheme 8



Scheme 9

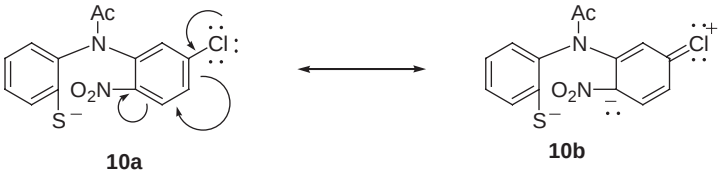
As an essential steric requirement for this step, the substituents must be in positions that enable transient intermediate formation with a five- or a six-membered ring (32JCS1488).

As shown in Scheme 6, the attack of the Y^- anion on the carbon atom (*) is followed by the displacement of the $-X^-$ moiety (31JCS3264, 39AR191, 53JCS4198, 58QR1, 51CRV362, 35JCS181). The propensity of X to be displaced is governed by the relative electronegativity of Y compared to X. This can be illustrated by the rearrangement of the compounds containing $-YH$ as $-NHAc$ and X = S, SO or SO_2 (35JCS181). When YH = OH (phenolic) the change takes place only if X = SO_2 or SO and not S.

Hydrogen bridges may affect the rearrangement, as for example in derivative **9** (88MI1, 57JPJ485, 66JMC116). In N-acylated and N-alkylated derivatives hydrogen bonding is not possible, and this is one of the important reasons why the N-acylation is necessary (Scheme 9).

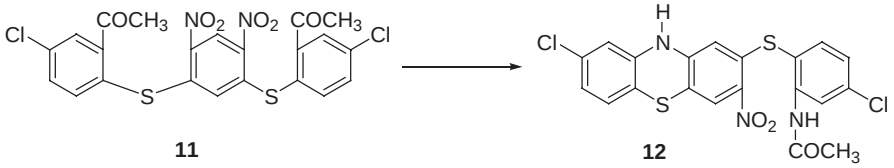
ii. The Cyclization. The next synthetic step in this preparation of phenothiazines is an aromatic nucleophilic substitution by the sulfur anion to the carbon atom carrying the nitro group. The electrophilic character of the carbon atom, which is affected by the neighboring substituents, influences this step. Thus, a halogen atom in the *ortho* or *para* position to the nitro group interferes with the ring closure, probably through a resonance effect rather than an inductive one. For example, the carbon atom in structure **10a** bears a partially negative charge (**10b**) and the nucleophilic attack does not take place (58JOC1804) (Scheme 10).

There are many examples in the literature for the preparation of phenothiazine derivatives by cyclization *via* a Smiles rearrangement: halogenated phenothiazines (92JHC1703, 84JHC893, 94PHA453, 93PHA620) substituted 1,2-dichloro- (92JHC1703), 1,3-dichloro- (93PHA620), 1,4-dichlorophenothiazines (94PHA453), substituted monofluoro-phenothiazines (98HEC277, 99JFC153) (3-F-1-Me-, 7-F-9-Me-, 1-Cl-3-F-, 3-Cl-5-F), trifluoro-phenothiazines (93JFC191, 97MI(1)672, 95HEC445, 95HEC315, 95HEC203), nitro-phenothiazines (98HEC277,



10a **10b**

Scheme 10



11 **12**

Scheme 11

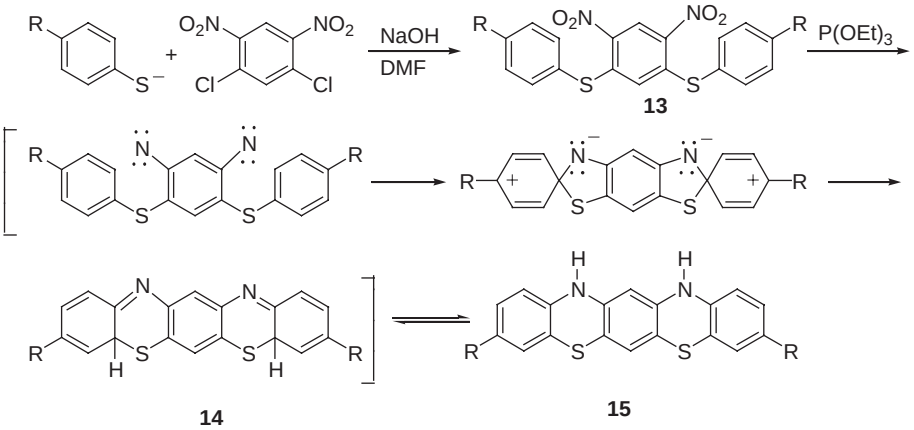
97MI(1)672, 95HEC445, 95HEC315, 95HEC203, 95HEC95, 80H(14)6831, 99PS(152)77, 84JHC893, 80JHC1325, 81H(16)1527 (1-nitro, substituted-1-nitro-, 1,7-disubstituted-, 3-alkoxy-7-substituted-, 3-Me-)), substituted, alkylated and alkoxylated derivatives (93JFC191, 97MI(1)672, 95HEC445, 95HEC315, 95HEC203, 95HEC95, 80H(14)6831, 99PS(152)77, 84H(22)1169 84JHC893 (1,3-dimethyl-, 1,4(6,9)-dimethyl, 1-methyl-3-chloro-, 7-phenoxy-)) and other compounds with combinations of substituents (93JFC191, 98HEC277, 95HEC445, 95HEC315, 95HEC203, 95HEC95, 80H(14)6831, 99PS(152)77, 84H(22)1169, 92JHC1703, 84JHC893, 99JFC153, 80JHC1325, 81H(16)1527, 94PHA689, 86PHA830, 94PHA453, 93PHA620, 92PHA945). The intramolecular cyclization (*via* the Smiles rearrangement) of 2-nitro-2′-(*β*-acetyl)-hydrazino-diphenyl sulfide yields 10-acetylaminophenothiazine (84PHA22).

Similarly, 10-*β*-dialkylaminophenothiazines were prepared from 2-nitro-2′-(*β*-dialkylaminoacetyl)hydrazino-diphenyl sulfides (cyclization followed by reduction with $LiAlH_4$) (78JHC969). Some of these products were screened for their biological activity and pharmaceutical properties.

Warburton et al. (57AJC502) have tried the synthesis of 1,4-benzothiazino[2,3-*b*]phenothiazine from 4,6-*bis*[(2-acetamido-4-chlorophenyl)thio]-1,3-dinitrobenzene **11** by a double Smiles rearrangement. Unfortunately, the reaction stops after the first rearrangement to yield phenothiazine derivative **12** (Scheme 11).

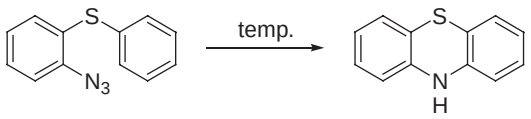
Other syntheses of phenothiazines *via* Smiles rearrangements fall into the next sections.

c. Reductive Cyclization of Nitrodiphenyl Sulfides (Cadogan Mechanism). Cadogan et al. (66JCS(CC)491) performed a reductive cyclization of *o*-nitrodiphenyl sulfide to phenothiazines using triethyl phosphite. This method allowed for the preparation of dialkyl-1,4-benzothiazino[2,3-*b*]phenothiazine derivative **15** (94JOC2743) obtained from 4-(1,1-dimethylpentyl)thiophenol **13** *via* dinitrene intermediate **14**, according to the Cadogan mechanism (Scheme 12) (69S11).



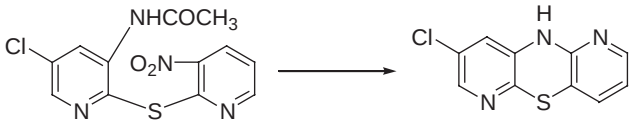
13 14 15

Scheme 12



16 1

Scheme 13



17 18

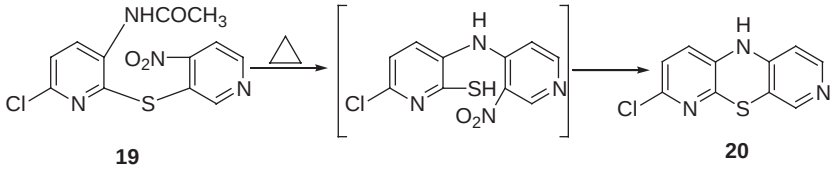
Scheme 14

Unsubstituted phenothiazine was also obtained by a nitrene mechanism from phenyl 2-azidophenyl sulfide **16** (53JA6335) (Scheme 13).

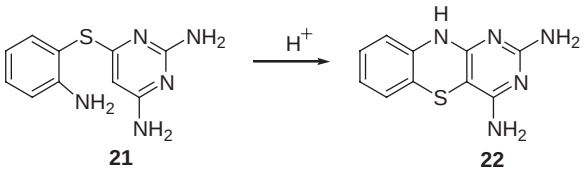
2. *Syntheses of Azaphenothiazine Derivatives*

a. Syntheses from Dipyridyl Sulfides. Diazaphenothiazines such as **18** (64JOC2652) have been prepared by an intramolecular Smiles rearrangement and subsequent cyclization of dipyridyl sulfides such as **17** (Scheme 14).

The synthesis of compound **18** takes place in boiling alcohol/acetone with potassium hydroxide as dehydrating agent, but in such systems a thermally induced rearrangement **19**→**20** (57YZ485) has also been observed (Scheme 15) depending on



Scheme 15



Scheme 16

the electronic nature of the substituents and their position. The π-deficient nature of the pyridine ring plays a role as well.

b. Syntheses from Pyrimidyl Phenyl Sulfides. Pyrimidyl phenyl sulfide **21** undergoes cyclization *via* a Smiles rearrangement to produce pyrimidyl benzothiazin **22** under acid catalysis (63JOC2652) (Scheme 16). An explanation of the Smiles rearrangement in acid catalysis will be given in Section II.B.1.b.i.

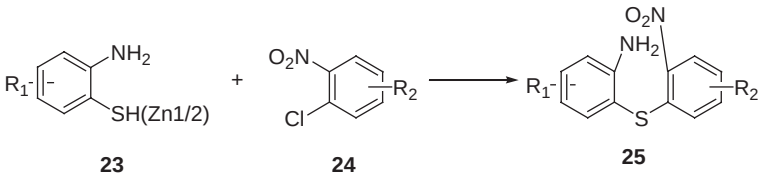
B. Syntheses of Sulfides

As shown in Schemes 1 and 2, sulfide precursors of phenothiazines may be disconnected in two ways: a′ and a″.

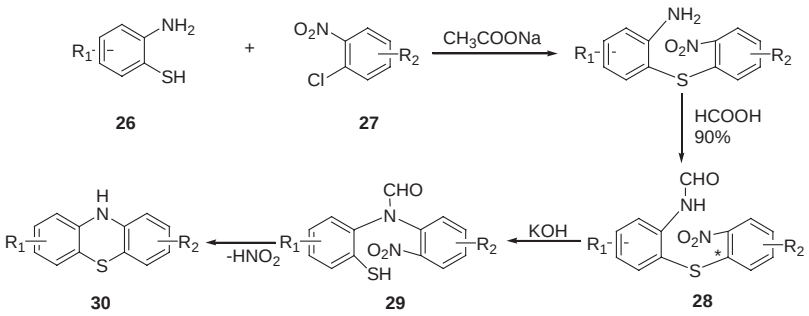
1. *Syntheses via "a"*

2-Aminobenzenethiols and their sodium or zinc salts such as **23** react with *o*-halonitrobenzenes **24** under alkaline conditions yielding 2-amino-2′-nitrophenyl sulfides (Scheme 17). The method is also used for the preparation of fused cycle derivatives: benzophenothiazines and azaanalogs.

a. Syntheses from Aminobenzenethiols and Halogeno-nitrobenzenes. Gupta et al. (93JFC191, 98HEC277, 97MI672, 95HEC445, 95HEC95, 80H(14)6831, 84H(22)1167, 92JHC1703, 84JHC893, 99JFC153, 81H(16)1527, 80JHC1325, 94PHA689, 86PHA830, 94PHA453, 93PHA620, 92PHA945, 79IJC(18B)274, 81JHC1527, 58YZ417, 87PHA830, 84H(22)1169) and other authors (95HEC315, 95HEC203, 99PS(152)77, 79CIL349) have prepared a large variety of substituted diphenyl sulfides from aminobenzenethiols **26** and halogeno-nitrobenzenes **27** under alkaline conditions (Scheme 18). The acyl or formyl **28** derivatives of these sulfides rearrange



Scheme 17



Scheme 18

via a Smiles rearrangement and the formyl intermediate **29** cyclizes readily to phenothiazine **30** through the loss of nitrous acid (see Section II.A.1.b).

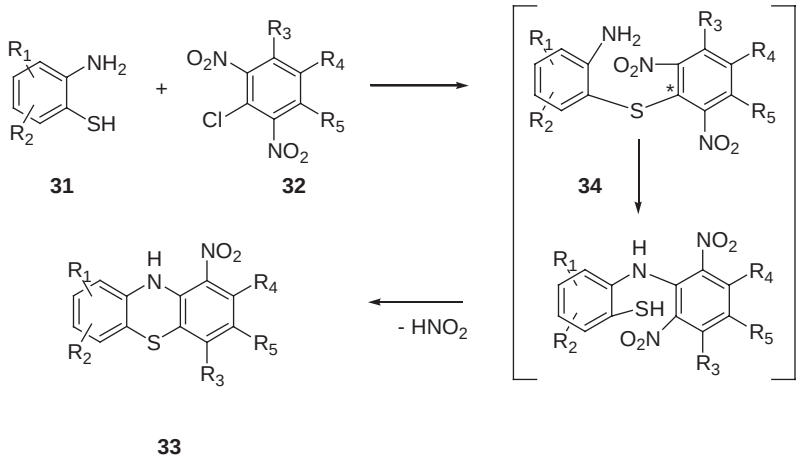
The reaction of 2-aminobenzenethiols **31** with halonitrobenzenes such as **32** (containing two nitro groups or one nitro group and one halogen atom at both *ortho* positions to the reactive atom) provides directly phenothiazines **33** instead of the expected diphenyl sulfides **34**. Gupta et al. have investigated this pathway and developed a one-pot method for the synthesis of substituted phenothiazines (98HEC277, 97MI672, 95HEC445, 95HEC95, 92JHC1703, 84JHC893, 99JFC153, 80JHC1325, 79IJC(17B)626, 79CIL349, 79SC457, 87SC229) (Scheme 19).

The increased resonance effect due to the presence of two nitro groups at both *ortho* positions and combined resonance and inductive effects enforced by one nitro and one halogen atom activate the Smiles rearrangement as well as the ring closure to such an extent that both processes take place instantaneously. However, the resonance effect in 2,4-dinitrochlorobenzene is not so pronounced and its reaction with 2-aminobenzenethiol does not go in one step (88MI1).

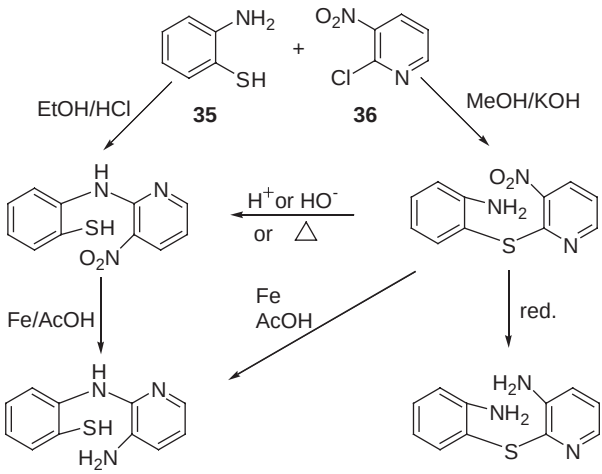
b. Syntheses of Sulfide Derivatives

i. Syntheses from Aminobenzenethiols and Halonitropyridines. 2-Aminobenzenethiol **35** reacts with 2-chloro-3-nitropyridine **36** in acidic and basic conditions to provide thiophenylnitropyridylamine **37** and aminophenylnitropyridyl sulfide **38** (88MI1) (Scheme 20), followed by reduction to give the corresponding aminoderivatives **39a** and **39b**.

The acid catalyzed Smiles rearrangement of phenyl pyridyl sulfide **38** is probably due to the protonation of the ring-nitrogen atom in pyridine that increases the ease of nucleophilic substitution (56JCS1563, 62JA2770) (Scheme 21).



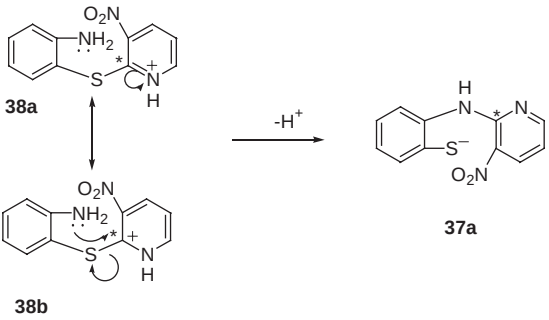
Scheme 19



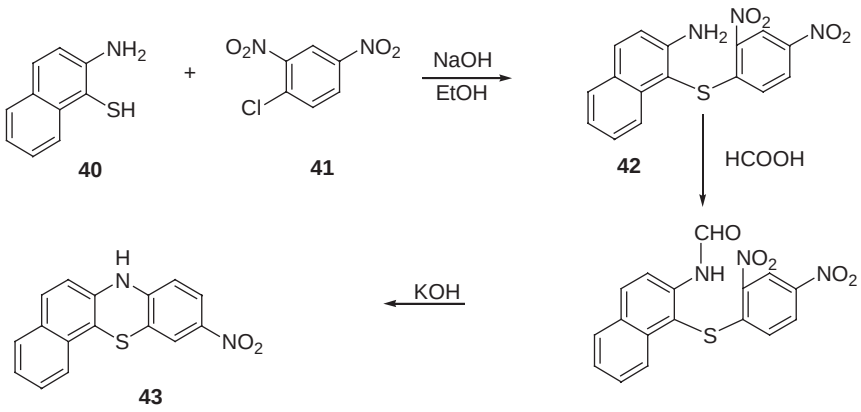
Scheme 20

2-Mercaptophenyl-3′-nitro-2′-pyridylamine **37a** does not undergo cyclization with ethanolic KOH even after 10 h reflux. The failure of cyclization has been attributed to the strong hydrogen bonding between the amino hydrogen atom and the *o*-nitro group (57JPJ485, 66JMC116). The reaction in the presence of DMSO provides 1-azaphenothiazine by cyclization. In systems such as DMSO + protic solvents, the mechanisms of DMSO-induced nucleophilic catalysis apparently depends upon the relative concentration of the solvent components (64JOC3262).

Attempts have been made to synthesize azaphenothiazines by a Smiles rearrangement of 2-formamidophenyl 3′-nitro-2-pyridyl sulfide and 2-formamidophenyl-3′-nitro-4′-pyridyl sulfide (88MI1, 58JOC1906).



Scheme 21



Scheme 22

However, 1-azaphenothiazines have been prepared (58JA1651) by hydrolysis of 1-acetyl-1-azaphenothiazine, obtained by Smiles rearrangement of 2-acetamidophenyl 3′-nitro-2′-pyridyl sulfides (in acetone-ethanol and KOH).

ii. Syntheses of Benzophenothiazine from Aminonaphthalenethiols and Chloronitrobenzenes. 2-Aminonaphthalenethiol **40** reacts with 2,4-dinitrochlorobenzene **41** (62JOC1659) yielding the 2,4-dinitrophenyl naphthyl sulfide **42**. The reaction is followed by a Smiles rearrangement and cyclization finally providing 7H-benzo[*c*]phenothiazine **43** (Scheme 22).

Nitrohalobenzenes containing two nitro groups at both *ortho* positions to the halogen atom react with 2-aminonaphthalenethiol yielding directly 8-nitro-7H-benzo[*c*]phenothiazines (71M760, 76BCJ2026). The explanation of this behavior is the same as in the case of 2-aminobenzenethiols and polynitrohalobenzenes containing two nitro groups at *ortho* position to the halogen atom.

Based on the reaction displayed in Scheme 22, one could expect that the phenothiazine ring could be prepared from aminobenzenethiols and 1,2-dihalogenobenzenes. However, the low reactivity of halogen atoms attached to the benzene ring makes this method difficult.

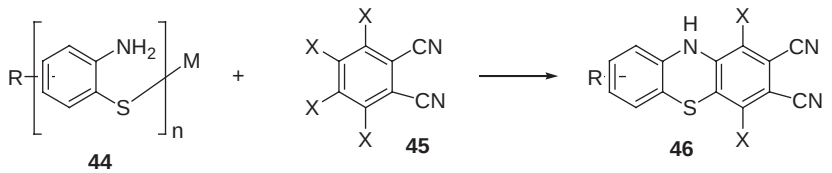
Nevertheless, some substituted phenothiazines **46** (R = H, alkyl, alkoxy, halogen; X = halogen) were synthesized by the reaction of tetrahalophthalonitriles **45** (X = halogen) with 2-aminothiophenol metal salts **44** (99JAP(K)171878) (Scheme 23).

If nitrogen-containing heterocyclic systems are used, the halogen atom becomes more reactive, and this is an elegant preparation method for azaphenothiazine derivatives.

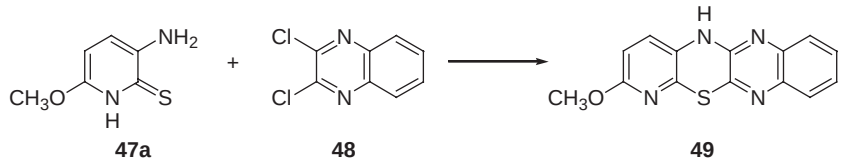
iii. Syntheses from 3-Aminopyridine-2-thiols. Triazaphenothiazine derivatives such as **49–51** (71IJS237, 73JOC4386, 77MI249, 78PS(4)79, 80JHC149) were synthesized by basic catalyzed condensation of 3-aminopyridine-2-thiol with quinoxalines and pyrazines *via* Smiles rearrangement (Schemes 24 and 25).

iii.a. Reactions with Quinoxalines. 2,3-Dichloroquinoxaline **48** (prepared from appropriately substituted *o*-phenylenediamines) reacts with 3-amino-6-methoxy-2-pyridine-thiol **47a** (by refluxing in alkaline DMF solution) yielding 7-methoxy-1,4,6-benzo[*b*]triazaphenothiazine **49** (25HCA16, 43JCS322, 48JCS777, 31JA245, 46JA1035, 53JCS2816, 73JOC4386) (Scheme 24).

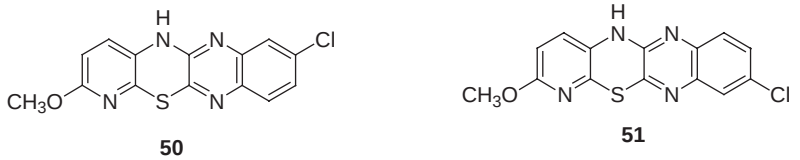
Other derivatives containing substituents in positions 7 and 12 have been analogously prepared (45JCS591). Using trichloroquinoxaline, the reaction produced a compound for which two structures are possible (**50** and **51**, Scheme 25).



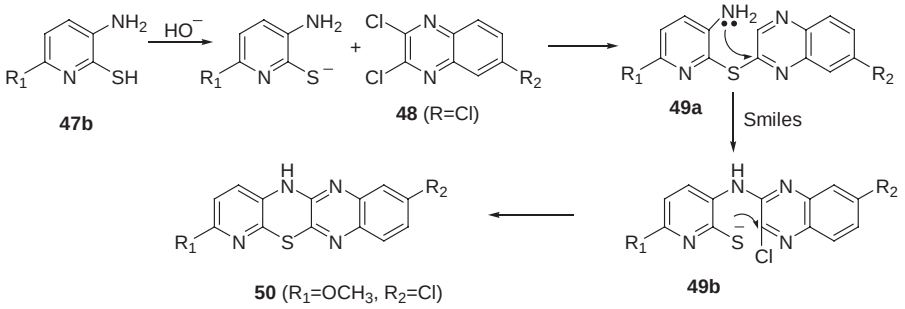
Scheme 23



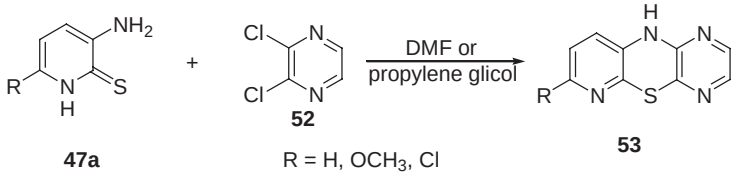
Scheme 24



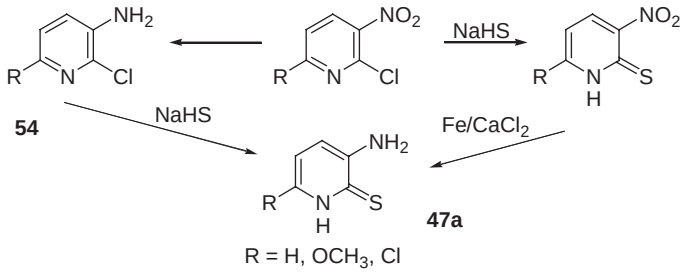
Scheme 25



Scheme 26



Scheme 27



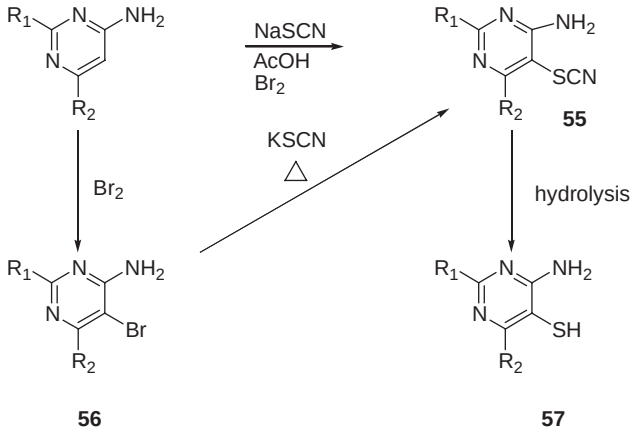
Scheme 28

The fact that the resulting products correspond to structure **50** demonstrates (45JCS591) that the condensation takes place *via* the Smiles rearrangement (Scheme 26).

iii.b. Reactions with Dichloropyrazines. 1,4,6-Triazaphenothiazine **53** was prepared (82JOC592) by condensation of 2,3-dichloropyrazine **52** with 3-aminopyridine-2-thione **47a** (Scheme 27).

There are several methodologies for the preparation of 3-aminopyridine-2-thione **47a** (64JOC2652, 54JCS4516) (Scheme 28), among them the reduction of the corresponding chloro-derivative **54** with sodium hydrosulfite or $Fe/CaCl_2$.

iv. Syntheses from Pyrimidinethiols and Quinoxalines. Tetraazaphenothiazines were prepared by condensation of 4-aminopyrimidine-5-thiols with quinoxalines in polar solvents (80JHC1587). The reaction produced a compound with two structural possibilities (see a similar example in Section II.B.1.b.iii.a), but again the final



Scheme 29

Scheme 30

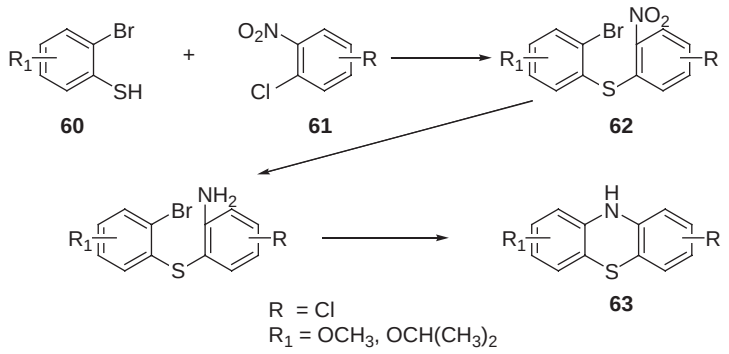
product indicated that the formation of tetraazaphenothiazine proceeded *via* a sulfide, which underwent a Smiles rearrangement (88MI1).

4-Aminopyrimidinethiols **57** required for this synthesis have been prepared from 4-amino-5-thiocyanatopyrimidine derivatives **55**, which are obtained by two methods: bromination of the corresponding 4-aminopyrimidine to give derivative **56**, and its subsequent treatment with potassium thiocyanate or by direct treatment of 4-aminopyrimidines with NaSCN and AcOH/Br_2 solution (63JOC1488, 73JOC4386, 69JCS(C)603, 67JCS2562) (Scheme 29).

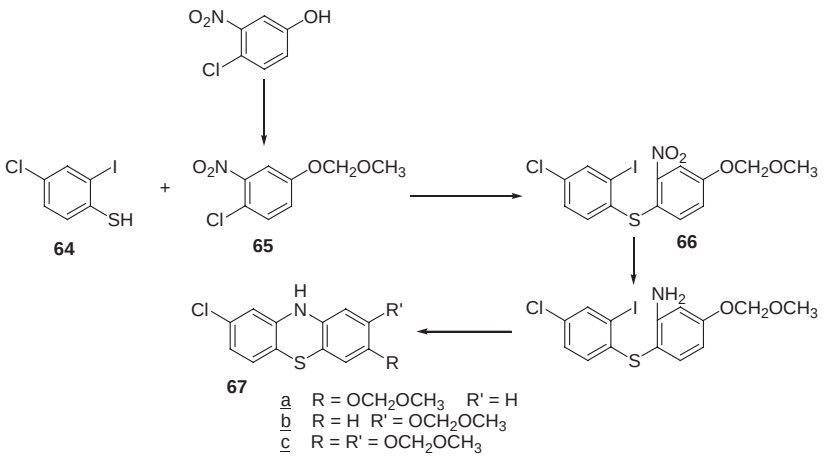
2. *Syntheses via "a'"*

This disconnection step leading to the synthesis of phenothiazines from fragments **58** and **59** is shown in Scheme 30. The preparation methods based on this scheme can be found in the chemical literature as preparations of phenothiazines by diphenyl sulfide intermediates from 2-bromo- or 2-iodo-benzenethiols and chloronitrobenzenes and as a special synthesis involving dithiocarbonates.

a. Syntheses from Halogenobenzenethiols and Chloronitrobenzenes. 2-Bromobenzenethiols **60** react with chloronitrobenzenes **61** yielding 2-nitro-2′-bromodiphenyl sulfides **62** that undergo an Ullmann-type cyclization with subsequent reduction, yielding phenothiazines **63** (88MI1) (Scheme 31). Similarly, N-formylated diphenyl sulfides react *via* a Smiles rearrangement yielding isomeric phenothiazines (64JOC2453).



Scheme 31



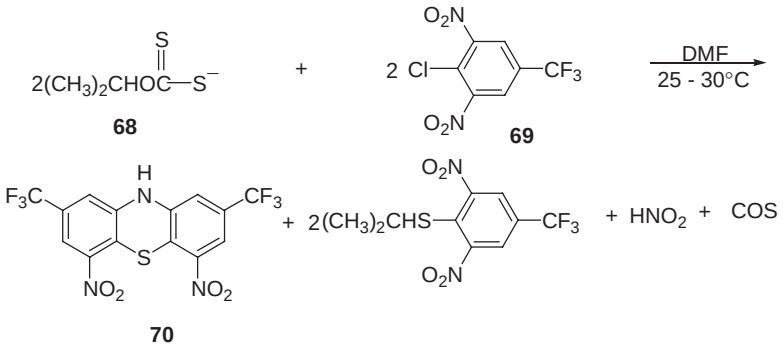
Scheme 32

2-Iodo-4-chlorobenzenethiol **64** reacts with *o*-halonitrobenzenes **65** to give diphenyl sulfides **66** that produce phenothiazines **67** on catalytic reduction followed by ring closure when heated with a copper–bronze catalyst (66JOC625, 77JHC107) (Scheme 32).

b. Syntheses from Dithiocarbonates. 4-Chloro-3,5-dinitrotrifluoromethylbenzene **69** reacts with potassium isopropyldithiocarbonate **68** leading to the corresponding trifluoromethylphenothiazine **70** (79PS(7)143, 77JOC2896, 78PS(4)267, 76JOC3564) (Scheme 33).

The reaction mechanism involves the formation of a sulfide intermediate **71** as depicted in Scheme 34.

A route to the preparation of trifluoromethylphenothiazine **70** involves the reaction of 4-chloro-3,5-dinitrotrifluoromethylbenzene **69** with sodium hydrosulfite in DMF *via* diaryl sulfide **71** (Scheme 35).



Scheme 33

III. Syntheses *via* "a–b"

The simultaneous a–b disconnection of a phenothiazine nucleus provides fragments **72** and **73** (Scheme 36). The following synthetic schemes corresponding to this fragment analysis have been described in the chemical literature:

(i) 2-Aminoarylthiols and halonitrobenzenes (see Section I);
(ii) 2-Aminoarylthiols and 1,4-quinones – where the aryl groups are benzene or naphthalene rings, and 1,4-quinones are substituted benzoquinones, naphthoquinones and anthraquinones (see Section III.A) and
(iii) 2-Aminobenzenethiols and cyclohexane-1,3-dione (see Section III.B).

A. Syntheses from 2-Aminoarylthiols and 1,4-Quinones

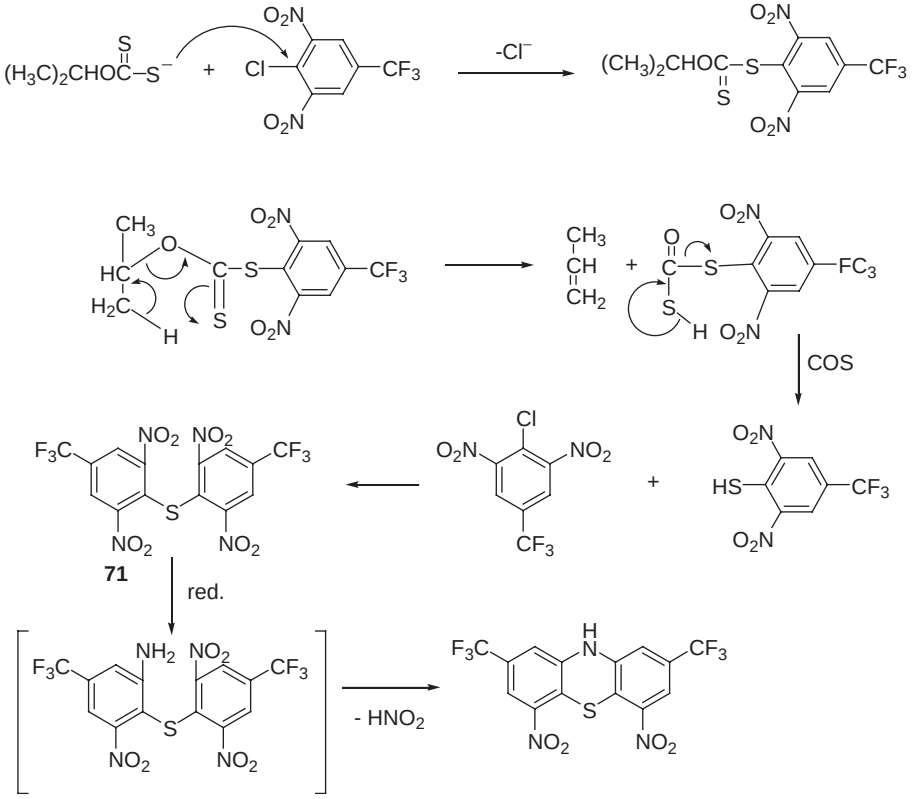
1. *Syntheses from 2-Aminobenzenethiols and Benzoquinones*

2-Aminobenzenethiols and their zinc salts **74** react with 1,4-benzoquinones such as **75** yielding phenothiazines **76** as depicted in Scheme 37.

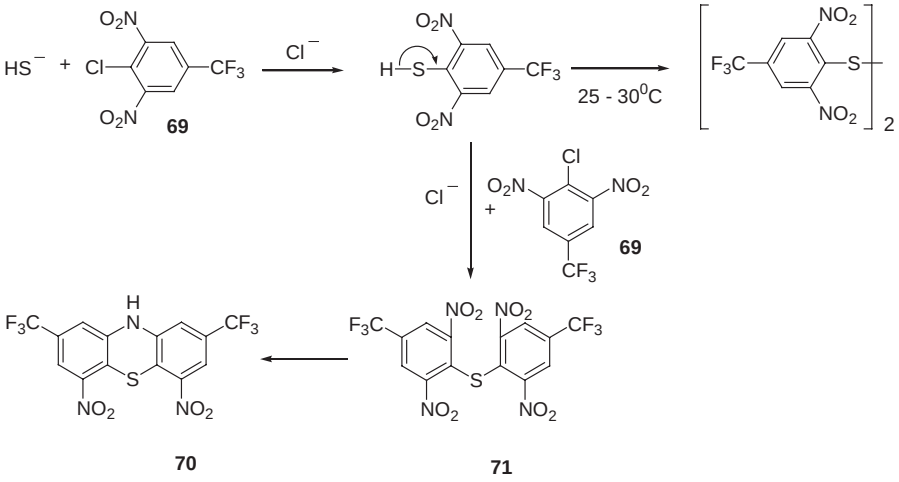
Both rings may carry different substituents. The mechanism of the reaction was investigated by Terdic (71LA(746)200, 78LA1285). Examples of derivatives synthesized by this approach are 7/8-chloro-1-methoxyphenothiazin-3-ones (from 2-methoxy-6-chloro-1,4-benzoquinones), 7-substituted 1-methoxyphenothiazin-3-ones, 1-methoxy-8-trifluoromethylphenothiazin-3-ones. Similarly were obtained 2-trifluoromethylphenothiazin-3-one, 2-methoxy-7/8-trifluoromethylphenothiazin-3-ones and 7-fluoro-2-methoxyphenothiazin-3-ones (88MI1). Trihalo-substituted phenothiazin-3-ones were prepared from chloranil or bromanil (88MI1) (Scheme 38).

The reaction has also been extended to 2,3-dimethyl- and 2,3,5-trimethyl-1,4-benzoquinones that afforded dimethyl- and trimethylphenothiazin-3-ones (84PHA355, 70JA1651).

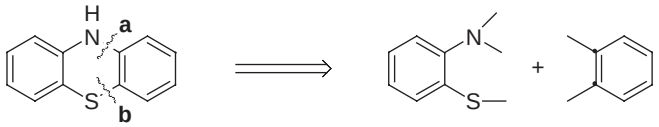
The condensation of 2,5-dithioalkyl-1,4-benzoquinones **81** with 2-aminobenzenethiol **80** yielded 1,4-dithioalkylphenothiazin-3-ones **82** (84KG334) (Scheme 39).



Scheme 34

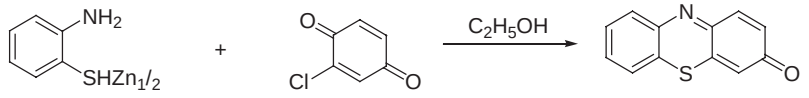


Scheme 35



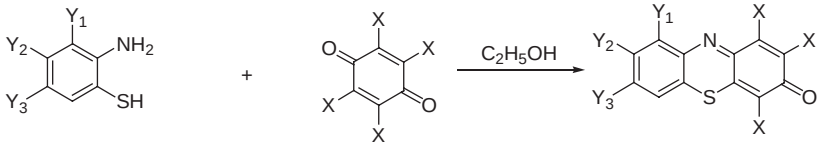
1 **72** **73**

Scheme 36



74 **75** **76**

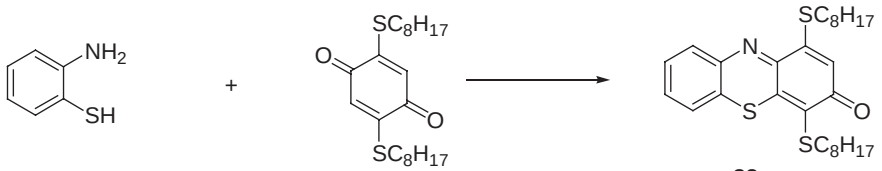
Scheme 37



77 **78** **79**

a:	X = Cl	Y_1 = Cl	b:	X = Br	Y_1 = Cl
c:	X = Cl	Y_1 = OCH_3	d:	X = Br	Y_1 = OCH_3
e:	X = Cl	Y_2 = CF_3	f:	X = Br	Y_2 = CF_3
g:	X = Cl	Y_3 = H	h:	X = Br	Y_3 = H
k:	X = Cl	Y_3 = Br	l:	X = Y_3 = Br	
m:	X = Cl	Y_3 = CH_3	n:	X = Br	Y_3 = CH_3

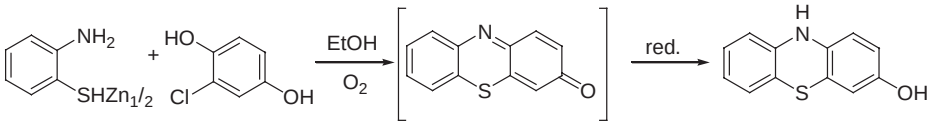
Scheme 38



80 **81** **82**

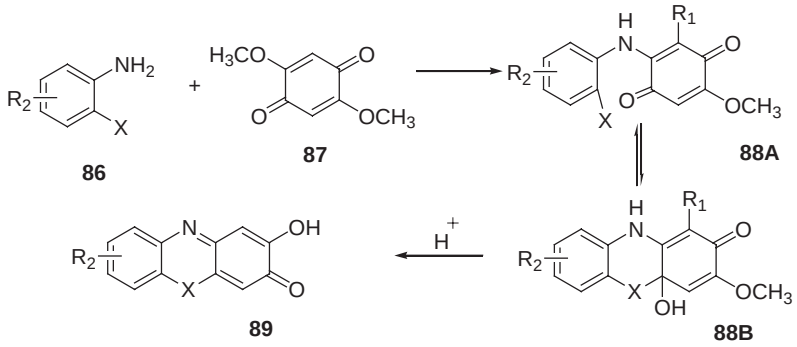
Scheme 39

Analogously, 4-acyl-1,2-dimethylphenothiazin-3-ones have been synthesized by the reaction of 2-aminobenzene-thiol and 2-acyl-5,6-dimethyl-1,4-benzoquinones (81JHC645). This method was also used to prepare hydroxyphenothiazines, hard to obtain in other ways. Thus, hydroxyphenothiazines such as **85** have been prepared



74 83 84 85

Scheme 40



86 87

c,d	R_1	R_2	X		R_1	R_2	X
1)	$COCH_3$	H	S-CH_2OCH_3	8):	$COCH_3$	4-CH_3	S-SO_3H
2):	CO_2 CH_3	H	S-CH_2OCH_3	9):	$COCH_3$	4-OCH_3	S-SO_3H
3):	$COCH_3$	5- CH_3	S-CH_2OCH_3	e			
4):	$COCH_3$	5- OCH_3	S-CH_2OCH_3	1):	$COCH_3$	H	S
5):	$COCH_3$	5-Cl	S-CH_2OCH_3	2):	CO_2 CH_3	H	S
6):	$COCH_3$	H	S- CH_3	3):	$COCH_3$	7- CH_3	S
7):	CO_2 CH_3	H	S- CH_3	4):	$COCH_3$	7- OCH_3	S

Scheme 41

by condensation of zinc salts of 2-aminobenzenethiols **74** and chlorohydroquinones **83** followed by reduction of the intermediate phenothiazones **84** (66JOC625) (Scheme 40).

2-Amino-5-fluorobenzenethiol reacts with chlorohydroquinones yielding in a similar way a phenothiazine carrying a fluorine atom on the nucleus (88MI1).

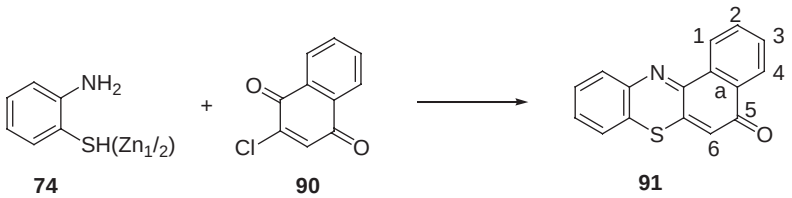
Oprean and Schaefer (72LA(765)1) have used protected 2-aminobenzenethiols **86** and 3-acetyl or 3-methoxy-carbonyl-2,5-dimethoxy-1,4-benzoquinones **87** to synthesize 2-hydroxy-3H-phenothiazin-3-ones **89** (Scheme 41). The reaction intermediate is 3-amino-1,4-benzoquinone **88A** whose tautomer **88B** undergoes dehydration under acid catalysis to provide the final compound **89**.

2. *Reactions with Naphthoquinones*

2-Aminobenzenethiols and their zinc salts **74** react with 1,4-naphthoquinones **90** in a manner similar to 1,4-benzoquinones providing benzophenothiazones **91**. The general reaction is depicted in Scheme 42.

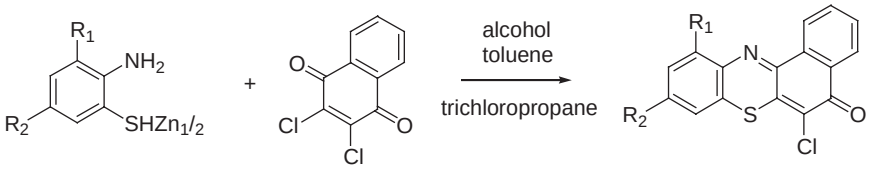
The nature of the products when using zinc thiolates depends on the solvent polarity. For instance, the condensation of zinc salts of substituted 2-aminobenzenethiols **92** with 2,3-dichloro-1,4-naphthoquinones **90** in alcohol, toluene or trichloropropane leads to substituted 6-chloro-5H-benzo[*a*]phenothiazin-5-ones **93** (88MI1, 93PS(80)23) (Scheme 43).

On the other hand, when dichloronaphthoquinone **90** is condensed with zinc thiolates such as **92** in pyridine, substituted benzo[*a*][1,4]benzothiazino[3,2-*c*]phenothiazines **94** are obtained (88MI1, 93PS(80)23). The reaction occurs *via* a Michael



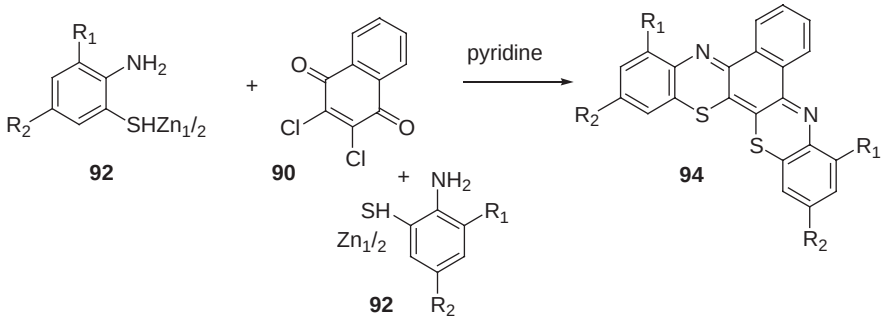
74 **90** **91**

Scheme 42



92 **90** **93**

Scheme 43



92 **90** **94** **92**

Scheme 44

condensation in which the mercaptide ion is added twice to the quinone system (Scheme 44).

It appears that the zinc chloride generated in the reaction inhibits further condensation with the product (Scheme 43) but the presence of pyridine may neutralize the effect caused by it (Scheme 44). This reaction was extended to a number of substituted 2-aminobenzenethiols in order to prepare substituted 6-chlorobenzophenothiazin-5-ones (88MI1, 93PS(80)23). Some of the resulting compounds were subjected to reduction, methylation and acetylation and a number of these products were screened for their antimicrobial activity.

Ueno et al. (82JHC167) have used 2-alkylthio-3-chloro- or 2-alkylthio/2-arylthio-1,4-naphthoquinones instead of dichloronaphthoquinones. The results were comparable to the compounds obtained by the photochemical reaction of 5H-benzo[a]phenothiazin-5-one with alkylthiols and thiophenol.

Analogously, 3-acetamido-2-chloro-1,4-naphthoquinone reacts with 2-aminobenzenethiol yielding 6-acetamido-benzophenothiazin-5-one (88MI1).

Substituted 6-anilino-5H-benzo[*a*]phenothiazin-5-one have been prepared by the condensation of substituted *p*-anilino-3-chloro-1,4-naphthoquinones (R = Br, OCH_3, OC_2H_5, CH_3) with 2-aminobenzenethiols (88MI1, 95PS(102)39, 82IJC(B)584, 83JHC1741).

This reaction allowed the preparation of substituted trifluoromethyl-5H-benzo[a]phenothiazin-5-one (88MI1).

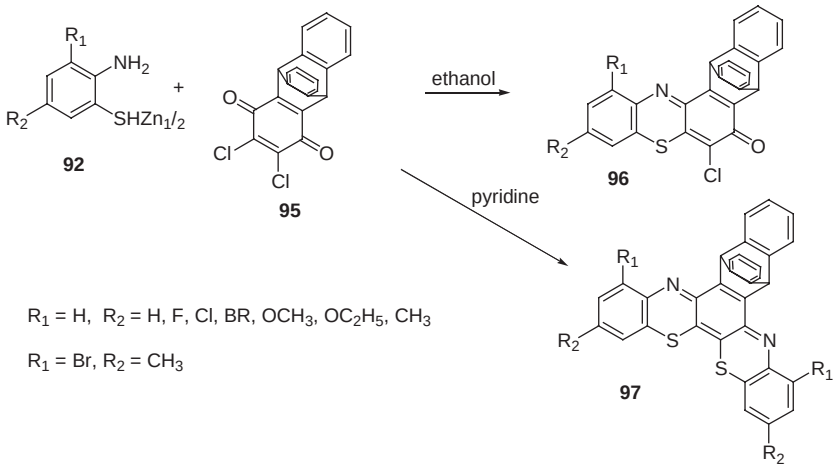
3. *Reactions with Anthraquinones*

2-Aminobenzenethiols and their salts react with anthraquinones yielding naphthophenothiazines. A number of substituted *endo*-12,17-*o*-phenylene-12,17-dihydro-naphtho[2,3-*a*]-1,4-benzothiazino[3,2′-*c*]phenothiazines and substituted *endo*-8,13-*o*-phenylene-8,13-dihydro-6-chloro-7H-naphtho[2,3-*a*]phenothiazin-7-ones have been synthesized (83PS(17)85, 82IJC(B)695) by the condensation of *endo*-9,10-*o*-phenylene-2,3-dichloro-9,10-dihydro-1,4-anthraquinone with substituted 2-aminothiophenol and their zinc mercaptides, respectively.

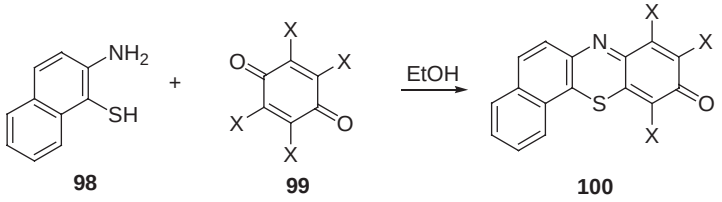
Substituted zinc 2-aminobenzenethiolates **92** form two different condensation products in different reaction media: in 95% ethanol, they yield compound **96** and in pyridine compound **97** (see a similar case in Section III.A.2) (Scheme 45). However, when reacting as the free substituted 2-aminobenzenethiols in pyridine only compound **96** forms. The formation of different products in alcohol and pyridine may be due to an increased reactivity of zinc salts in pyridine as compared to alcohol (88MI1).

4. *Syntheses from Aminonaphthalenethiols and Benzoquinones*

A similar reaction, in which functional groups and rings trade places, is depicted in Scheme 46. 2-Aminonaphthalenethiols **98** or their zinc salts react with halogeno-*p*-benzoquinones (chloranil or bromanil) **99** (12JA702) in alcoholic solution to give 8,9,11-trihalogeno-7H-benzo[c]phenothiazin-10-ones **100**.



Scheme 45



Scheme 46

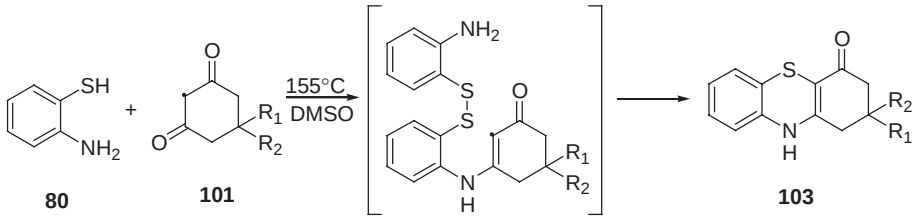
B. Syntheses from 2-Aminobenzenethiols and Cyclohexane-1, 3-diones

2-Aminobenzenethiol **80** undergoes a condensation reaction with cyclohexane-1, 3-diones **101** in DMSO yielding 2,3-dihydro-1H-phenothiazin-4(10H)-ones **103** (75JCS(CC)760) (Scheme 47), *via* intermediate **102** produced by the oxidation of 2-aminobenzenethiol to *bis*(*o*-aminophenyl) disulfide under the reaction conditions, followed by condensation with diones **101** to afford 2,3-dihydro-1H-phenothiazin-4(10H)-ones.

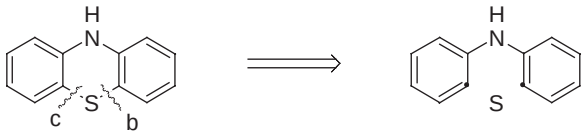
Jain et al. (93PHA546) have obtained a number of 2,3-dihydro-2,2-dimethyl-1H-phenothiazin-4(10H)-ones in a similar one-step synthesis.

IV. Syntheses *via* "c–b" from Diphenylamines

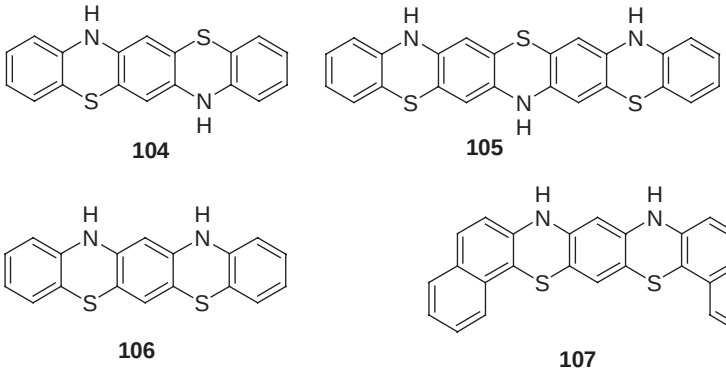
A simple retrosynthetic analysis consists in the disconnection of a phenothiazine ring according to the Scheme 48, involving the insertion of a sulfur atom into the diphenylamine molecule, a reaction known as "thionation", which was used in the first synthesis of phenothiazine, accomplished in 1883 by Bernthsen (1883CB2896).



Scheme 47



Scheme 48



Scheme 49

The very simple and, probably, the most efficient thionating agent, is sulfur in the presence of diiodine (84KG334, 81JHC645, 1883CB2896, 13JPR1, 11GEP244348), Lewis acids (11GEP222879, 44USP2360295) or an SO_2 atmosphere (54CRV797, 90FRP2635523) that lowers the temperature and time requirements and increases the yields. The solvents are also very important and their influence was discussed (59JOC623, 56JOC347).

Andreani et al. (91JHC295, 89SM477) synthesized ladder oligophenothiazines (**104** and **105**), by direct catalyzed insertion of elemental sulfur in anilino-substituted phenothiazines and *p*-oligoanilines (Scheme 49).

Silberg and Cristea (96HEC117) reported the synthesis of 1,4-benzothiazino[2, 3-*b*]phenothiazine (**106**) and of its dibenzoanalogue: dibenzo[*c*,l]-16H, 18H-triphenodithiazine (**107**) by thionation of the corresponding amines (Scheme 49).

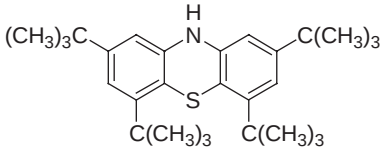
Nodiff et al. (70JHC203) have synthesized 7,8-dimethoxychlorpromazine hydrochloride by the Goldberg reaction, involving the condensation of 3-chloro-acetanilide with 4-bromoveratrol, thus obtaining a diphenylamine, which, upon thionation, yielded two isomeric phenothiazines. Similar syntheses produced 3,7-dioctylphenothiazine (99MI96), pyrazolo(3,4-*b*)- and pyrazolo(4,3-*c*)-phenothiazine (95H487), 1-arylamido-2-oxo-4-methylpyrido[*b*]-phenothiazine (97IJC(B)70), 11,12-*bis*(aryl-amido/imidoalkyl)-12H-benzo(*b*)-phenothiazine (87IJC(B)1) and 1-(*p*-arylidenophenyl)-2-oxo-4-methylpyrido(*b*)-phenothiazine (99IJC(B)1111). Some of these compounds show interesting biological properties.

A new and particularly efficient method is based on microwave irradiation. Villemin and Vlieghe (98SUL191) have reported the synthesis of phenothiazine from diphenylamine and sulfur, using diiodine as catalyst in a very short time and with very good yields: an equimolar mixture of diphenylamine (20 mmol), octasulfur (5 mmol), and diiodine (2 mmol) was irradiated in an open quartz tube with focused microwaves. Phenothiazine was obtained in a yield of 87% with a release of hydrogen sulfide after only 2 min of irradiation. They have also investigated the effects of different Lewis acids as catalysts instead of diiodine in the electrophilic thionation of diphenylamine: aluminum chloride, zinc chloride and bismuth chloride (Table 1). Although reported conversions are high, the presence of phenothiazine–metal complexes makes the purification of phenothiazine more difficult than in the presence of diiodine.

The same authors obtained phenothiazine by direct irradiation (200 W, 5 min) of a mixture of aniline, anilinium iodide and octasulfur. After extraction, phenothiazine was obtained in a 70% yield. In this reaction, the catalyst seems to be iodine formed by decomposition *in situ* of anilinium iodide. By such an activation of the reaction mixture, Silberg et al. (98SC337) carried out the preparation of the crowded 2,4,6,8-tetra-*tert*-butyl-10-H-phenothiazine, the first 2,4,6,8-homogeneously tetrasubstituted derivative of this heterocycle, practically inaccessible by other thionation procedures (Scheme 50).

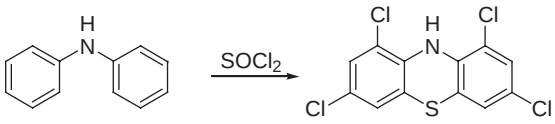
Table 1. Synthesis of phenothiazine under microwave irradiation (200 W, 5 min)

Catalyst	Yield (%)
$AlCl_3$	72
$ZnCl_2$	65
$BiCl_3$	46



108

Scheme 50



109 **110**

Scheme 51

The preparation of N-substituted phenothiazines from the corresponding diphenylamines is also possible by using $SOCl_2$ in benzene as a thionating agent (63BRP890912). There is no mention of chlorination as a side reaction (1885LA(230)77, 1888CB2056), although with S_2Cl_2, which is less reactive in this respect, chlorination seems to accompany the thionation (68AHC325).

Kanô and Fujimoto (57MI393) obtained polychlorophenothiazines using thionyl chloride as a thionating agent. Unsubstituted diphenylamine **109** yielded 1,3,7,9-tetrachlorophenothiazine **110** (Scheme 51).

3-Substituted diphenylamines react in the same way, and the formation of small amounts of 4-substituted phenothiazines is observed, not unusual for thionation reactions (57MI393, 59BCJ294).

Nitrodiphenylamines and, surprisingly, *N*-phenyltoluidines, did not react in this way to yield phenothiazines (57MI393). Also surprising is the failure of thionation in the case of 2-chlorodiphenylamine, compared to the normal behavior of 4-chlorodiphenylamine (59BCJ294).

Other C-substituted diphenylamines bearing electron–donor substituents (OH, OCH_3, NH_2, etc.) underwent cyclization to chlorinated phenothiazines by $SOCl_2$, the chlorine atom generally entering *ortho* to the preexistent substituents (33GEP562268).

N-substituted diphenylamines also yielded phenothiazines on treatment with $SOCl_2$ (33GEP562268). In this way, *N*-acetyldiphenylamine was quantitatively converted into tetrachlorophenothiazine, while *N*-phenyldiphenylamine (triphenylamine) gave 3,7-dichloro-10-(4′-chlorophenyl)-phenothiazine in 91% yield. In the first case, the chlorine atoms in positions 1 and 9 promote the removal of the acyl group from position 10; in the second case, the bulky N-substituent prevents the replacements of hydrogen from positions 1 and 9 by chlorine. The behavior of *N*-methyldiphenylamine is intermediate in this respect: 3,7-dichloro-10-methylphenothiazine was isolated in 7% yield, along with tetrachlorophenothiazine (68AHC325).

The conversion of diphenylamines into chlorophenothiazines by $SOCl_2$ obviously involves two principal processes, namely the cyclization and the chlorination. The question arises as to which is the first step (59BCJ294). Phenothiazine, 2-chloro-, and 4-chlorophenothiazine are chlorinated by thionyl chloride yielding products identical to those obtained from the corresponding diphenylamines, whereas 2,4,2′,4′-tetrachlorodiphenylamine cannot be cyclized on treating with $SOCl_2$, suggesting that ring closure takes place prior to chlorination (68AHC325).

The reaction of diphenylamines with $SOBr_2$ and SO_2Cl_2 leads only to halogenated diphenylamines (57MI393).

Two patents claim the preparation of phenothiazine-sulfones from substituted diphenylamines (with at least one free position *ortho* to the amino group) using oleum with 60–70% SO_3 at 80–125 °C (33GEP562268, 34BRP420444).

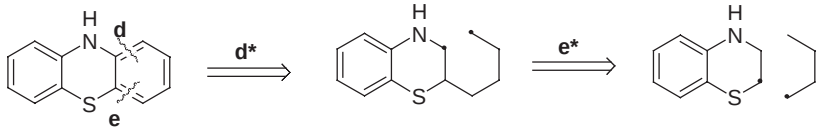
Phenothiazines can be prepared on an industrial scale by using sulfur as the thionating agent and iodide or aluminum chloride as catalysts. There are also some references on the use of zeolite (97MI(2)1849) or phosphotungstic acid (95JAP(K)138243) as catalysts.

V. Syntheses *via* "d–e" Scheme

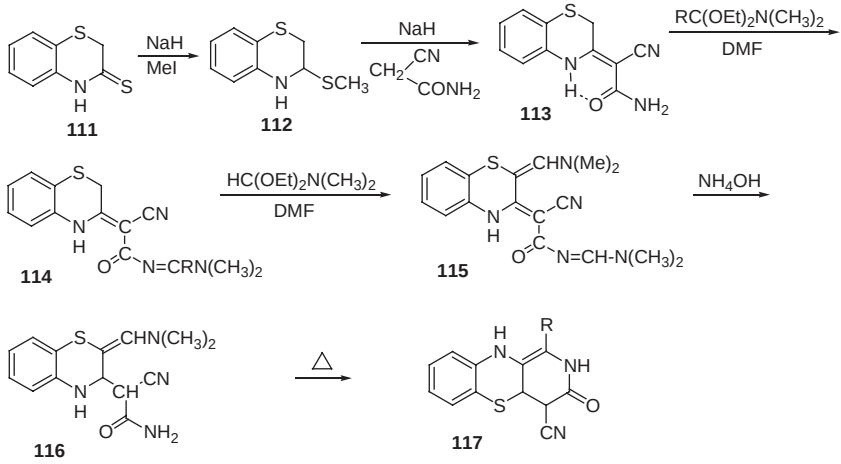
Retrosynthetic analysis does not recommend the C–C bonds disconnection because these are more difficult to reconnect synthetically (Scheme 52).

The unsubstituted phenothiazine ring has not been prepared in this way, but there are some azaphenothiazines that have been obtained by thermal cyclization, following this general scheme.

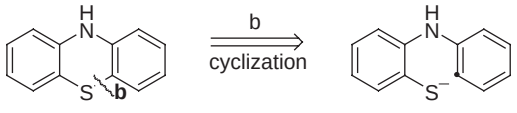
Azaphenothiazines **117** (80TL421, 83JMC845) have been synthesized *via* thermal cyclization from 2H-1,4-benzothiazine-3(4H)-thione **111** (69JMC290). The intermediate was a cyanoacetamide adduct **113** that has been converted into dimethylaminoethylene **115** and then in the monoaminoethylene amide **116** (Scheme 53).



Scheme 52



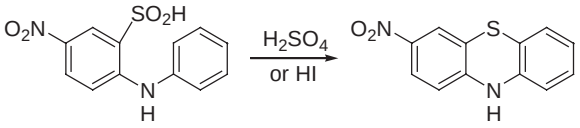
Scheme 53



Scheme 54

118

Scheme 55



119 **120**

Scheme 56

VI. Syntheses *via* "b" Scheme

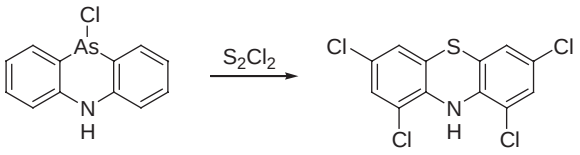
This sequence represents a step in the synthesis by cyclization *via* a Smiles rearrangement (Section II.A.1.b) and in the condensation reactions of aminobenzenethiols with quinones (Scheme 54).

Practically, the phenothiazine ring must be easily obtained by cyclization from compounds like **118** (Scheme 55), therefore the limiting step is only the preparation of starting material **118**.

Krishna and Jain have synthesized 3-nitrophenothiazine **120** from 4-nitrodiphenylamino-2-sulfinic acid **119** and H_2SO_4. Similarly, Evans and Smiles (35JCS1263) have obtained the same compound by using hydroiodic acid as a catalyst (Scheme 56).

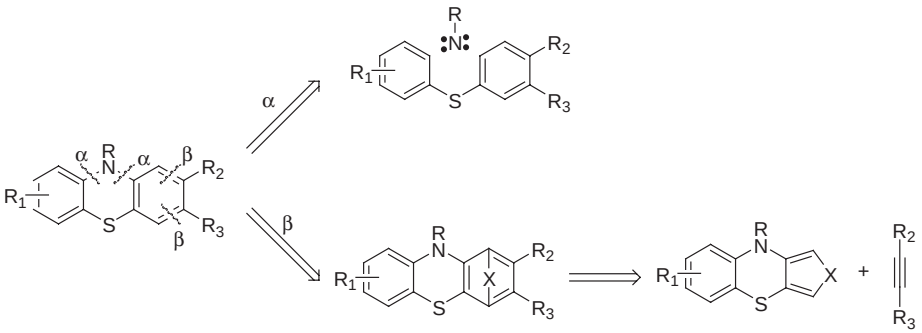
VII. Synthesis by Substitution

Spasov and Zhechev (53MI67) obtained phenothiazine derivative **122** from 10-chloro-5,10-dihydro-phenarsazine **121** by substitution of its arsenic atom with sulfur (Scheme 57).



121 **122**

Scheme 57



Scheme 58

VIII. Final Remarks

The authors hope that this review of known routes to the phenothiazine ring by this retrosynthetic approach will provide a straightforward guide to those interested in preparing a given derivative of this class. Other new preparations could fill in the gaps in the retrosynthetic schemes presented in Section I.

Scheme 58 shows two possible approaches to the phenothiazine ring that, to the authors' knowledge, have not been explored yet.

The "α" route would imply the attack of a nitrene onto a diaryl sulfide, thus being the "nitrogen equivalent" of the thionation reaction. As to the "β" route, this would be a ring interconversion reaction, making use of the diene character of less aromatic five-membered rings, like furan, oxazole, etc. The reader is encouraged to come with his own ideas and the field of this interesting heterocycle will be the great beneficiary of such efforts.

Acknowledgements

The authors are very much indebted to Professor A. R. Katritzky for his valuable advice and to Mr. Dan Porumb for his contributions to the preparation of the manuscript. Ioan A. Silberg gratefully acknowledges the enthusiastic support of his research group in carrying on investigations in the field of phenothiazine chemistry.

References

11GEP222879 F. Ackermann, Ger. Pat. 222, 879, 1911.
11GEP244348 F. Ackermann, Ger. Pat. 244, 348 [CA 1 1911(1911)].
12CB2012 A. Bernthsen, *Ber. deut. chem. Ges.*, 45, 2012 (1912).
12JA702 H. A. Torrey and W. H. Hunter, *J. Am. Chem. Soc.*, **34**, 702 (1912).
13JPR1 E. Knoevenagel, *J. Prakt. Chemi.*, **89**, 1 (1913).
1876CB1035 C. Lauth, *Ber. deut. chem. Ges.*, **9**, 1035 (1876).
1883CB2896 A. Bernthsen, *Chem. Ber.*, **16**, 2896 (1883).
1885LA(230)77 A. Bernthsen, *Liebigs Ann. Chem.*, **230**, 77 (1885).
1888CB2056 E. Holzmann, *Chem. Ber.*, **21**, 2056 (1888).
25HCA16 F. Kehrman and C. Bener, *Helv. Chim. Acta*, **8**, 16 (1925).
31JA245 F. W. Bergstrom and R. A. Ogg, *J. Am. Chem. Soc.*, **53**, 245 (1931).
31JCS3264 A. A. Levy, H. C. Rains, and S. Smiles, *J. Chem. Soc.*, 3264 (1931).
32JCS1488 A. A. Levy and S. Smiles, *J. Chem. Soc.*, 1488 (1932).
33GEP562268 I. G. Farbenindustrie, Ger. Pat. 562, 268 [CA 27 5196 (1933)].
34BRP420444 I. G. Farbenindustrie, Br. Pat. 420, 444 [CA 29 3530 (1935)].
35JCS1234 F. Galbraith and S. Smiles, *J. Chem. Soc.,* 1234 (1935).
35JCS1263 W. J. Evans and S. Smiles, *J. Chem. Soc.*, 1263 (1935).
35JCS181 W. J. Evans and S. Smiles, *J. Chem. Soc.*, 181 (1935).
39AR191 H. B. Watson, *Ann. Rep. Prog. Chem.*, **36**, 191 (1939).
43JCS322 H. McIlwain, *J. Chem. Soc.*, 322 (1943).
44USP2360295 A. H. Widiger, US Pat. 2,360, 295 [CA 39 1179 (1945)].
45JCS591 W. A. Petrow and E. L. Rewald, *J. Chem. Soc.*, 591 (1945).
46JA1035 J. R. Stevens, K. Pfister, and F. J. Wolf, *J. Am. Chem. Soc.*, **68**, 1035 (1946).
46MI363 B. N. Halpern, *Compt. Rend. Soc. Biol.*, **140**, 363 (1946).
48JCS777 R. D. Haworth and S. Robinson, *J. Chem. Soc.*, 777 (1948).
48MI197 M. J. Vanderbook et al., *Pharmacol. Exptl. Therap.*, 94, 197 (1948).
50JA888 J. G. Michels and E. D. Amstutz, *J. Am. Chem. Soc.*, **72**, 888 (1950).
50MI(1)124 G. M. Findlat, *"Recent Advances in Chemotherapy"* 3rd edition, Vol. 1, p. 124, The Blakiston Company, Philadelphia (1950).
51CRV362 J. F. Bunnet and R. E. Zahler, *Chem. Rev.*, **49**, 362 (1951).
52MI206 H. Laborit, P. Huguenard, and R. Allaume, *Presse Med.*, **60**, 206 (1952).
53JA6335 P. A. Smith, B. B. Brown, R. K. Putney, and R. F. Reinsch, *J. Am. Chem. Soc.*, **75**, 6335 (1953).
53JCS2816 J. K. Landquist, *J. Chem. Soc.*, 2816 (1953).
53JCS4198 G. M. Bennet, *J. Chem. Soc.*, 4198 (1953).
53MI67 A. Spasov and M. Zhechev, *Bull. Inst. Chim. Acad. Bulgare Sci.*, **2**, 67 (1953).
54CRV797 S. P. Massie, *Chem. Rev.*, **54**, 797 (1954).
54JCS4516 Y. Ahmad and D. H. Hey, *J. Chem. Soc.*, 4516 (1954).
56AJC397 J. Cymerman-Craig, W. P. Rogers, and M. E. Tate, *Aust. J. Chem.*, **9**, 397 (1956).
56JCS1563 N. B. Chapmann and D. Russell-Hill, *J. Chem. Soc.*, 1563 (1956).
56JOC28 A. Roe, J. A. Montgomery, W. A. Yarnall, and V. A. Hoyle Jr., *J. Org. Chem.*, **21**, 28 (1956).
56JOC347 S. P. Massie and P. K. Kadaba, *J. Org. Chem.*, **21**, 347 (1956).
57AJC502 K. J. Farrington and K. J. Warburton, *Aust. J. Chem.*, **10**, 502 (1957).
57JA4375 H. L. Yale, F. Sowinski, and J. Bernstein, *J. Am. Chem. Soc.*, **79**, 4375 (1957).
57JPJ485 Y. Maki, *J. Pharm. Soc. Jpn.*, **77**, 485 (1957).
57MI393 H. Kanô and M. Fujimoto, *Pharm. Bull. (Tokyo)*, **5**, 393 (1957).

57USP2769002 P. J. Buisson, P. Gailliot, and J. Gaudechon, US Pat. 2,769,002 [CA 51 6709 (1957)].
57YZ485 Y. Maki, *Yakugaku Zasshi*, **77**, 485 (1957) [CA 51 14738 (1957)].
58JA1651 H. L. Yale and F. Sowinski, *J. Am. Chem. Soc.*, **80**, 1651 (1958).
58JA2021 B. F. Hrutford and J. F. Bunnett, *J. Am. Chem. Soc.*, **80**, 2021 (1958).
58JOC1804 R. J. Galbreath and R. K. Ingham, *J. Org. Chem.*, **23**, 1804 (1958).
58JOC1906 A. J. Saggiomo, P. N. Craig, and M. Gordon, *J. Org. Chem.*, **23**, 1906 (1958).
58QR1 J. F. Bunnet, *Q. Rev.*, **12**, 1 (1958).
58YZ417 T. Takahashi and Y. Maki, *Yakugaku Zasshi*, **78**, 417 (1958) [CA 52 14622 (1958)].
59BCJ294 M. Fujimoto, *Bull. Chem. Soc. Jpn.*, **32**, 294 (1959).
59JOC623 P. K. Kadaba and S. P. Massie, *J. Org. Chem.*, **24**, 623 (1959).
59JOC968 A. Roe and W. F. Little, *J. Org. Chem.*, **24**, 968 (1959).
62JA2770 J. D. Reinheimer, J. T. Gerig, R. Garst, and B. Schrier, *J. Am. Chem. Soc.*, **84**, 2770 (1962).
62JOC1659 J. A. Van Allan, G. A. Reynolds, and R. E. Adel, *J. Org. Chem.*, **27**, 1659 (1962).
63BRP890912 Sandoz Ltd., Br. Pat. 890,912 [CA 58 1472 (1963)].
63JOC1488 A. P. Philips, N. B. Mehta, and J. Strelitz, *J. Org. Chem.*, **28**, 1488 (1963).
64JOC2453 E. A. Nodiff and M. Hausman, *J. Org. Chem.*, **29**, 2453 (1964).
64JOC2652 O. R. Rodig, R. E. Collier, and R. K. Schlatzer, *J. Org. Chem.*, **29**, 2652 (1964).
64JOC3262 C. A. Kingsbury, *J. Org. Chem.*, **29**, 3262 (1964).
66JCS(CC)491 J. I. G. Cadogan, R. K. Mackie, and M. J. Todd, *J. Chem. Soc. Chem. Commun.*, **15**, 491 (1966).
66JMC116 O. E. Rodig, R. E. Collier, and R. K. Schlatzer, *J. Med. Chem.*, **9**, 116 (1966).
66JOC625 E. A. Nodiff and M. Hausman, *J. Org. Chem.*, **31**, 625 (1966).
67JCS2562 J. A. Baker and S. A. Hill, *J. Chem. Soc. (C)*, 2562 (1967).
68AHC325 C. Bodea and I. A. Silberg, *Adv. Heterocycl. Chem.*, **9**, 325 (1968).
69JCS(C)603 J. A. Baker and P. V. Chatfield, *J. Chem. Soc. (C)*, 603 (1969).
69JMC290 R. N. Prasad, *J. Med. Chem.*, **12**, 290 (1969).
69S11 J. I. G. Cadogan, *Synthesis*, **1**, 11 (1969).
70JA1651 J. M. Anderson and J. K. Kochi, *J. Am. Chem. Soc.*, **92**, 1651 (1970).
70JHC203 E. A. Nodiff, K. Tanabe, F. Schierle, S. Morosawa, T. W. Hoffman, K. Takeda, and A. Manian, *J. Heterocycl. Chem.*, **7**, 203 (1970).
71IJS237 C. O. Okafor, *Int. J. Sulfur Chem.*, **68**, 237 (1971).
71LA(746)200 M. Terdic, *Liebigs Ann. Chem.*, **746**, 200 (1971).
71M760 R. L. Mital and A. P. Taunk, *Monatsh Chem.*, **102**, 760 (1971).
72LA(765)1 I. Oprean and W. Schaefer, *Liebigs Ann. Chem.*, **765**, 1 (1972).
73JOC4386 C. O. Okafor, *J. Org. Chem.*, **38**, 4386 (1973).
73JOC4386 C. O. Okafor, *J. Org. Chem.*, **238**, 4386 (1973).
75JCS(CC)760 S. Miyano, N. Abe, and K. Sumoto, *J. Chem. Soc. Chem. Commun.*, **18**, 760 (1975).
76BCJ2026 R. R. Gupta and S. K. Jain, *Bull. Chem. Soc. Jpn.*, **49**, 2026 (1976).
76JOC3564 J. J. D'Amico, C. C. Tung, W. E. Dahl, and D. J. Dahm, *J. Org. Chem.*, **41**, 3564 (1976).
77JHC107 A. Zirinis, J. K. Suzuki, D. Dickson, and R. A. Laiter, *J. Heterocycl. Chem.*, **14**, 107 (1977).
77JOC2896 J. J. D'Amico, C. C. Tung, W. E. Dahl, and D. J. Dahm, *J. Org. Chem.*, **42**, 2896 (1977).

77MI249 C. O. Okafor, M. Steenberg, and J. P. Buckley, *Eur. J. Med. Chem.*, **12**, 249 (1977).
78JHC969 C. Corral, J. Lissavetzky, and G. Quintanilla, *J. Heterocycl. Chem.*, **15**, 969 (1978).
78JHC1137 C. Corral, J. Lissavetzky, and G. Quintanilla, *J. Heterocycl. Chem.*, **15**, 1137 (1978).
78LA1285 M. Terdic and I. Valter, *Liebigs Ann. Chem.*, 1285 (1978).
78PS(4)79 C. O. Okafor, *Phosphorus Sulfur*, **4**, 79 (1978).
78PS(4)267 J. J. D'Amico, C. C. Tung, W. E. Dahl, and D. J. Dahm, *Phosphorus Sulfur*, **4**, 267 (1978).
79CIL349 N. K. Goswami, S. K. Jain, and R. R. Gupta, *Chem. Ind.*, 349 (1979).
79IJC(17B)626 R. R. Gupta, S. K. Jain, and N. K. Goswami, *Indian J. Chem.*, **17B**, 626 (1979).
79IJC(18B)274 N. K. Goswami, S. Jain, and R. R. Gupta, *Indian J. Chem.*, **18B**, 274 (1979).
79PS(7)143 J. J. D'Amico, C. C. Tung, and W. E. Dahl, *Phosphorus Sulfur*, **7**, 143 (1979).
79SC457 K. Ojha, S. K. Jain, and R. R. Gupta, *Synth. Commun.*, **9**, 457 (1979).
80H(14)6831 R. R. Gupta, S. K. Jain, N. K. Goswami, and G. S. Kalwania, *Heterocycles*, **14**, 6831 (1980).
80JHC149 C. O. Okafor, *J. Heterocycl. Chem.*, **17**, 149 (1980).
80JHC1325 R. R. Gupta, K. G. Ojha, and M. Kumar, *J. Heterocycl. Chem.*, **17**, 1325 (1980).
80JHC1587 C. O. Okafor, *J. Heterocycl. Chem.*, **17**, 1587 (1980).
80TL421 R. J. Chorvat and S. E. Radak, *Tetrahedron Lett.*, **21**, 421 (1980).
81H(16)1527 R. R. Gupta, G. S. Kalwania, and M. Kumar, *Heterocycles*, **16**, 1527 (1981).
81JHC645 Y. Ueno, Y. Takeuchi, J. Koshitani, and T. Yoshida, *J. Heterocycl. Chem.*, **18**, 645 (1981).
81JHC759 A. J. Lin and G. Kasino, *J. Heterocycl. Chem.*, **18**, 759 (1981).
81JHC1527 R. R. Gupta, G. S. Kalwania, and M. Kumar, *J. Heterocycl. Chem.*, **18**, 1527 (1981).
82IJC(B)584 G. K. Oberoi, R. Agarwal, and R. L. Mital, *Indian J. Chem. Sec. B*, **21**, 584 (1982).
82IJC(B)695 R. L. Mital, G. K. Oberoi, S. Jain, and M. Anand, *Indian J. Chem. Sec. B*, **21**, 695 (1982).
82JHC167 Y. Ueno, Y. Takeuchi, J. Koshitani, and T. Yoshida, *J. Heterocycl. Chem.*, **19**, 167 (1982).
82JOC592 C. O. Okafor, *J. Org. Chem.*, **47**, 592 (1982).
83JHC1741 N. L. Agarwal and C. K. Atal, *J. Heterocycl. Chem.*, **20**, 1741 (1983).
83JMC845 R. J. Chorvat, B. N. Desai, S. E. Radak, J. Bloss, J. Hirsch, and S. Tenen, *J. Med. Chem.*, **26**, 845 (1983).
83PS(17)85 S. K. Jain and N. L. Agarwal, *Phosphorus Sulfur*, **17**, 85 (1983).
84H(22)1169 R. R. Gupta and R. Kumar, *Heterocycles*, **22**, 1169 (1984).
84JHC893 R. R. Gupta, G. S. Kalwania, and M. Kumar, *J. Heterocycl. Chem.*, **21**, 893 (1984).
84KG334 G. Afanasieva, V. Vysokov, and O. N. Chupakin, *Khim. Geterotsikl. Soedin.*, **3**, 334 (1984).
84PHA22 R. Schneider and A. Buge, *Pharmazie*, **39**, 22 (1984).
84PHA355 Y. Ueno, *Pharmazie*, **39**, 355 (1984).
86PHA830 R. R. Gupta and R. Kumar, *Pharmazie*, **41**, 830 (1986).
87IJC(B)1 V. K. Pandey, P. Garg, S. Ram, and S. C. Bhar, *Indian J. Chem. Sec. B*, **26**, 1 (1987).
87PHA830 R. R. Gupta and R. Kumar, *Pharmazie*, **42**, 830 (1987).

87SC229 R. R. Gupta and R. Kumar, *Synth. Commun.*, **17**, 229 (1987).

88MI1 R. R. Gupta (ed.), "*Phenothiazines and 1,4-Benzothiazines*" Elsevier, Amsterdam, Oxford, New York, Tokyo (1988)

89SM477 C. Della Casa, F. Andreani, P. Costa Bizzari, M. Florini, E. Salatetii, L. Grossi, and W. Prozo, *Synth. Met.*, **29**, E477 (1989).

90FRP2635523 J. P. Duchesne, Fr. Pat. 2,635,523 [CA 113 152446 (1990)].

91JHC295 F. Andreani, P. Costa Bizzari, and C. Della Casa, *J. Heterocycl. Chem.*, **28**, 295 (1991).

92JHC1703 R. R. Gupta, V. Saraswat, A. Gupta, M. Jain, and V. Gupta, *J. Heterocycl. Chem.*, **29**, 1703 (1992).

92PHA945 R. S. Rathore, M. Jain, A. Gupta, V. Saraswat, V. Gupta, and R. R. Gupta, *Pharmazie*, **47**, 945 (1992).

93JFC191 R. R. Gupta, M. Jain, R. S. Rathore, and A. Gupta, *J. Fluorine Chem.*, **62**, 191 (1993).

93PHA546 M. Jain, V. Gupta, C. M. Rajoria, and R. R. Gupta, *Pharmazie*, **48**, 546 (1993).

93PHA620 V. Saraswat, A. Gupta, V. Gupta, and R. R. Gupta, *Pharmazie*, **48**, 620 (1993).

93PS(80)23 R. Sharma, R. D. Goyal, and L. Prakash, *Phosphorus Sulfur*, **80**, 23 (1993).

94JOC2743 A. Kistenmacher, M. Baumgarten, and V. Enkelmann, *J. Org. Chem.*, **59**, 2743 (1994).

94PHA453 S. K. Mukherjee, D. C. Gautam, A. Gupta, R. S. Rathore, D. Rai, and R. R. Gupta, *Pharmazie*, **49**, 453 (1994).

94PHA689 M. Jain, S. K. Gupta, V. Saraswat, and R. R. Gupta, *Pharmazie*, **49**, 689 (1994).

95H487 G. Boyer, J. P. Galy, and J. Barbe, *Heterocycles*, **41**, 487 (1995).

95HEC95 M. Jain and R. R. Gupta, *Heterocycl. Commun.*, **1**, 95 (1995).

95HEC203 N. K. Goswami, *Heterocycl. Commun.*, **1**, 203 (1995).

95HEC315 V. Gupta and A. Gupta, *Heterocycl. Commun.*, **1**, 315 (1995).

95HEC445 A. M. Al-Abdalla, M. Jain, and R. R. Gupta, *Heterocycl. Commun.*, **1**, 445 (1995).

95JAP(K)138243 T. Kayano and T. Inoe, Jpn. Kokai 95 138,243 [CA 123 169639 (1995)].

95PS(102)39 S. Shukla and L. Prakash, *Phosphorus Sulfur*, **102**, 39 (1995).

96HEC117 I. A. Silberg and C. Cristea, *Heterocycl. Commun.*, **2**, 117 (1996).

97IJC(B)70 V. K. Pandey and M. Gupta, *Indian J. Chem. Sec. B*, **36**, 70 (1997).

97MI(1)672 R. K. Rathore and R. R. Gupta, *Asian J. Chem.*, **9**, 672 (1997).

97MI(2)1849 B. J. Zuo, Y. D. Ma, Y. Tian, and L. Wang, *Chin. Chem. Lett.*, **8**, 849 (1997) [CA 128 61467 (1998)].

98HEC277 M. Y. Hamadi, R. Gupta, and R. R. Gupta, *Heterocycl. Commun.*, **4**, 277 (1998).

98SC337 S. V. Filip, I. A. Silberg, E. Surducan, M. Vlassa, and V. Surducan, *Synth. Commun.*, **28**, 337 (1998).

98SUL191 D. Villemin and X. Vlieghe, *Sulfur Lett.*, **21**, 191 (1998).

99IJC(B)1111 V. K. Pandey and S. R. Pathak, *Indian J. Chem. Sec. B*, **38**, 1111 (1999).

99JAP(K)171878 S. Fujita and Y. Kumagayo, Jpn. Kokai 99 171,878 [CA 131 73661 (1999)].

99JFC153 N. Sharma, R. Gupta, M. Kumar, and R. R. Gupta, *J. Fluorine Chem.*, **68**, 153 (1999).

99MI96 T. Jiao, Q. Liu, and L. D. Xuebao, *Ziran Kexueban*, **35**, 96 (1999) [CA 131 58795 (1999)].

99PS(152)77 K. G. Ojha, P. Mathur, N. Jaisinghani, and P. Adwani, *Phosphorus Sulfur*, **152**, 77 (1999).

Fluorine-containing Heterocycles. Part IV. Electrochemical Fluorination of Heterocyclic Compounds

Georgii G. Furin

Novosibirsk Institute of Organic Chemistry, Siberian Division of the Russian Academy of Sciences, 630090 Novosibirsk, Russia

I. Introduction

In recent years, fluorinated heterocyclic compounds have found wide use as pharmaceuticals and agrochemicals due to their high and specific physiological activity (94AHC1, 95M1, 82M8, 91M10, 94M3, 87JCP1119). This gave impetus to research aimed at syntheses of heterocyclic systems with various fluorine-containing fragments and especially those with perfluoroalkyl groups. These compounds serve to create new drugs and agricultural agents, as well as intermediates for syntheses of various materials.

Recent growth of research into fluoroorganic chemistry has led to the discovery of fluorinated compounds with unique structures, many of which possess specific biological and pesticidal activities. Growth in production is expected in the near future in the pesticide sector.

Today the primary goal is seeking unique approaches to studies of the effects of the perfluorinated organic moiety on the physical and chemical properties of compounds. At any level of modern development, fundamental research is stimulated by the demand for advanced materials based on new substances possessing improved properties to satisfy consumer requirements and capable of operating in relatively

ADVANCES IN HETEROCYCLIC CHEMISTRY
VOLUME 90 ISSN: 0065-2725 DOI: 10.1016/S0065-2725(05)90004-4

stringent conditions. In this context, fluorinated materials not occurring in nature but imparting new properties to molecules play an extremely important role.

Heterocyclic compounds are also employed for syntheses of advanced technological materials. Their major applications are:

(1) as liquid dielectrics (perfluorinated compounds having no biological activity);
(2) effective new generation fluorinating reagents possessing mild fluorinating activity and high regioselectivity (heterocyclic compounds and especially nitrogen-containing compounds with N–F bonds);
(3) new types of solvents – so-called ionic liquids;
(4) metal- and alloy-protecting agents used to prevent atmospheric and salt corrosion;
(5) special substances for sustained fluorescence and laser radiation sources.

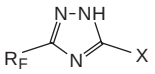
Many new applications have appeared in recent years because of the increased understanding of the unique properties of fluorine compounds. Introduction of fluorine atoms into organic compounds is, therefore, of great scientific and practical interest in our effort to create new highly effective, biologically active substances and materials with interesting properties (82M8, 92M9, 91M10, 91M11, 99M12). Research into this field of organic chemistry has substantially promoted the development of synthetic fluorine chemistry. Novel reagents and synthetic procedures have appeared in great numbers (01M13, 96M14, 00M15, 91M16).

Illustrative are a few examples of technological applications. Perfluorinated tetrahydrofurans (perfluorobutyltetrahydrofuran, perfluorotetrahydrofuran, and perfluoroisopentyltetrahydrofuran) are excellent dielectric materials possessing low toxicity. For example, for perfluorotetrahydrofuran its toxicity or $LD_{50} = 5–10$ g/kg.

Perfluoroalkyl cumarins (80JOC2283, 78JOC1975), pyridonaphthyridines (77JHC1109), and pyrrolonequinolines (77USP4026898) are employed as substances generating laser radiation and sustained fluorescence. 1,8-Naphthyridines and 1,2-dihydropyrido[2,3-*b*][1,8]-naphthyridines exhibit stable fluorescence in ethanol in the range 393–482 nm (80JOC2283). 2-Keto-4-trifluoromethyl-1,6,6,7,8-pentamethyl-6,7-dihydro-1 *H*,2 *H*,8*H*-pyrido[3,2-*f*]indole is a source of indigo-blue laser radiation (77USP4026898).

7-Amino-4-trifluorocumarin and its amino acid and peptide salts are used for fluorescent labeling of amino acids and peptides in biological studies (80JOC2283). Fluorine-containing triazoles are used to protect metals and alloys from atmospheric and salt corrosion (Scheme 1).

Owing to the presence of a perfluorinated alkyl substituent, surface energy decreases, increasing metal hydrophobicity. However, the heterocyclic ring of triazole inhibits this process and keeps molecules from the adsorbed layer on the metal due to covalent and ionic interactions. These processes increase the corrosion resistance of



$R_F = F(CF_2)n$, n = 6, 8; $F[CF(CF_3)CF_2O]mCF(CF_3)$- , m = 1-3, 8-10
X = NH_2, SH, OH

Scheme 1

aluminum, copper, steel, and their alloys. Several compounds from this class are anticorrosion agents, more effective than perfluorocarboxylic acid derivatives with similar perfluorinated fragments.

2-Pentafluoroethyl-2-fluoro-3,3-*bis*(trifluoromethyl)-5-methyloxalane is used as a diluent for rare metal extractants and as a solvent for extractants; 2-pentafluoro-2(2,2,2-trifluoro-1-trifluoromethylethyl)-1,3-dioxolane is known for its dielectric oil applications (86JAP(K)183281).

The synthesis of fluorine-containing physiologically active compounds is closely related to drug design (84JSOC786). Effects of fluorine introduction in organic (particularly, physiologically active) compounds fall into a number of categories. The fluorine atom occupies nearly the same volume, as does the hydrogen atom. When fluorine is substituted for hydrogen, enzymes (acceptors) in a living body do not discriminate between the unsubstituted substance and the related substance with fluorine substituted for hydrogen (similarity effect). Metabolism of unsubstituted and fluorine-substituted compounds takes place in much the same way. The C–F bonds are more stable than the C–H bonds. They are not broken, and further metabolism, therefore, occurs abnormally, which leads to various consequences. As fluorine is the most electronegative element, its incorporation into molecules changes the dipole moment and pK_a of the compound, altering its reactivity and giving rise to physiological effects. When fluorine is substituted for hydrogen, the compound becomes more hydrophobic, the effect being maximal when the CF_3 group is introduced. These differences are utilized in drug design. Fluorine compounds began to attract the attention of researchers after analgesic activity had been found in fluorine-containing steroids.

Fluorinated derivatives have been synthesized for all known substances possessing biological activity, and the mechanisms of their physiological action (''masking effect,'' ''blocking fluorination,'' etc.) have been studied. Among these substances are heterocyclic compounds with perfluoroalkyl groups. Perfluorinated heterocyclic compounds are mostly liquids with low surface tension; these are good solvents for gases (in particular, for oxygen), satisfying the requirements to oxygen carriers. They are easily exhaled and easily emulsified, giving stable emulsions, which are useful properties for blood substitutes. Emulsions of this type are expected to be used for on-table transfusion and lavage during surgical operations (82M1).

Apart from blood transfusion, an important application of artificial blood is as a perfusate for tentative conservation of organs during surgery, because the stability of its emulsion over long periods of time is very helpful in this case. For this, one often employs perfluorinated morpholins and perfluoroalkyltetrahydrofurans.

Perfluorinated compounds are generally nontoxic substances; they do not undergo structural changes during metabolism provided that these are ultrapure substances. However, despite its low toxicity, artificial blood is a foreign body to the organism when it is introduced in large amounts. Therefore, it is highly desirable that these substances leave the organism within a certain period of time.

The synthesis of highly pure perfluorinated heterocyclic compounds is important not only for medicine, but also for several industrial sectors (liquid dielectrics and electrolytes, materials for medicine, etc.) (95M1, 92M9).

Direct selective fluorination of organic molecules is an extremely important technique used in various fields of medical and materials chemistry (96M14). It affords

numerous substances with desired properties, additionally possessing high biological activity. Partially fluorinated heterocyclic compounds have been the focus of attention for researchers because of their high biological activity. They are used as intermediates for the synthesis of pharmaceuticals and agrochemicals. However, their synthesis is often nonselective and limited. Therefore, work is being pursued to find selective fluorinating agents for introducing fluorine atoms and perfluoroalkyl groups into organic molecules (91M26, 86JFC(31)231). The electrochemical method seems to be an ideal procedure for direct fluorination, especially because this is a one-step process performed under mild conditions (91M27). The high yield, as well as selectivity, makes it very attractive, but few examples of direct fluorination are now available (91T705, 96YOKK7, 02YOKK42, 82JFC(19)427, 85EA1075, 99TL7819, 00T8877, 03JAP(K)073874, 00PES2000).

For syntheses of fluoroorganic products, hydrogen fluoride and fluorine are very important reagents. Their reactions with heterocyclic compounds are the most direct and economical ways to obtain fluorinated derivatives. Electrochemical fluorination (ECF) on nickel electrodes in HF leads to perfluorinated compounds with complex structures, which are not readily accessible by known procedures. Growth of interest in this method of fluorine introduction has stimulated new investigations (96M14, 00M15). This is an industrial procedure, also employed for syntheses of perfluorinated compounds (64M17). Over the past three decades, anhydrous hydrogen fluoride has become an industrial product of top priority because of its utility for ECFs. Its high miscilirity makes it a good solvent for organic compounds.

Electrolytic fluorination on platinum electrodes in electrolytes containing conducting complexes of hydrogen fluoride with tertiary amines is a variety of ECF that leads to monofluorinated derivatives (93JOC4200, 95JFC(73)121). Owing to the mild conditions and regioselectivity, as well as safe and easy work with the fluorinating system, this is a promising process, especially for syntheses of compounds difficult to prepare with one or two fluorine compounds (94M18, 94RHC155, 97JSOC301, 98JFC(87)215, 98EA(43)2503, 97PES74, 04JFC(125)7, 98JFC(92)177, 01M19, 94JSOC1063, 99M20, 98PJ1118, 99RHC1, 97JFC(83)31, 83M22). This method is reviewed in (99RHC1, 97JFC(83)31, 83M22, 98RHC67, 98F1118, 93JES858, 91AA31, 97JES626, 97M23, 01M23, 89T4431). Analysis of the published data testifies the appearance of a new powerful method of selective fluorination, whose capabilities cannot be overestimated (03FN, 88JFC(39)435, 01M25, 94TL9237, 92JOC6074, 93JOC4200, 93JES858, 95BMCL1293).

In contrast to a standard redox system, an electrochemical (anode–electrolyte–cathode) system has spatially separated oxidative (anode) and reductive (cathode) components of the redox reaction. The oxidative anode and reductive cathode potentials can be smoothly adjusted and maintained with a high degree of precision within the limits of stability of the given electrolytic medium provided that an external DC source is used.

The two fluorination techniques are complementary; they create real opportunities for syntheses of perfluorinated organic compounds, as well as mono- and difluoroorganic molecules. In both cases, hydrogen fluoride acts as a solvent and a fluorinating agent, and the fluoride ion plays an extremely important role. Anhydrous hydrogen fluoride is widely used together with organic bases in anode fluorinations. This procedure proved very useful for fluorine introduction into organic molecules.

Section IV analyzes methods of fluorine introduction in organic molecules by discussing the ECF method in order to overview and rationalize the available material on syntheses and applications of fluorinated heterocyclic compounds based on modern knowledge in this field. Is it possible for modified electrochemical techniques to produce a pronounced effect when applied on a large-scale basis? Is there any opportunity to reject the old expensive and unsafe procedures for the production of fluorinated materials based on heterocyclic frameworks and to replace them by more economical, safe, and ecologically clean procedures? These issues are examined in Section IV.

II. Electrochemical Properties of Electrolytes Containing Anhydrous Hydrogen Fluoride

The group of new electrolytes containing anhydrous hydrogen fluoride includes the complexes $Et_3N \cdot 3HF$ (93EA619, 95TL6511, 96JPC99), $R_4NF \cdot nHF$ (96Y0KK7, 95M27, 93EA1123), and $Py \cdot nHF$ (88JFC(39)435, 96JFC(77)65), which are not viscous at room temperature and possess high electrical conductivity and electrochemical stability. Table 1 illustrates the electrical conductivity of their MeCN solutions.

The anode potential depends on the system used, which restricts the use of particular organic compounds for fluorination (Table 2) (70IZV1207).

Table 1. Electrical conductivity of MeCN solutions of $R_4NF \cdot nHF$ and $Et_3N \cdot 3HF$ (1 mol/dm^3) (93EA619)

Electrolyte	Conductivity (10^{-1} S/cm)
$Me_4NF \cdot 2HF$	56.9
$Et_4NF \cdot 2HF$	72.9
n-$Pr_4NF \cdot 2.2HF$	65.8
n-$Bu_4NF \cdot 2.2HF$	48.1
$Et_3N \cdot 3HF$	36.3
$Me_4NF \cdot 2.8HF$	59.2
n-$Pr_4NF \cdot 3HF$	67.2
n-$Bu_4NF \cdot 3HF$	50.8
$Me_4NF \cdot 4HF$	116.4
$Et_4NF \cdot 4HF$	89.8

Table 2. Anode potentials for selected electrolytes (Pt electrodes) (70IZV1207)

Electrolyte system	Anode potential (2 mA/cm^2)
M TBAP/MeCN	2.82
$Et_3N \cdot 3HF$	2.62
M $Et_3N \cdot 3HF$/MeCN	2.52
$Et_3N \cdot 3HF$/sulfolane	1.90
$Et_3N \cdot 3HF$/THF	1.46
1.0 M $Et_3N \cdot 3HF$/DME	1.22

Using hydrogen fluoride complexes with bases as electrolytes leads to selective introduction of one fluorine atom (95JCS(PI)1327, 76UK1222, 71DAK369, 76IZV1418, 70DAK1322, 84JOC2803, 71IZV1369, 93CJC122, 83JJC6, 87M28, 83JES2170, 79USP4146443). Platinum remains the most popular material for electrodes, but good results are also obtained with anodes of other materials (e.g., graphite, or rhenium). The best solvent for electrolytic fluorination is acetonitrile. However, other solvents, for example, dimethoxyethane (DME), are also useful. In the standard procedure, conditions are as follows: platinum electrodes, potential 1.76–2.55 V, current equivalent is 2–10 F/mol (for the preparation of monofluorinated derivatives); Et_3N/nHF, Et_4NF/nHF, Py/HF (30:70) employed as electrolytes.

Conductivity measurements (56JA5183) gave the refined values of specific conductivity of anhydrous hydrogen fluoride and characteristics of proton and fluoride ion mobility in HF (56JA5187). The specific conductivity of anhydrous hydrogen fluoride is $1.6 \times 10^{-6}\,\Omega$/cm at 0 °C.

The diversity of radical processes during ECFs indicates that the latter do not differ much from reactions of organic compounds with metal fluorides of variable valence. However, this is not always so. Therefore, the nature of the electrodes used in ECFs was treated in detail (00JAP(K)160382, 00JAP(K)204492).

Owing to its high selectivity and good yields, ECF is promising not only as the general procedure for syntheses of fluoroorganic compounds, but also as a method for the preparation of fluorine-containing heterocyclic compounds. The method is effective for obtaining partially fluorinated compounds; however, the general low selectivity and difficulties in isolating products make this process unprofitable.

Fluorination of organic compounds, including fluorine addition at the multiple bond and substitution of fluorine for hydrogen in the hydrocarbon chain, is a redox process because fluorine has the maximal possible electron affinity (4.15 eV) and the maximal standard redox potential (2.87 V).

III. Electrolytic Fluorination of Heterocyclic Compounds in Trialkylamine Complexes with Anhydrous Hydrogen Fluoride

A. Electrolytic Fluorination of Heterocyclic Compounds whose Substituents Contain no Heteroatoms

Direct (electrochemical) fluorination of heterocyclic compounds has developed substantially in recent years (85EA1075, 88JFC(39)435, 99JOC3346, 98JFC(87)137). However, the yields of fluorination products varied from low to unsatisfactory. This was demonstrated for pyrroles, thiophenes, and furans (02JOC9379, 03H15), which gave less than 6% yields of product in $Et_4NF \cdot 4HF$ and $Et_3N \cdot 3HF$ electrolytes. 4-Methylthiazole (02JOC9379) and 3-benzoyl-4-carbomethoxy-1,1-dioxothiazoline (02TL4805) are not fluorinated by this method at all. Anode fluorination of (4-*R*-arylthiazol-2-yl)acetonitrile forms a monofluorinated product – (4-*R*-aryl-5-fluoro-5*H*-thiazol-2-ylidene)acetonitrile ($R =$ H, Cl, CN, NO_2, MeO) – as the major reaction product (03H15). Other reaction products are (4-*R*-aryl-5-fluorothiazol-2-yl)acetonitrile and (4-*R*-arylthiazol-2-yl)fluoro-acetonitrile. A mixture of

products of fluorine exchange for hydrogen and 2,5,5-trifluorothiazoline sulfides is obtained during anodic ECFs of 2-thiazolyl sulfides with Me, $MeCOCH_2$, and $HC{\equiv}CCH_2$ substituents at the sulfur atom. 2-Thiazolyl monosulfides led to 5-fluorothiazoline sulfide and (cyanofluoromethylthio)thiazole (02JOC9379) (Scheme 2).

Owing to the presence of electron-accepting substituents in an heterocyclic compound, fluorination is drastically accelerated, giving high yields of fluorination product (02JOC9379, 03H15, 02TL4805, 94TL9237, 91JCS(CC)1027, 94JOC5937168, 01PES33, 01JOC7020, 00JOC3920, 90GC1749). *N*-methylpyrazoles with a carbonyl group in the α position relative to the nitrogen atom are electrolytically fluorinated in Py · 9HF at 20 °C to form fluoropyridizinones (90GC1749, 86BSCF955). The $Et_3N \cdot 3HF$ system may be used as an electrolyte (89JPP09-29364).

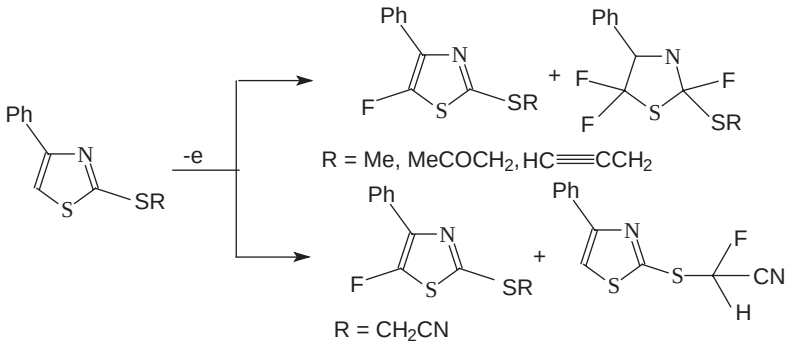
In the case of 4-thiazolidinone **1**, the $Et_3N \cdot 3HF$/MeCN system proved rather effective and convenient for anodic fluorination, which is a highly regioselective reaction giving monofluorinated derivative **2**. These are the first examples of effective anodic fluorination of sulfur-containing heterocyclic compounds (92JOC3755, 90JOC6074). Subsequent oxidation with peracids affects the sulfur atom to form **3** (Scheme 3).

Anodic fluorinations of *N*-benzoyl-, *N*-acetyl-, and *N*-formylthiazolidines in DME occur with high regioselectivity and give 5-mono-fluorinated thiazolines (01JOC7020, 00JOC3920, 90JOC6074) (Scheme 4).

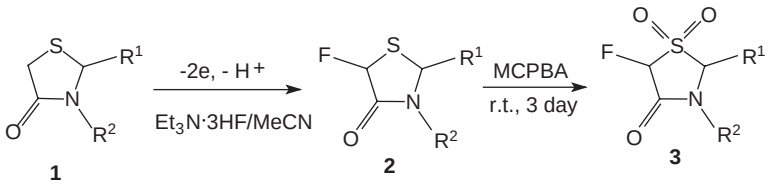
For 2-substituted 1,3-dithiolan-4-ones, anodic fluorinations in $Et_4NF \cdot 4HF$ and $Et_3N \cdot 3HF$ give monofluoro derivatives with a high regioselectivity (Table 3) (02T9273). Anodic difluorinations of 2-alkylthio-4-methyloxazoles using $Et_4NF \cdot nHF$ ($n = 4$, 5) lead to 2-alkylthio-4,5-difluoro-4-methyl-2-oxazolines, the α position relative to the sulfur atom remaining intact in these reactions (02H623).

An approach to the synthesis of fluorinated amino acids was developed based on successful fluorination of five-membered heterocycles (02TL4805). 1,3-Oxazolidines were easily synthesized from L-serine and L-thionine and were further subjected to anodic fluorination in the presence of $Et_4NF \cdot 4HF$ and $Et_3N \cdot 4HF$ electrolytes. The α carbon atom relative to the carboxyl group was involved in a regioselective reaction, which gave an α monofluoro product (Scheme 5).

Anodic fluorination of 4-*R*-2*H*-1,4-pyrido[3,2-*b*]-1,4-oxazin-3-ones (R = Me, Et, CH_2COOEt, CH_2Ph) is performed in 1,2- DME; this highly regioselective reaction

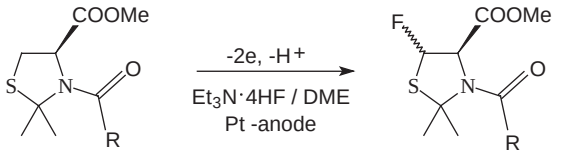


Scheme 2



R^1	R^2	Yield **2**, %	*cis:trans*	Yield **3**, %	*cis:trans*
1-naphthyl	Me	79	29:71		
Ph	H	14	35:65		
Ph	Me			42	35:65
Ph	CMe_3			59	45:55
Ph	Ph	84	43:57		
$PhCH_2$	Ph			65	46:54

Scheme 3



R	F/mole	Yield, %	de (%)
Ph	5.0	78 (50 *)	94
Me	5.5	(53 *)	80
H	5.5	52 (40 *)	59
Tol	5.0	91 (60 *)	95

*Yield of the isolated product

Scheme 4

forms 2-fluorinated derivatives (yields 45%, 60%, 40%, and 51%, respectively) (02T9273).

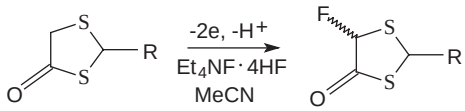
Mono- and difluoro derivatives of *s*-triazole[3,4-*b*][1,3,4]-thiadiazine are regioselectively formed when the latter reacts with $Et_4NF \cdot 4HF$, $Et_3N \cdot 3HF$, $Et_4NF \cdot 5HF$ and $Et_3N \cdot 5HF$ in DME (Table 4) (00TL273).

Other heterocyclic compounds behave similarly (Scheme 6).

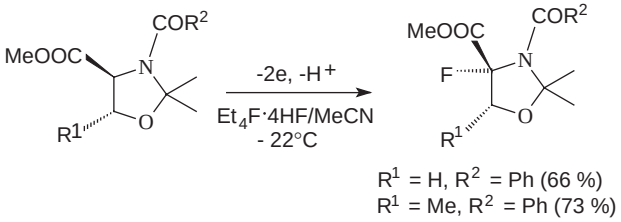
Anodic fluorination of 3-benzyl-1-thiochromones and thiochroman-4-ones, in particular, of (*Z*)-3-benzylidene-2,3-dihydrothiochroman-4-one, yields two monofluoro derivatives due to substitution of hydrogen at the α position relative to the sulfur atom of the heterocyclic ring and fluorine addition at the double bond (01JOC7030) (Scheme 7).

3(4-Chlorobenzyl)thiochromone behaves in much the same way (01JOC7030) (Scheme 8).

Table 3. Fluorination of 2-substituted 1,3-dithiolan-4-ones (Pt anode, 0.1 mol/dm^3, $NaClO_4$/MeCN, 100 mV/s) (02T9273)



R	E_p^{ox} (V) (vs. SSCE)	F/mol	Yield (%)	*cis:trans* ratio
n-Pr	2.20	3.1	72	48:52
		11.5	26	44:56
i-Pr	2.23	3.4	62	44:56
		7.3	20	48:52
Ph	2.16	3.3	63	60:60
		7.2	55	48:52
o-Tol	2.15	2.8	54	33:67
		7.7	49	40:60
Mesityl	2.03	2.8	57	20:80
		7.1	50	27:73



Scheme 5

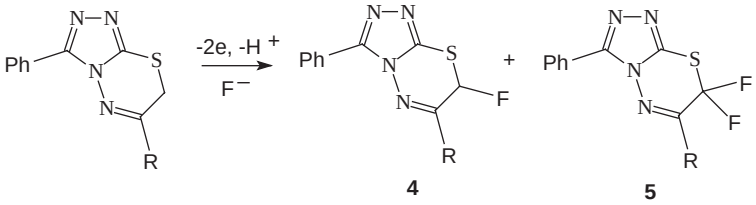
This reaction fails to form 2-fluoro-1-thiohomoisoflavone, while anodic fluorination of 2-arylthiochromone affords 3-fluorothioflavone and 2,3,3-trifluorothioflavone (01JOC7030, 01SL1938) (Scheme 9).

Anodic fluorination of (+)-(1*R*,2*R*,4*R*)-7,7-dimethyl-*N*,*N*-*bis*(1-ethyl-methyl)-5-oxo-spiro[bicyclo[2,2,1]heptane-2,3′-[1,3]oxathiolane]-1-metha-nesulfonamide leads to (+)-(1*R*,2*R*,4*R*,4′*S*)-4′-fluoro-7,7-dimethyl-*N*,*N*-*bis*(1-ethylmethyl)-5-oxo-spiro[bicyclo[2,2,1]-heptane-2,2′-[1,3]oxathiola-ne]-1-methanesulfonamide (03JFC(121)93).

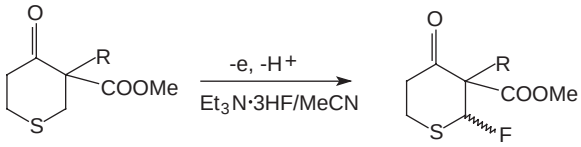
Anodic fluorination of 2-substituted 1,3-dithiolan-4-ones (87M28) and 1,3-oxathiolan-5-ones **9** give monofluoro derivatives **10** (Scheme 10, Table 5) (03JFC(121)93, 99JOC133) (Scheme 10).

In $Et_4NF \cdot 4HF$ 2-substituted 1,3-dithiolan-4-ones are converted into mono-fluoro derivatives (98EA(43)1985). Table 5 presents data on anodic fluorination of 2-substituted 1,3-oxathiolan-5-ones, forming monofluoro derivatives **10** (03JFC(121)93, 99JOC133). The fluoride ion plays a very important role in this process. As can be seen from Table 5, the $Et_3N \cdot 3HF$ system is unsuitable for anodic fluorination of the

Table 4. Anodic fluorination of substituted s-triazole[3,4-*b*][1,3,4]-thiadiazines (00TL273)



R	E_p^{ox} (V) (vs. SSCE)	Electrolyte	F/mol	4	5
CH_3	2.24	$Et_3N \cdot 3HF$	3	42	0
		$Et_4NF \cdot 4HF$	3	8	1.0
Ph	1.79	$Et_4NF \cdot 4HF$	2	67	—
4-$NO_2C_6H_4$	1.89	$Et_4NF \cdot 4HF$	2.5	68	—
4-$CH_3C_6H_4$	1.71	$Et_4NF \cdot 4HF$	4	40	—



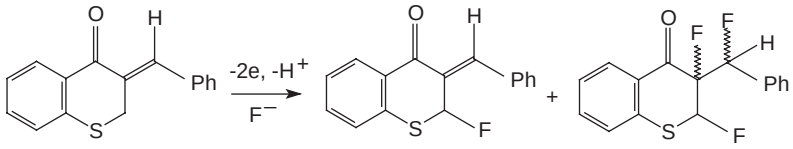
R	Yield, %	Stereoselectivity, %
Me	7	100
CH_2Ph	27	76

Scheme 6

given heterocycle. When subjected to anode fluorination in the $Et_4NF \cdot 4HF$ electrolyte, 4-arylthio-1,3-dioxolan-2-one ($E_p^{ox} = 1.9$ eV) gives two products, whose ratio depends significantly on the solvent used (00JCS(CC)1617, 01T9067). In CH_2Cl_2, fluorodesulfonation takes place to form 4-fluoro-1,3-dioxolan-2-one; however, in DME the reaction gives a mixture of products among which 4-fluoro-4-phenylthio-1,3-dioxolan-2-one is the major product ($E_p^{ox} = 2.2$ eV) (Scheme 11).

A difluoro product is formed when the anode fluorination potential is higher than 2.2 eV (Scheme 12).

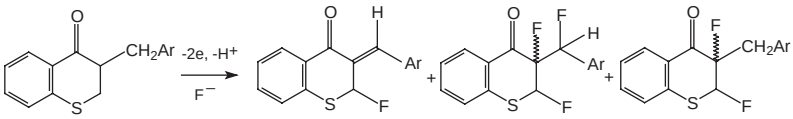
When fluorination is carried out in a cell with a single cathode and anode in the presence of $Et_3N \cdot 5HF$ or $Et_4NF \cdot 4HF$ electrolytes and in CH_2Cl_2 as a solvent, the product is 4-fluoro-1,3-dioxolan-2-one; in dimethoxyethane, the anodic fluorination product is the α fluorinated derivative (01TL4861, 87CP1119). Anodic fluorination of 4-phenylthiomethyl-1,3-dioxolan-2-one in $Et_3N \cdot 3HF$, $Et_3N \cdot 5HF$, $Et_4NF \cdot 4HF$ systems (MeCN and DME as solvents) forms a mixture of mono- and difluoro



E^{o}_{red}, V			
1.70	$Et_4NF \cdot 4HF$/DME	81 (94*)	5
	$Et_4NF \cdot 4HF$/MeCN	58 (83*)	12
	$Et_4NF \cdot 3HF$/DME	78 (100*)	
	$Et_3N \cdot 4HF$/DME	42 (68*)	20
	$Et_3N \cdot 3HF$/DME	35 (76*)	11

* Selectivity, %

Scheme 7

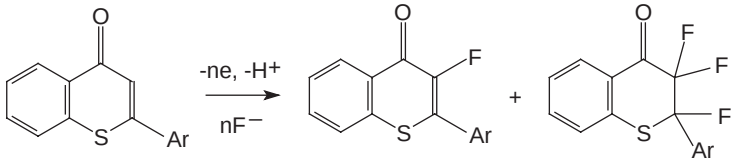


Ar = 4-ClC_6H_4

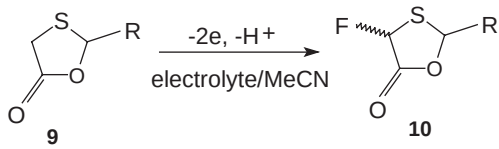
E^{o}_{red}, V 1.90 **6** **7** **8**

System	Compound		
	6	**7**	**8**
$Et_4NF \cdot 4HF$/DME	61	14	13
$Et_4NF \cdot 3HF$/DME	56	19	-

Scheme 8



Scheme 9

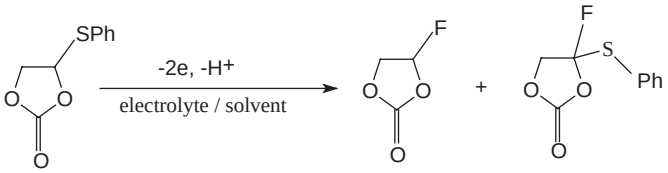


Scheme 10

Table 5. Anode monofluorination of 2-substituted 1,3-oxathiolan-5-ones*(99JOC133)

R	E_p^{ox} (V)	Electrolyte	Oxidation potential (V)	F/mol	Yield of 10 (%)	*cis*/*trans* ratio
Et	2.34	$Et_3N \cdot 3HF$	2.3	3.4	0	
		$Et_4NF \cdot 4HF$	2.1	2.6	86	47/53
n-Pr	2.32	$Et_3N \cdot 3HF$	2.2÷2.3	3.6	5.4	d
		$Et_4NF \cdot 4HF$	2.1	2.2	67	45/55
i-Pr	2.44	$Et_3N \cdot 3HF$	2.2	2.2	0	
		$Et_4NF \cdot 4HF$	2.1	2.4	78	43/57
Ph	1.88	$Et_3N \cdot 3HF$	1.6	4.0	0	
		$Et_4NF \cdot 4HF$	2.0	2.3	70	45/55
4-CNC_6H_4	2.17	$Et_3N \cdot 3HF$	2.2	3.4	0	
		$Et_4NF \cdot 4HF$	2.0	3.2	66	39/61

*Pt electrodes; 0.1 M $NaClO_4$/MeCN.



Ph	Electrolyte	Solvent		Yield, %
C_6H_5	$Et_4NF \cdot 3HF$	CH_2Cl_2	29	16
	$Et_4NF \cdot 3HF$	DME	5	40
	$Et_4NF \cdot 4HF$	CH_2Cl_2	53	trace
	$Et_4NF \cdot 4HF$	DME	28	54
	$Et_4NF \cdot 5HF$	CH_2Cl_2	67	trace
4-ClC_6H_4	$Et_4NF \cdot 4HF$	DME	20	80
	$Et_4NF \cdot 5HF$	CH_2Cl_2	96	0

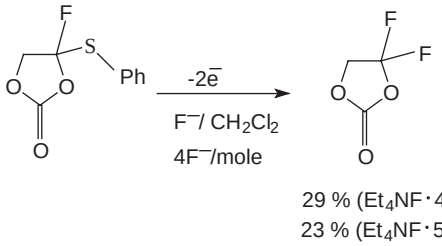
Scheme 11

derivatives; fluorination occurs at the carbon atom in the α position relative to the sulfur atom (01TL4861) (Scheme 13). The yield of the difluoro derivative increases with the temperature and with the amount of current passed through the electrolyte.

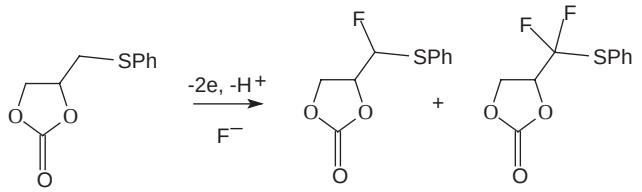
This is probably the first example of solvent effect on the selectivity of anodic fluorination.

Electrochemical oxidation of 2,2-diphenyl-1,3-dithiane in $Et_3N \cdot 4HF$ forms difluorodiphenylmethane (92CL1995) (Scheme 14).

Monofluorinated β-lactams are of considerable interest as intermediates for syntheses of fluorine-containing antibiotics and as building units for syntheses of amino acids and sugars. Thus, regioselective anodic monofluorination of 3-phenylthio-2-azetidinones and 4-phenylthio-2-azetidinones leads to 3- and 4-substituted

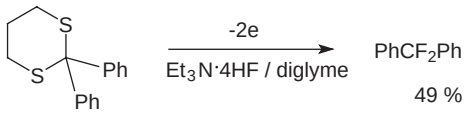


Scheme 12



$Et_3N \cdot 3HF/CH_2Cl_2$, 2 F/mole , 20°C	48 %	4 %
$Et_3N \cdot 3HF$/DME, 8 F/mole, 20°C	40 %	8 %
$Et_3N \cdot 3HF$/DME, 8 F/mole, 40°C	73 %	trace
$Et_3N \cdot 3HF$/DME, 48 F/mole, 40°C	trace	68 %

Scheme 13



Scheme 14

2-azetidinones (Table 6) (97JES841). The yield of the monofluorination product is strongly dependent on the electrolyte used. It is interesting that the Py/(HF)*n* system does not work in this case (93JOC4200).

In the general case, electrolytic fluorination of N-substituted lactams in $Et_3N \cdot 3HF/MeCN$ or $Et_3N \cdot 5HF$ electrolytes is a selective reaction that affects the carbon atom in the α position relative to the nitrogen atom of the lactam to form a monofluorination product in high yield (99IJC151).

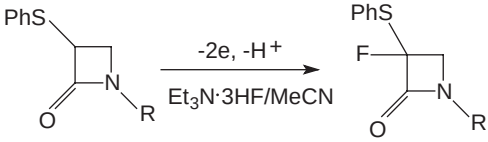
If the SR group lies at any position other than α to the C = O group of the heterocycle, it is substituted by the fluorine atom during anodic fluorination (01SL1269) (Scheme 15).

Fluorodesulfonation occurs irrespective of the presence of other substituents in the heterocyclic ring (01SL1269) (Scheme 16).

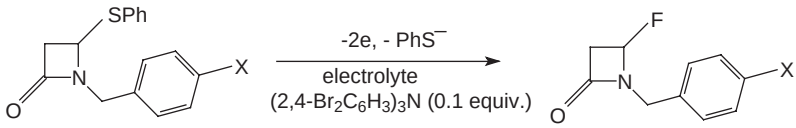
The mechanism of this process was represented as follows (Scheme 17) (01SL1269, 80NJC453).

If azetidin-2-one has an $SiMe_3$ group in position 4, the reaction is accompanied by fluorodesilylation into a fluoro derivative (Table 7) (95JCS(PI)1327).

Table 6. Anode fluorination of azetidinones (99ACS887)

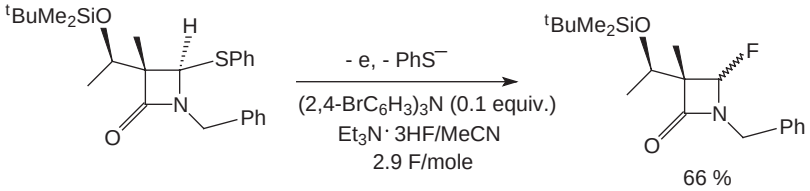


R	Electrolyte	V (vs. SSCE)	F/mol	Yield (%)
Et		1.8	2.5	65
Pr^i	$Et_3N \cdot 3HF$	1.8	2.3	77
	$Et_4NF \cdot 3HF$	1.5	2.0	64
	$Py/(HF)_n$	1.9	2.2	Traces
	$Et_3N \cdot 2HF$	1.7	13.2	33
Bu^n		1.8	2.4	92
Bu^t		1.9	2.5	67
c-C_6H_{11}		1.8	2.5	84
$PhCH_2$		2.0	4.0	68



Electrolyte	$Et_3N \cdot 3HF$ / MeCN			$Et_4NF \cdot 3HF$
X	H	Me	Br	H
Yield, %	83	71	quantitative	43

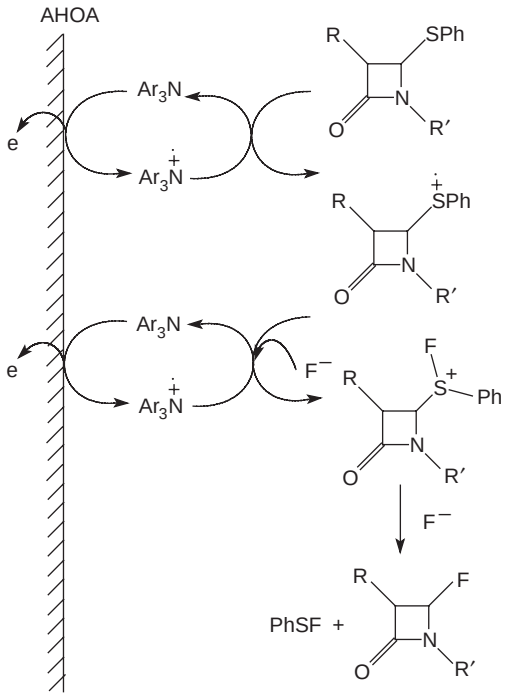
Scheme 15



Scheme 16

Smooth reactions take place if anodic fluorination is performed with 1-naphthalenes in $Et_3N \cdot 3HF$ or with oxyindole and 3-oxo-1,2,3,4-tetrahydro-isoquinoline in $Et_4N \cdot 3HF$ when the substrates contain CN, COOEt, or SPh groups (97SL655, 97JOC8773, 03GC512) (Scheme 18).

The nature of the electrodes is important to the product yield, as shown below for oxoindole. Higher yields of the fluorinated product are obtained when increased amounts of hydrogen fluoride are used (97SL655, 97JOC8773) (Scheme 19).



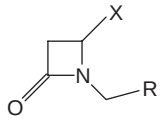
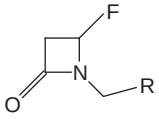
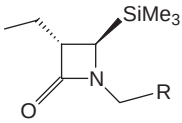
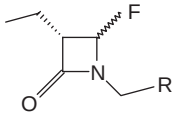
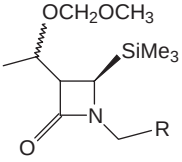
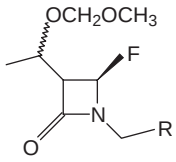
Scheme 17

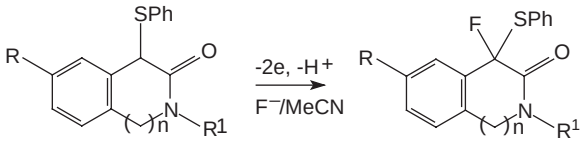
High regioselectivity in $Me_4NF \cdot 4HF$ was also reported for 1-(4-tolyl)-5-methyl-3(phenylthio)- and 1-phenyl-3(phenylthio)-2-indolones (yield of the monofluoro derivatives are 64% and 50%, respectively) (97SL655, 97JOC8773). A similar reaction of 2-benzyl-4(phenylthio)-1,2,3,4-tetrahydro-3-isoquinolinone gave a 4-fluorosubstituted product (71%) (97SL655). In the course of anode fluorination of oxoindole in $Et_4N \cdot 3HF$/MeCN in the absence of an SPh group, the benzene ring is fluorinated, while the heterocyclic system remains intact (97JOC8773) (Scheme 20).

Regioselective monofluorinations of 1-aryl-3(phenylthio)oxyindole and 2-substituted 3-oxo-4(phenylthio)-1,2,3,4-tetrahydroisoquinoline in $Me_4NF \cdot 4HF$ and in $Et_4NF \cdot 3HF$ form 3-fluorinated oxyindole and 4-fluorinated isoquinoline with good yields (97JOC8773). In the $Me_4NF \cdot 4HF$ system, the carbon anode proved to be more effective than the Pt anode. However, anodic fluorination of phthalides in the presence of $Et_3N \cdot nHF$ ($n = 3$–5) gives 3-fluoro derivatives with the benzene ring remaining unaffected (03GC512). Using MeCN, CH_2Cl_2, or DME as solvents leads to very low yields of the desired product, but the latter increase drastically in the presence of 1-ethyl-3-methylimidazolium triflate [emim][OTf] (Scheme 21).

Phthalides have an extremely high oxidative potential (2.86 V) (03GC512). Selective fluorination also takes place in the case of carbonyl-containing heterocyclic compounds. Thus mono- and difluoro derivatives of 4-(metho-xyphenyl)acetone and ethyl 4-(methoxyphenyl)acetate (87TL2359, 98JFC(87)215) and fluoroindanes (90TL3137) are produced by anodic fluorination of hydrocarbon substrates in the

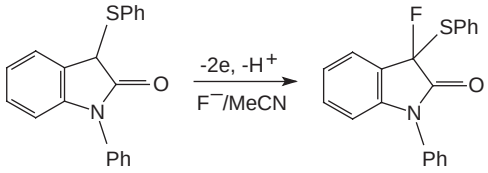
Table 7. Electrochemical synthesis of 4-fluoroazetidin-2-ones (95JCS(PI)1327)

Compound	Electrolyte	F/mole	Product	Yield, %
 X = SiMe$_3$, R = Ph	$Et_3N \cdot 3HF$	8.0		80
SiMe$_3$, Ph	$Et_3N \cdot 2HF$	20.0		49
SiMe$_3$, Ph	Py ·nHF	4.0		66
SiMe$_3$, Ph	$Bu_4N \cdot BF_4$	4.0		pitch
SiMe$_3$, Pr	$Et_3N \cdot 3HF$	18.0		78
 *trans*-	$Et_3N \cdot 3HF$	14	 *cis*/*trans* = 1/1	88
 *trans*-	$Et_3N \cdot 3HF$	10	 *trans*-	75



n	R	R^1	Electrolyte	F/mole	Yield, %
0	H	Ph	$Me_4NF \cdot 4HF$	3.5	64
0	Me	4-MeC_6H_4	$Me_4NF \cdot 4HF$	3	50
1	H	Ph	$Et_4NF \cdot 3HF$	2.6	71
1	H	$PhCH_2$	$Et_4NF \cdot 3HF$	2	70

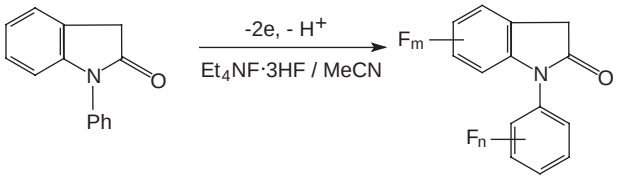
Scheme 18



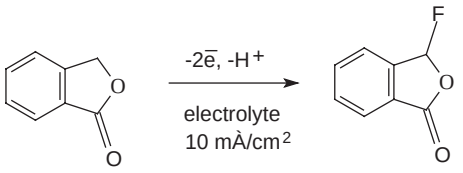
Yield, %

Anode	$Et_4NF \cdot 3HF$	$Me_4NF \cdot 4HF$
Pt	58	64
Carbon	28	60
C-steel	36	59
C-felt	21	42

Scheme 19



Scheme 20



Medium	Electrolyte	Yield, %
MeCN	$Et_3N \cdot 5HF$	16
CH_2Cl_2	$Et_3N \cdot 5HF$	23
DME	$Et_3N \cdot 4HF$	0
	$Et_3N \cdot 3HF$	17
	$Et_3N \cdot 5HF$	16
[emim][OTf]	$Et_3N \cdot 3HF$	78
	$Et_3N \cdot 4HF$	70
	$Et_3N \cdot 5HF$	90

Scheme 21

$Et_3N \cdot 3HF$ electrolyte. Smooth reactions take place when anodic fluorinations are performed with 1-naphthalenes in $Et_3N \cdot 3HF$ and with oxyindole and 3-oxo-1,2,3,4-tetrahydro-isoquinoline in $Et_4NF \cdot 3HF$ when the substrates contain CN, COOEt, or SPh groups (97SL655, 97JOC8773, 03GC512).

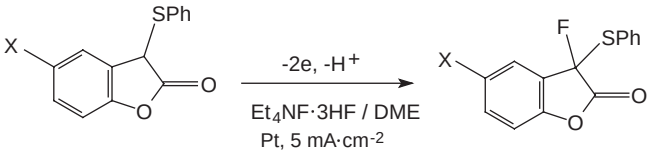
The examples below serve to illustrate the important role of the SPh group in anode fluorination of substrates containing this group. Fluorination of 3-phenylthio-2-benzofuran on a Pt anode in $Et_4NF \cdot 3HF$/DME gives a monofluoro product (99JFC(99)189) (Scheme 22). The reaction occurs at the heterocyclic carbon atom bonded to the SPh substituent.

In the case of α-phenylthiobenzothiazolylacetonitrile, there are two monofluorinated products, one of which is derived by replacing the SPh group by the fluorine atom. The product yield depends on the voltage (99JFC(99)189) (Scheme 23).

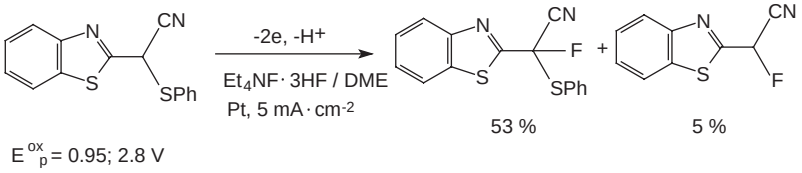
Ethyl isonicotinate (83JES2170), pyrazole (Table 5) (99JFC(99)189, 89JAP(K)0129364), pyridine (85EA1075), and 1,10-phenanthroline (99JOC3346) are fluorinated at the heterocyclic ring and the methyl group. However, the yields are low.

Ethyl 1-methyl-5-fluoropyrazole-4-carboxylate **12** and ethyl 1-fluoromethyl-5-fluoropyrazole-4-carboxylate **13** are the products of electrochemical fluorination of ethyl 1-methylpyrazole-4-carboxylic acid **11** on a platinum anode in 70% HF/Py/Et_3N (99TL7819) (Scheme 24). The maximum yield is 40% (selectivity of fluorine attack at position 5 is 83%) (Table 8).

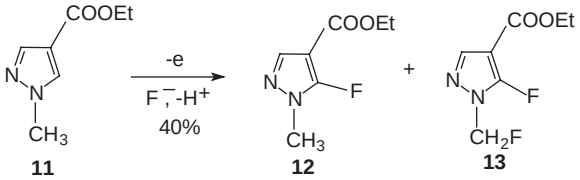
Anodic fluorination of pyridine in $Et_3N \cdot 3HF$ gives 2-fluoropyridine in 22% yield (85EA1075). Because the heterocyclic ring contains electron-accepting substituents,



Scheme 22



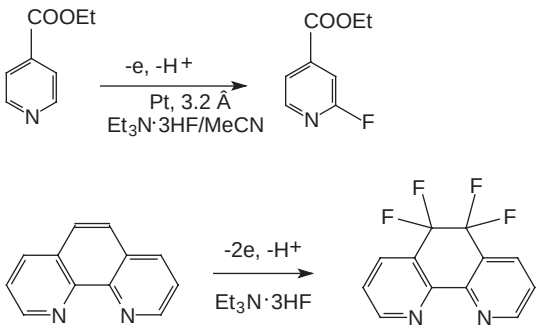
Scheme 23



Scheme 24

Table 8. Anodic fluorination of ethyl 1-methylpyrazole-4-carboxylate (99TL7819)

Anode	System	Solvent	Voltage (V)	Product ratio (**12:13**)	Yield (%)
Pt	HF/Py	MeCN	2.5	25:75	16
	HF/Py/Et_3N(0.3)	MeCN	2.5	57:43	23
	HF/Py/Et_3N(0.6)	MeCN	2.5	83:17	40
	HF/Py/Et_3N(1.0)	MeCN	3	100:0	18
	HF/Py/Et_3N(0.6)	THF	2.7	100:0	2
	HF/Py/Et_2NPh	MeCN	2.5	92:8	39
C	HF/Py/Et_3N	MeCN	2/1	97:3	31



Scheme 25

direct fluorination of the ring is hindered, and the 2-fluoro derivative is formed in low yield (98JFC(87)137). For example, ethyl 2-fluoroisonicotinate is obtained by electrolysis of ethyl isonicotinate in $Et_3N \cdot 3HF$/MeCN (yield 30%, conversion 76%) (98JFC(87)137) (Scheme 25).

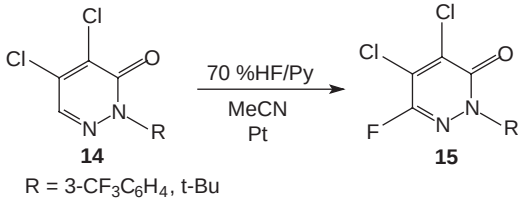
Nitrogen-containing heterocyclic compounds are fluorinated at the α position relative to the nitrogen atom of the heterocycle. ECF of *N*-ethylthiopyridone using a Ni–NiO anode and a Ni cathode with $R_4NF \cdot nHF$ or $R_3N \cdot nHF$ ($n = 1$–6) (in the presence of $LiClO_4$) employed as electrolytes in an acetonitrile−DME solvent system gives 2-fluoro-4-ethyl-4thiopyridine (yield 66.9%) (83JPP6429366). Another example is anodic fluorination of pyridazin-3-ones **14** in 70% HF/Py/MeCN on Pt electrodes at room temperature, which leads to monofluoro derivatives **15** (03JAP(K)3137867) (Scheme 26).

Anodic fluorination of 2*H*-1,4-benzothiazin-3(4*H*)-ones **16** in acetonitrile in the presence of $Et_3N \cdot 3HF$ forms monofluoro derivatives **17**; in this reaction, fluorine is substituted for hydrogen in the α position relative to the sulfur atom (92TL7017) (Scheme 27).

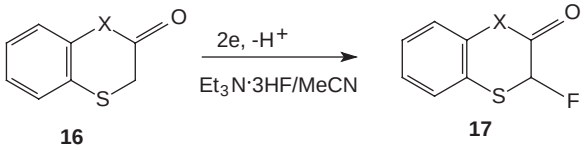
N-substituted 1,4-benzoxazinones are electrochemically fluorinated on Pt electrodes in 1,2-DME containing the $Et_4NF \cdot 4HF$ electrolyte to form the corresponding 2-monofluorinated products with high yields, the reactions being highly regioselective (01SL1644) (Scheme 28).

For biologically active flavones, for which the first E_p^{ox} is 2.36–2.52 V (Scheme 29), anodic fluorination leads to di- and trifluoro derivatives (99JOC3346).

Anodic fluorination of flavone and 6-chloroflavone in $Et_3N \cdot 3HF$ and $Et_4NF \cdot 4HF$ yields the 3-monofluoro derivative **19** as the major product and a

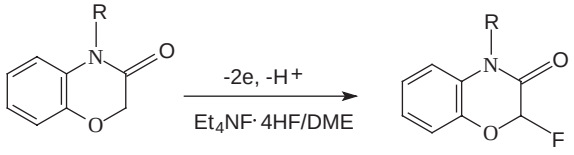


Scheme 26



X		F/mole	Yield of **17**, %
NH	3.0	15	0
NHCOPh	2.0	2.2	77
N-Pr^{i}	1.5	2.5	88
n-Me	1.6	2.1	68

Scheme 27

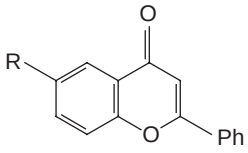


R	E^{ox}_{p}(B)	F/mole	Yield, %
Me	1.60	2	66
CH_2COOEt	1.64	2	48
CH_2Ph	1.63	2	51
H	1.63	7	60

Scheme 28

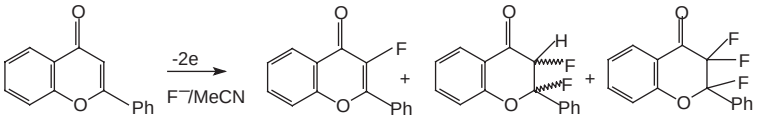
small amount of the 2,3-difluoro derivative (the reaction is conducted at 30 °C) (01SL1938, 98SL973). The ratio of compounds in the mixture depends on the electrolyte used (99JOC3346) (Scheme 30).

Moderate yields of monofluoro derivatives are obtained when caffeine, guanosine tetraacetate, and uridine triacetate are electrochemically oxidized in $Et_3N \cdot 3HF$ (Table 9) (94TL9237).



R	H	Me	Cl
E_p^{ox}, V vsSSCE	2.50	2.36	2.52

Scheme 29



18 19 20 21

Electrolyte	Yield, %		
	19	**20** (*cis:trans*)	**21**
$Et_3N{\cdot}3HF$	43	0	6
$Et_3N{\cdot}5HF$	9	28(3/1)	4
$Et_4NF{\cdot}3HF$	3	54(2/1)	6
$Et_4NF{\cdot}4HF$	7	68(2/1)	9

The temperature plays a key role in this process:

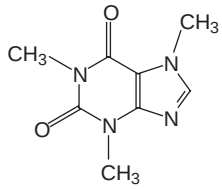
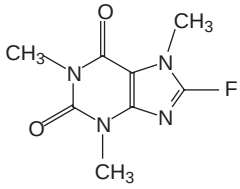
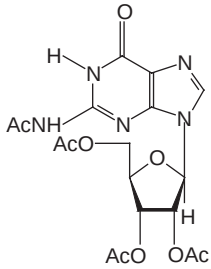
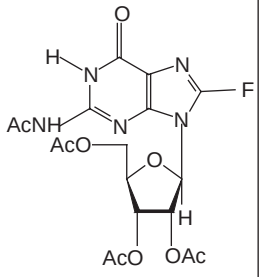
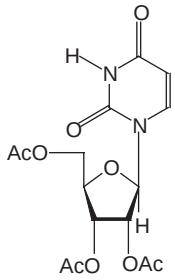
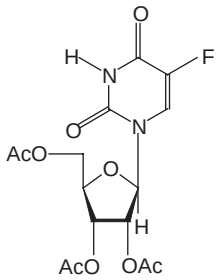
Temperature, °C	- 10	0	10	20	30
Yield of **19**, %	9	27	31	43	58
Yield of **21**, %;	traces	3	4	6	19

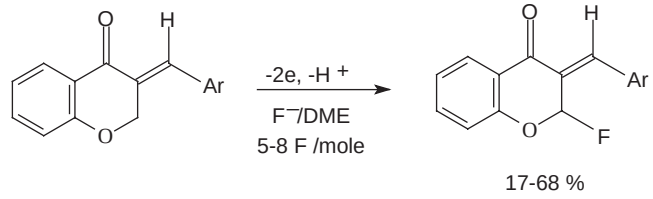
Scheme 30

Anode fluorination of (*E*)-3-benzylidene-2,3-dihydrochromagn-4-one is a highly regioselective reaction forming a monofluorinated product; it occurs at the carbon atom in the α position relative to the ring oxygen (01TL2513, 01JOC7691) (Scheme 31).

High regioselectivity is observed during anodic fluorination of α-phenyl-sulfenyl-substituted lactams **22** in $Et_3N \cdot 3HF/MeCN$ on Pt electrodes. Hydrogen in the α

Table 9. Electrochemical oxidation of caffeine and related compounds (MeCN, Et3N · 3HF) (94TL9237)

Compound	Potential oxidation (V) (vs.SSCE)	Time h	Product	Yield %
	5	17		40.3
	3	10		6.3
	C.C.E. 100 mA	5.5		4.6



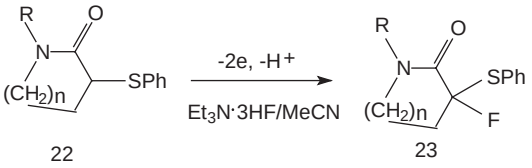
Ar = Ph, 4-ClC$_6$H$_4$, 4-BrC$_6$H$_4$

Electrolyte : $E_4NF \cdot 4HF$, $Et_4NF \cdot 3HF$, $Et_3N \cdot 4HF$

Scheme 31

position relative to the SPh group is substituted for fluorine irrespective of the size of the cycle of **23** (99ACS887, 92TL7017) (Scheme 32).

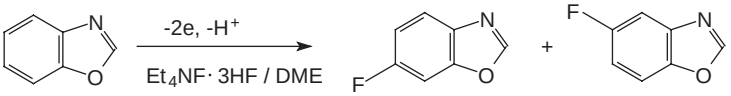
In the case of β-phenylsulfenyl-β-lactam, β-fluorinated β-lactam is formed in good yield (01SL1269).



22 23

n	R	Anode potential, V, vs SSCE	F/mole	Yield of **23**, %
1	Me	1.8	2.5	85
1	cyclohexyl	1.8	2.5	84
2	Me	2.0	2.2	69
3	Me	1.9	4.0	mixture of compounds

Scheme 32



E^{o}_{red} 2.32 total yield 7 %

Scheme 33

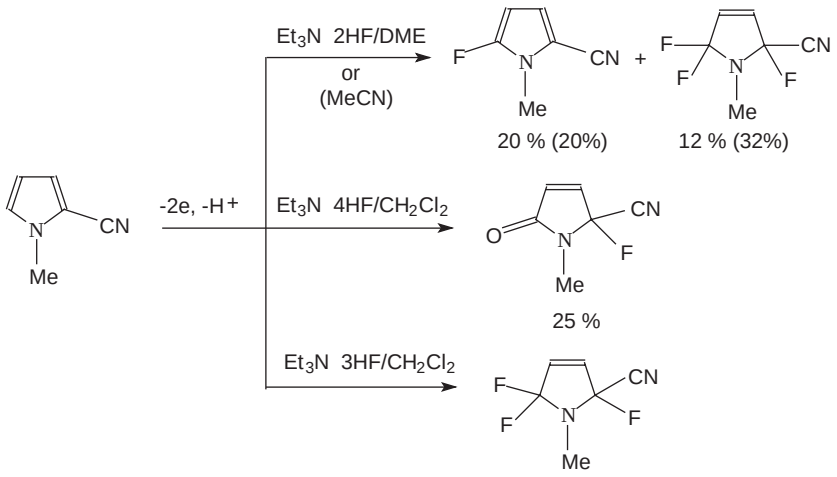
Two monofluorinated products with very low yields result from anodic fluorination of benzoxazole (99JFC(93)159) (Scheme 33).

The same tendency persists for benzothiazole (97JOC9173) and oxyindole (03GC512).

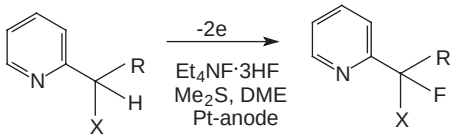
Highly selective anodic fluorination is feasible for a number of nitrogen-containing heterocycles: thiolane, oxathiolane, dithiolane, thiazolinone, 2*H*-1,4-benzothiazin-3(4*H*)-one, 3*H*-1,4-benzooxathian-2-one, oxindole, and tetrahydroisoquinoline. These reactions are performed in $Et_3N \cdot 3HF$/MeCN or $Et_4NF \cdot mHF$ ($m = 3, 4$) as electrolytes (97PES65). ECF of 2-benzothiazolyl and 5-chloro-2-benzothiazole sulfides in $Et_4NF \cdot 3HF$ leads to α-monofluorinated sulfides with good yields (97JOC9173).

High selectivity of anodic fluorination is observed for 1-methyl-1*H*-pyrrole-2-carbonitrile; this reaction is conducted in $Et_3N \cdot 2HF$ and leads to the corresponding 5-fluoropyrrole and 2,5,5-trifluoro-1-methyl-3-pyrroline-2-carbonitrile (97JOC9173, 97PES65, 02S2597, 01TL4857). Subsequent hydrolysis of the reaction product gives 5,5-difluoro-1-methyl-3-pyrrolin-2-one (01TL4857) (Scheme 34).

The effect of electrolyte on the fluorination products was demonstrated for 1-methylpyrrole having electron-accepting substituents (e.g., CN) in the 2-position (01EC467). Thus a trifluoro product is preferably formed in $Et_3N \cdot 3HF$, while the reaction in $Et_3N \cdot 2HF$ leads to monofluoro derivatives as the sole products.



Scheme 34



1.70 V, X = PhS, R = COOEt (55 %)
2.00 V, X = PhS, R = CN (56 %)

Scheme 35

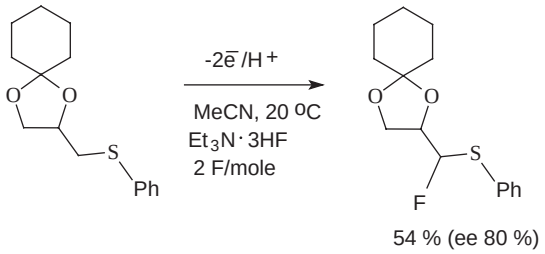
B. Anodic Fluorination of Compounds having a CH Fragment and Electron-Accepting Groups

Acceptable yields of fluoro derivatives are achieved in anodic fluorinations of substituted aromatic and heterocyclic compounds with mobile protons in the α position relative to the major ring. Platinum is generally used for electrodes, $Et_3N \cdot 3HF$ being the most effective system for these processes (88JFC(87)203) (Scheme 35).

Anodic fluorination of (*R*)-4[(phenylthio)methyl]-2-spirocyclohexyl-1,3-dioxolane in $Et_3N \cdot 3HF$/MeCN as electrolyte forms a monofluorinated product, the reaction being highly diastereoselective (04JOC1276) (Scheme 36). This is a general reaction; it is performed with sulfides containing both heterocycles and substituents with oxygen atoms (Table 10).

Konno and Fuchigami (97JOC8579) made the major contribution to the understanding of the mechanisms of anode fluorination processes (88FRP2604189). The effect of sulfur-containing substituents on anodic fluorination is inherent in both aromatic and heterocyclic compounds (01T8817, 02T9273, 02T9278) (Scheme 37).

Thus during anodic fluorination in $Et_4NF \cdot 3HF$ or $Et_3N \cdot 3HF$ electrolytes in DME, nitrogen-containing sulfides, for example, heterocyclic propargyl sulfides undergo smooth fluorination involving the carbon atom in the α position relative to



Scheme 36

the sulfur atom, the acetylenic group and heterocycle remaining intact (Table 11) (01T8817, 02T9273, 02T9278).

Some of the widely accepted fluorinating agents such as *N*-fluoropyridinium salts proved to be absolutely inert in these reactions (Scheme 38) (97JOSC301, 86BCJ3625, 95JOC6563). Therefore, electrochemical oxidation can be understood as an alternative to known fluorination procedures, and one can expect that this method will be further developed and applied to other organic substrates.

Anodic fluorination of 2-thiazolyl methyl sulfide, 2-thiazolyl propargyl sulfide, and 2-thiazolyl acetonyl sulfide leads to the products of exchange and addition at the heterocyclic ring but not to the product of substitution of the hydrogen atom of the CH_2 fragment lying in the α position (Table 12) (02JOC9379).

The hydrogen atom of the CH_2 fragment undergoes α-substitution only in the case of the CN substituent (Scheme 39).

Electrolytic fluorination of 2-benzothiazolyl, and 5-chloro-2-benzothiazolyl sulfides gives the corresponding α-monofluorinated sulfides (99JFC(93)159, 97JOC9173, 97PES65, 02S2597, 01TL4857, 00SL999) (Scheme 40).

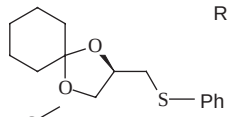
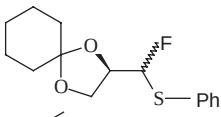
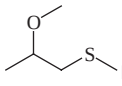
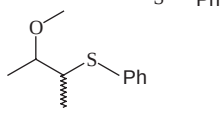
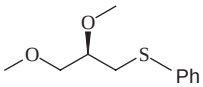
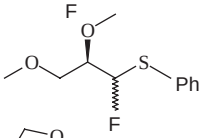
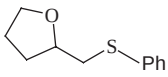
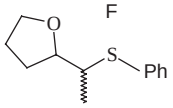
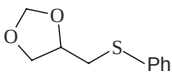
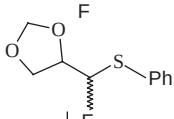
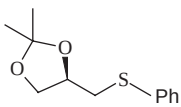
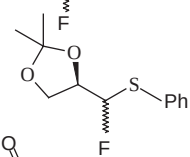
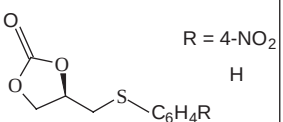
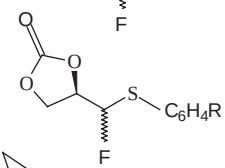
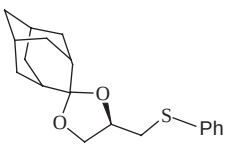
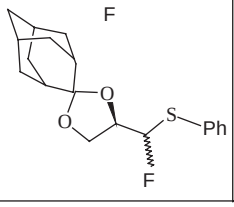
Anodic monofluorination of five-membered nitrogen-containing heterocyclic (1,3,4-thiadiazolyl, 1,3,4-oxadiazolyl, 1,3,4-thiazolyl) sulfides is highly regioselective when performed in electrolytes $Et_4NF \cdot 4HF$, $Et_4NF \cdot 5HF$, $Et_3N \cdot 3HF$, $Et_3N \cdot 5HF$ in the presence of dipolar aprotic solvents (MeCN, DME) (95JOC7654, 01PES25). The yield of the monofluorinated product depends strongly on the structure of the heterocycle (Table 13).

It should be noted, however, that flurodesulfurization can occasionally take place. For example, anodic fluorination of 3-phenylthiophthalide in the presence of $Et_3N \cdot 3HF$ leads to a fluorodesulfurization product and to the product of hydrogen substitution in the α position relative to the SPh group (03GC512) (Scheme 41). The product ratio depends on the character of the medium.

Fujigami et al. (90JOC6074, 92TL7017, 97JOC8579) obtained α-monofluoro sulfides in selective anodic fluorination of nitrogen-containing heterocyclic sulfides whose methylene group contained an electron-accepting substituent. Pulse electrolysis of pyridines and pyrimidines in $Et_3N \cdot 3HF$/MeCN with Pt electrodes at 25 °C formed monofluorinated derivatives (91T3969, 94TL7245) (Scheme 42). The yield of the fluorinated product increases when the α position contains electron-accepting groups.

High regioselectivity was also observed during anodic fluorination of 2-pyrimidyl and 2-pyridyl sulfides containing electron-accepting substituents using $Et_4NF \cdot nHF$ ($n = 3, 4$) and $Et_3N \cdot 3HF$ in DME (Tables 14 and 15) (91T3969).

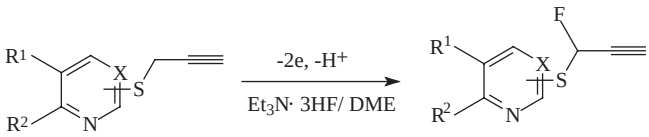
Table 10. Anodic fluorination of sulfides having oxygen-containing heterocyclic and oxygen substituents (04JOC1276)

Compound	Product	Yield (%)	ee (%)
 R = H		54	80
4-Cl		77	70
4-NO_2		67	58
		10	30
		30	60
		28	60
		51	68
		45	70
 R = 4-NO_2		49	13
H		22	13
		22	55

Anodic fluorination of 4-oxo-2-quinazolinol sulfides and 2-benzoxazolyl sulfides (Table 16) (91T3969) involves the α-carbon atom of the substituent at the sulfur atom (99JOC138) (Scheme 43). The sulfur-containing fragment is eliminated from the heterocyclic system, and the heterocycle is fluorinated.

The role of the solvent (DME) is merely solvation of the Et_4N^+ cation, which facilitates the generation of an unsolvated fluoride ion in the system. Therefore, the $Et_4NF \cdot 4HF$/DME system is more effective for anodic fluorination than $Et_4NF \cdot 4HF$.

Anodic monofluorination of 5-methyl- and 6-methyl-4-oxo-2-pyrimidyl sulfides using $Et_4NF \cdot 4HF$ is a highly regioselective process (Table 16) (91T3969). DME is



$R^1 = R^2 = H$, X = CH;
$R^1 = R^2 = H$, X = N;
$R^1, R^2 = (CH{=}CH)_2$, X = CH

Scheme 37

Table 11. Anodic fluorination of sulfides in dimethoxyethane

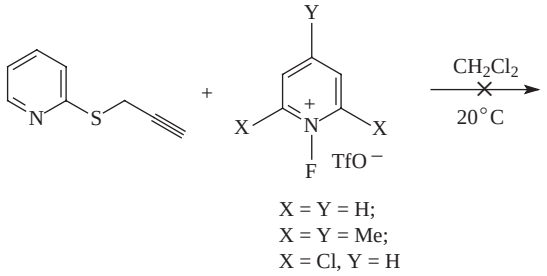
Substrate	E_p^{ox} V) (vs. SSCE)	Electrolyte	Yield of monofluorinated product (%)*	References
2-Pyridyl	1.92	$Et_4NF \cdot 4HF$	15†	97JOSC301
		$Et_4NF \cdot 4HF$	35	
		$Et_4NF \cdot HF$	40	
		$Et_3N \cdot 3HF$	55	
4-Pyridyl	1.90	$Et_3N \cdot 3HF$	58	97JOSC301
2-Pyrimidyl	2.2	$Et_3N \cdot 3HF$	60	14897JOSC301
		$Et_4NF \cdot 4HF$	63	99EC445, 99JOC7935
2-Quinolyl	1.92	$Et_3N \cdot 3HF$	35	97JOSC301
		$Et_4NF \cdot nHF$ ($n = 3, 4$)		99JOC138
2-Benzothiazolyl	1.95	$Et_4NF \cdot 4HF$	7	97JOSC301
		$Et_3N \cdot 3HF$	15	
		$Et_4NF \cdot 3HF$	22	
2-Oxo-2-pyrimidyl		$Et_4NF \cdot 4HF$		00JOC8685
2-(5-Chlorobenzothiazolyl)-methyl 2-pyridyl sulfide	2.04 1.74	$Et_4NF \cdot 3HF$ $Et_4NF \cdot 4HF$	35	97JOSC301 99JOC138
Thiadiazolyl		$Et_4NF \cdot 4HF$		01JOC5633
Oxadiazolyl		$Et_4NF \cdot 4HF$		00JOC8685

*In 0.1 M $Bu_4N \cdot BF_4$/MeCN.
†In acetonitrile.

employed as a solvent, while acetonitrile proved to be absolutely unacceptable. Good yields of α-fluorinated products were observed in both cases.

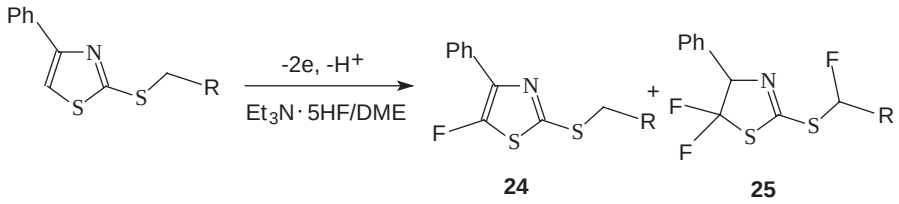
Pyridines with an SCH_2R group in the α position also undergo anodic fluorination, forming monofluoro derivatives (94TL7245) (Scheme 44).

Owing to the presence of a CN group in the β position (2-pyridyl sulfide **28**), anodic fluorination in the presence of a base yields a bicyclic heterocycle (2-fluorothieno[2,3-*b*]pyridine **30**). Perhaps, the first step of the reaction is anodic monofluorination of 2-pyridyl sulfide to α fluoromethyl–pyridyl sulfide. In basic media, the



Scheme 38

Table 12. Anodic fluorination of sulfides with a thiazolyl substituent (02JOC9379)



R	E_p^{ox} (V) (vs. SSCE)	F/mol	Yield (%)	**24**	**25**
H	1.5	3		25	28
H	1.5	6		10	55
$COCH_3$	1.65	3		20	23
$COCH_3$	1.65	6		8	50
C≡CH	1.57	3		—	60

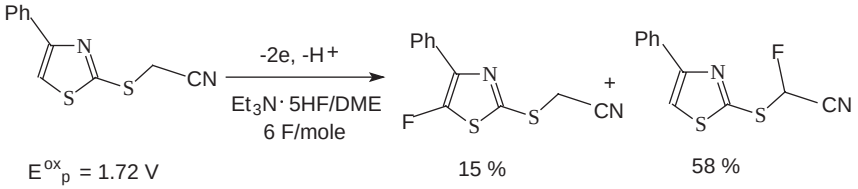
product is thienopyridineimine. In the presence of ethanol, it forms intermediate **29**, whose diethylcarbonate-eliminating aromatization leads to product **30** (Scheme 45).

Note that fluorination of these heterocyclic compounds by *N*-fluoropyridinium and *N*-fluoro-3,5-dichloropyridinium triflates is unsuccessful (01TL4861). Electrochemical anodic fluorination was carried out for 4-(7-trifluoromethyl)-quinolyl sulfides **31** in $Et_4NF \cdot nHF$ ($n = 3, 4$) and $Et_3N \cdot 3HF$ in DME. The corresponding α monofluoro derivatives **32** of these sulfides are formed in good yields (Table 17) (98JFC(91)153). When $X =$ COMe, compound **33** is also formed (yield 7%) (Scheme 46).

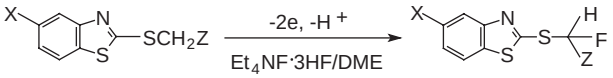
For 2-quinolyl sulfides **34**, the reaction gives three products **35–37** (Table 18) (Scheme 47).

Anodic fluorination of ethyl α-2 (pyrimidylthio)acetate in $Et_4NF \cdot 4HF$ electrolyte and in acetonitrile or 1,2-DME as solvent gives an α-monofluorinated product in quantitative yield (82M29). DME proved to be the most effective solvent; acetonitrile was less effective, but its mixture with DME gave good results (01TL4861).

When the heterocyclic ring contains an SMe group, a methyl hydrogen is replaced by a fluorine, giving a moderate yield of the substitution product (Scheme 48).



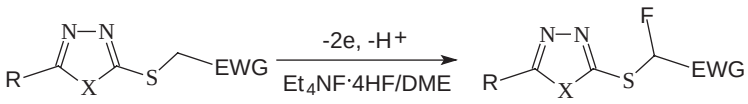
Scheme 39



E^{o}_{red}, V	2.02	1.82	1.82	2.04	1.95	1.90
X	H	H	H	Cl	Cl	Cl
Z	CN	CO_2Me	COMe	CN	CO_2Me	COMe
Yield, %	48	62	46	51	82	58

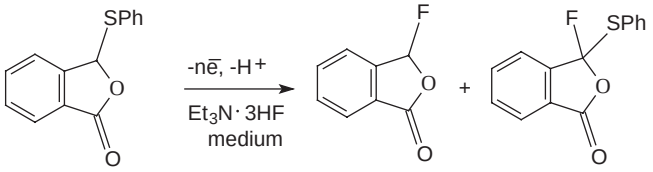
Scheme 40

Table 13. Anodic monofluorination of heterocylic sulfides (95JOC7654)



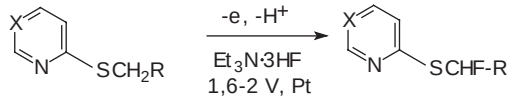
Sulfide			E_p^{ox} (V) (vs. SSCE)	Product yield (%)
R	*X*	EWG		
Me	S	COOMe	2.16	88
		COMe	2.06	70
		CN	2.31	52
		H	2.00	58
Ph	O	COOMe	2.11	40
		COMe	2.08	38
		H	2.02	26
		CN	2.26	10
H	NH	COOEt	1.68	2
H	NMe	H	1.54	5
Ph	NPh	COOEt	1.76	18

Thus a new approach to inaccessible sulfur and selenium derivatives with S-CHF, SCF_2, and Se-CHF fragments has been developed. Some of these compounds possess high biological activity (01TL4861). Although there is some ambiguity concerning the commercial applications, electrolytic fluorination is still an area of active



Medium		Yield, %
MeCN	44	-
CH_2Cl_2	86	-
THF	6	22
DME	9	72
[emim][OTf] $Et_3N\cdot 5HF$	83	trance

Scheme 41



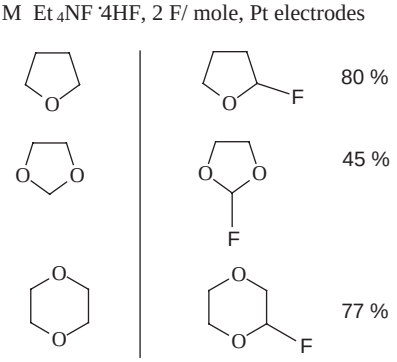
X	R	Potential, V vs SSCE	F/mole	Yield, %
CH	CN	1.6	5	76
CH	COOEt	1.6	5	76
CH	H	1.6	5	traces
CH	CH_2CN	1.6	6	traces
CH	$PO(OEt)_2$	1.6	6	traces
CH	SMe	1.6	5	traces

Scheme 42

interest. The possibility of shifting the fluorination center from the aromatic ring to the functional groups, for example, to fragments with an active methylene group creates real prospects for working out convenient procedures for the synthesis of inaccessible monofluoro derivatives. Synthesis of polyfluorinated hydrocarbons by electrolytic fluorination also seems to be quite feasible.

Anodic fluorination of cyclic ethers occurs with ring cleavage, giving difluoro derivatives with fluorine atoms flanking the carbon chain (00T8877) (Scheme 49).

Five- and six-membered cyclic ethers, lactones, and cyclic carbonates do not undergo cleavage during anodic fluorination in methylene chloride in the presence of $Et_3N\cdot 5HF$ or $Et_4NF\cdot nHF$ ($n = 4, 5$). The reaction leads to monofluorinated cyclic products (02TL1503).



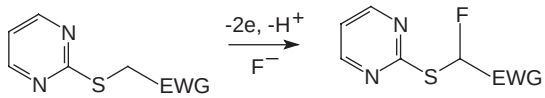
Anodic oxidation of dithioketals with *para*-iodoanisole in acetonitrile in the presence of $Et_3N \cdot 3HF$ as an electrolyte forms gem-difluoro derivatives of diarylmethane (94JOC7190) (Scheme 50). (Difluoroiodo)arenes possess a high fluorinating ability. These substances need not be isolated pure; one can employ their solutions in acetonitrile.

(Chlorofluoroiodo)arenes are formed when anodic oxidation is carried out in the presence of chloride ion (Scheme 51).

The resulting arenes are good fluorinating agents. Again isolation of pure products is not needed and it suffices to use solutions. When the solution is allowed to react with dithioacetals, gem-difluorodiarylmethanes are obtained (Scheme 52).

Thus monofluorination using trialkylamine complexes with anhydrous hydrogen fluoride as electrolytes is an important procedure leading to monofluorinated organic compounds; the potential of this method is steadily increasing as further

Table 14. Anodic fluorination of 2-pyrimidyl sulfides (91T3969)



E^{o}_{red} (V)	EWG	Electrolyte	F/mol	Yield (%)
2.14	$COCH_3$	$Et_4NF \cdot 4HF$	8	81
	COMe	$Et_4NF \cdot 3HF$	9	65
	COMe	$Et_3N \cdot 3HF$	8	92
2.23	COOEt	$Et_4NF \cdot 4HF$	7	98
	COOEt	$Et_4NF \cdot 3HF$	7	87
	COOEt	$Et_3N \cdot 3HF$	9	84
2.45	CN	$Et_4NF \cdot 4HF$	12	39
	CN	$Et_4NF \cdot 3HF$	12	38
	H	$Et_4NF \cdot 4HF$	10	63
	H	$Et_4NF \cdot 3HF$	10	52

Table 15. Anodic fluorination of 4-oxopyrimidyl sulfides in Et4NF · 4HF/DME (91T3969)

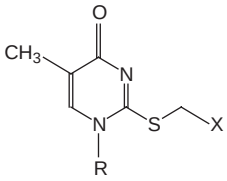
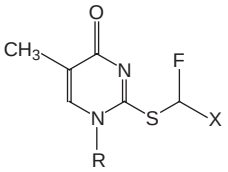
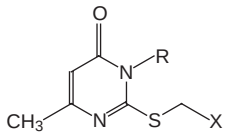
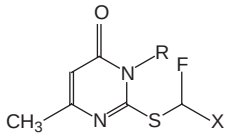
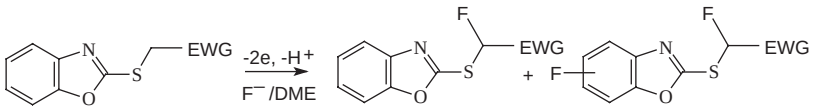
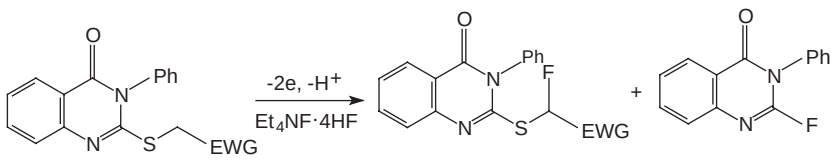
Compound	R	X	E_p^{ox} (V)(vs.SSCE)	F/mol	Product	Yield (%)
	COPh	COOEt	2.09	9		75
	COPh	COMe	2.00	5.5		70
	COPh	H	1.82	6		77
	COPh	COOEt	2.30	10		75
	COPh	COMe	2.01	5		74
	COPh	H	1.80	6.5		78

Table 16. Anodic fluorination of 2-benzoxazolyl sulfides (91T3969)



26 **27**

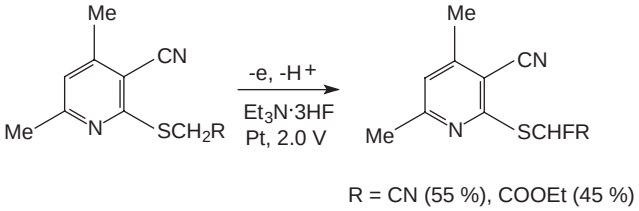
EWG	E_p^{ox} (V) (vs. SSCE)	Electrolyte	Yield (%) 26	27
$COCH_3$	2.08	$Et_4NF \cdot 4HF$	39	8
COOEt	1.96	$Et_4NF \cdot 4HF$	35	13
		$Et_3N \cdot 3HF$	29	8
CN	2.22	$Et_4NF \cdot 4HF$	17	6
		$Et_3N \cdot 3HF$	12	8
H	1.90	$Et_4NF \cdot 4HF$	2.2	2



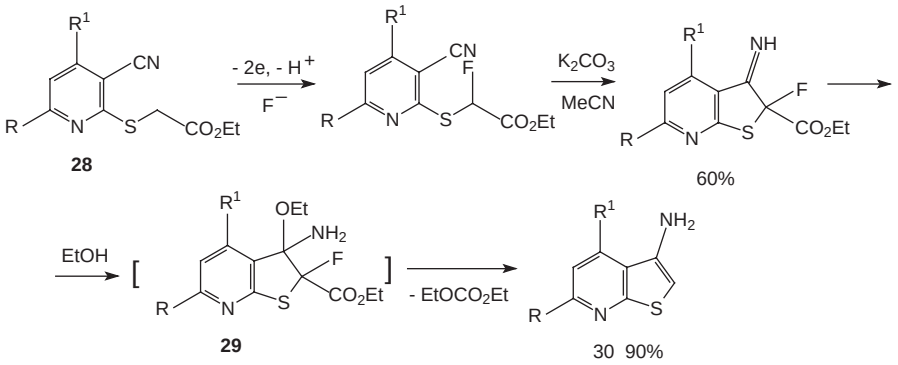
E^{o}_{red} = 2.01

EWG = COOEt	20		8
COMe	30		2

Scheme 43



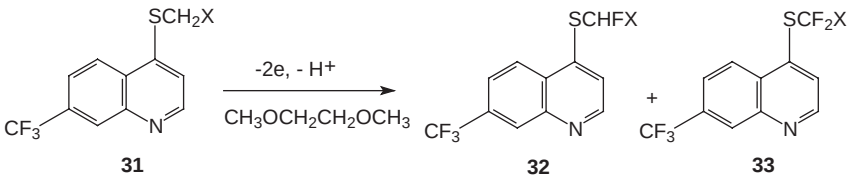
Scheme 44



Scheme 45

Table 17. Anodic fluorination of 4(7-trifluoromethyl)quinolyl sulfides (DME) (98JFC(91)153)

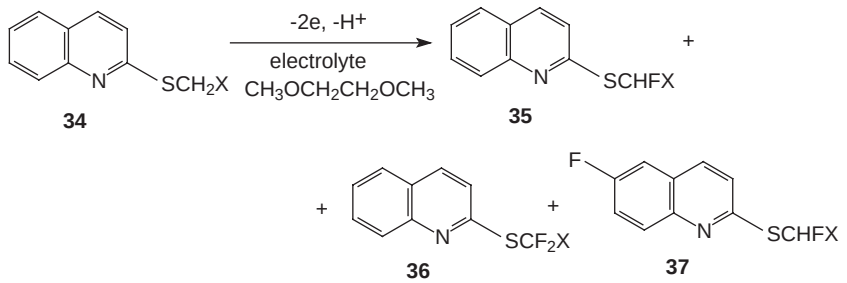
X	E_p^{ox} (V) (vs. SSCE) Pt electrode 0.1 M Bu_4NBF_4	Electrolyte	F/mol	Yield of **32** (%)
COMe	1.92	$Et_4NF \cdot 3HF$	4	96
		$Et_4NF \cdot 4HF$	2.5	62
COOEt	2.04	$Et_4NF \cdot 3HF$	4.5	83
		$Et_3N \cdot 3HF$	6	67
CN	2.14	$Et_4NF \cdot 4HF$	4	86
		$Et_4NF \cdot 3HF$	4	87
		$Et_3N \cdot 3HF$	6	77



Scheme 46

Table 18. Anodic fluorination of 2-quinolyl sulfides (98JFC(91)153)

X	E_p^{ox} Pt anode	Electrolyte	F/mol	Yield (%)		
				35	**36**	**37**
	0.1 M Bu_4NBF_4					
COMe	1.70	$Et_4NF \cdot 4HF$	4	54	8	5
		$Et_4NF \cdot 3HF$	6	50	8	5
		$Et_3N \cdot 3HF$	7	55	8	5
		$Et_3N \cdot 3HF$	6	64		
		$Et_3N \cdot 3HF$	4	28		
COOEt	1.76	$Et_4NF \cdot 4HF$	4	62		5
		$Et_4NF \cdot 3HF$	4	54		5
		$Et_3N \cdot 3HF$	6	69		7
CN	1.91	$Et_4NF \cdot 4HF$	8	61		12
		$Et_4NF \cdot 3HF$	8	52		12
		$Et_3N \cdot 3HF$	8	62		12

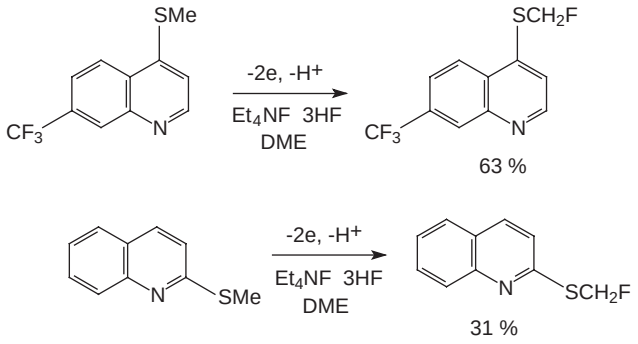


Scheme 47

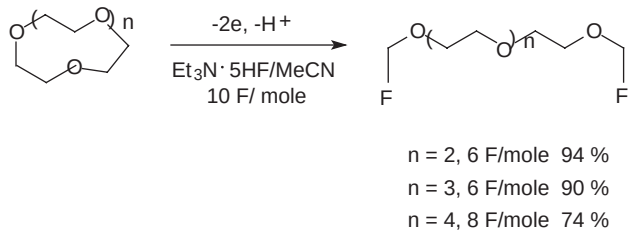
improvements are made. The reaction has been extended to various classes of compounds, which led to considerable progress in syntheses of monofluorinated aromatic and heterocyclic compounds. The synthesized monofluorinated materials have found important practical applications. Further improvements in production processes remain challenging to satisfy the growing technological demands. Subsequent research will seek to elaborate the existing procedures and to find new approaches and solutions. To reveal the specific features of fluorinations due to the presence of fluorine atoms and to gain new insights into the mechanisms of fluorination seems no less important than to describe the behavior of organic substances during fluorination.

IV. Electrochemical Fluorination of Organic Compounds in Anhydrous Hydrogen Fluoride

The impressive advances in commercial production of perfluorinated organic compounds are due to Simons' ECF procedure developed in 1949 (86JFC(33)337,



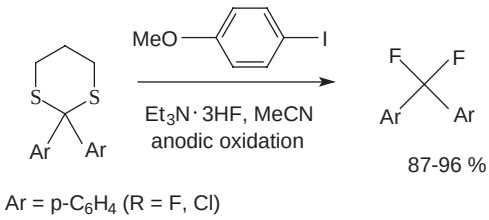
Scheme 48



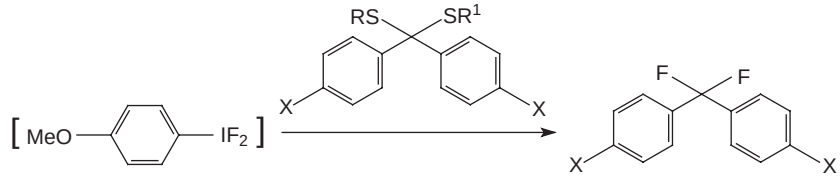
Scheme 49

50USP2519983, 50USP2500388, 86M337, 00M7, 86M4, 84M32). By this method a wide range of organic substrates can be perfluorinated in a single step. For nearly 60 years ECF has been used as a versatile method for the production of perfluorinated compounds bearing different functional groups. Results in this field are reported in a great number of papers, patents and reviews (96M14, 00JFC(105)181, 02JFC(115)21, 01JFC(1 1 1)21, 97M34, 94M35, 04JFC(125)139).

This method was put into production at 3M plants, which had a monopoly on manufacturing products by the ECF method. According to this technique, an organic substance dissolved in anhydrous hydrogen fluoride is electrolyzed on nickel electrodes at temperatures below the boiling point of the electrolyte and at electrode voltages ruling out the liberation of elemental fluorine (86CIT31, 90BE471, 96JFC(79)71). When the anode potential exceeds 3.5 V, the organic substrate is fluorinated, while potentials higher than 5.0 V (cell potential 7.5–8 V) lead to decomposition of the carbon chain and hence to many by-products (79JAE685). Elemental fluorine starts to separate at electrode voltages above 7 or 8 V, which leads to complete decomposition of the organic substrate accompanied by explosions in the electrolyzer. Nevertheless, it is postulated that the process occurs by anodic discharge of fluoride ion and secondary interactions with the organic substance. This method has quickly gained acceptance as a procedure for the synthesis of functional fluorocarbons, in particular, perfluorocarboxylic acids and their derivatives, perfluoroalkane sulfoacids, perfluorotrialkylamines, etc.

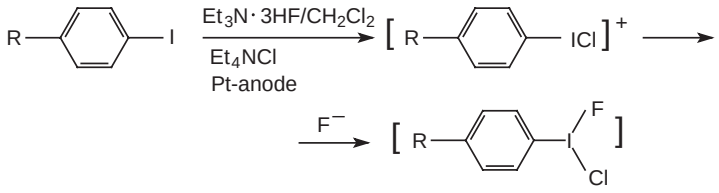


Ar = p-C_6H_4 (R = F, Cl)



R	R^1	X	Baxon, %
-$(CH_2)_3$-		Cl	89
		H	69
		Me	79
		MeO	78
-$(CH_2)_2$-		H	79
Ph	Ph	H	62

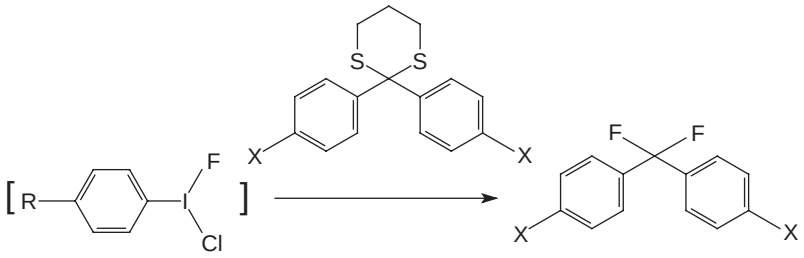
Scheme 50



Scheme 51

Major advantages of this process are as follows:

- a direct process using commercial hydrogen fluoride as a fluorinating agent;
- a one-step process leading to perfluorocarbon compounds from hydrocarbon materials;
- synthesis of polyfluorinated compounds with functional groups;
- formation of perfluorinated heterocyclic compounds by cyclization of the intermediate radicals;
- using relatively simple equipment applicable to both continuous and batch processes;



R	X	Anodic potential V vs SSCE	F/mole	Yield, %
MeO	Cl	1.8	5.0	51
Me	H	1.9	5.3	75
H	Cl	2.0	6.1	59

Scheme 52

- synthesis of compounds unobtainable by other procedures or obtainable with lower yields.

Equipment for ECF, including a bipolar electrolyzer, a gas trap, an apparatus for condensation of hydrogen fluoride from electrolysis gases, and an electrolyte cooling system, are described elsewhere (94USP5322597, 95RUP2026889).

ECF is generally not a selective process. It is accompanied by

- decomposition of the carbon skeleton of the starting compound;
- cleavage of carbon–heteroatom bonds;
- cyclization;
- ring contraction in a number of heterocyclic compounds;
- ring cleavage at the C–C bond;
- isomerization of the starting skeleton, forming branched or linear structures.

As ECF of organic compounds occurs in anhydrous hydrogen fluoride, its outcome depends strongly on the nature of the ions or ionic complexes of substrates generated in solution.

When the process is conducted in anhydrous hydrogen fluoride, heterocyclic compounds are protonated to give electron-conducting solutions. In this respect, hydrogen fluoride proved to be a convenient medium for ECF. Since elemental fluorine is not liberated in the course of fluorination, the process can take place directly in a binary electric layer. Consequently, in order to take part in the process, the preliminarily deprotonated organic molecule must be specifically adsorbed on the anode.

A safe procedure and preservation of the functional groups of the substrate are important advantages of ECF over other fluorination techniques.

Low yields of the desired product, high-energy consumption, and difficulties in creating a rational technology are major disadvantages of ECF. The ECF process is accompanied by decomposition of the carbon skeleton of the substrate molecule, although this side effect is less pronounced than in fluorinations with elemental fluorine (53USP2631151, 86JFC(32)77, 90USP4929317, 88EUP271272, 87JFC(35)557). Therefore, optimum reaction conditions must be chosen for each individual ECF process. For example, the need for product purification of follow-up fluorination with CoF_3 or elemental fluorine catalysts is a serious problem encountered by the synthesis of perfluorocarbons as artificial blood components, dictated by the need to eliminate toxic impurities.

The diversity of radical processes accompanying ECF suggests there is little discrepancy, if any, with interactions of organic compounds with fluorides of metals with variable valences. However, this is not always so.

A. Oxygen-Containing Perfluorinated Heterocyclic Compounds

Artificial blood design occupies an important place in areas of medical research dealing with cardiovascular diseases. Perfluorinated dialkyl ethers and cyclic ethers are compounds that hold great promise for these applications. Therefore, syntheses of oxygen-containing perfluorinated heterocyclic compounds of high purity are of great interest. These compounds are expected to provide good solubility of oxygen and to stabilize the emulsion.

Cyclic ethers such as tetrahydrofurans, 1,4-dioxane, and oxalanes subjected to ECF in anhydrous HF are converted into perfluorinated derivatives (Tables 19 and 20) (85JES2424, 67ZOB1229, 74ZPK590) (Scheme 53).

However, ECF of these compounds gives tary products, as well as by-products such as perfluoroacyl fluorides, perfluorodialkyloxyethane, etc. The undesirable effects can be partially eliminated and satisfactory yields of perfluorinated derivatives (Table 19) can be obtained by using oxolanes and oxanes for ECF (74GER2313862, 74ZOR2031, 80ZPK858). Furthermore, cyclic ethers are obtained in better yields when alkyl carboxylic acids are employed as substrates. For example, in the case of methyl 3-methoxypropionic ether, the yield of perfluorotetrahydrofuran reaches 46% (91USP4983747) (Scheme 54).

Perfluorinated oxanes can be synthesized by ECF of oxanes. Perfluorinated epoxides and oxetanes, however, are obtained with difficulty because of cationoid polymerization of the initial three- and four-membered heterocycles in anhydrous HF. Perfluorinated oxolanes are obtained with good yields from oxolanes (Table 20) (94M30, 75ZPK2206).

ECF of 2,5-dimethyloxolane was carried out in an electrolyzer under the following conditions: anode current density 3.5 A/dm^2, voltage 5.2–5.4 V, temperature 5–6 °C, amount of electricity 214– A/h (78JFC(12)359).

Even for primary alcohols, ECF forms cyclic ethers along with perfluoroacyl fluorides as by-products (Table 19) (91JFC(51)53, 76BCS1888) (Scheme 55).

Trifluoroacetic acid anhydride is obtained in 36–45% yield (current efficiency 32–50%) from acetic anhydride (87JFC(35)557, 53USP2644823, 71M31). Carboxylic

Table 19. Electrochemical fluorination of cyclic ethers (90JFC(49)409, 88CL1887) and alcohols (91JFC(51)53)

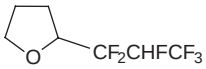
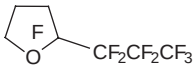
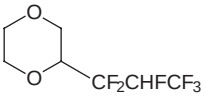
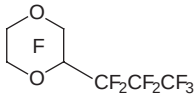
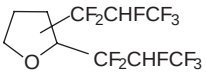
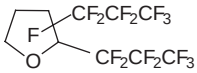
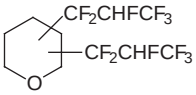
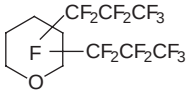
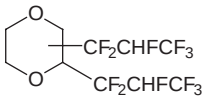
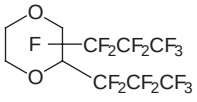
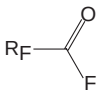
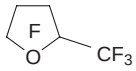
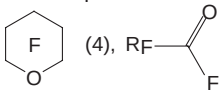
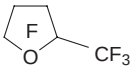
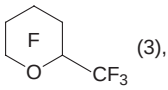
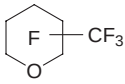
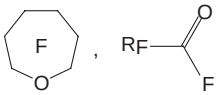
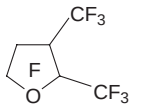
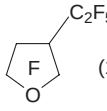
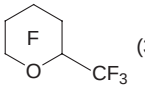
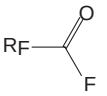
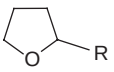
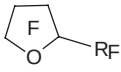
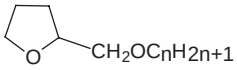
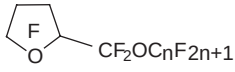
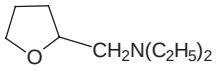
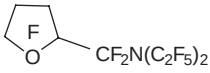
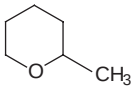
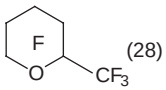
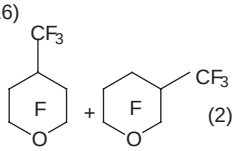
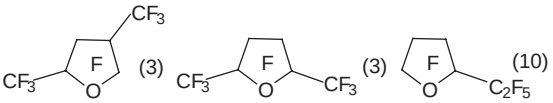
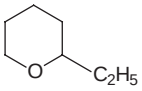
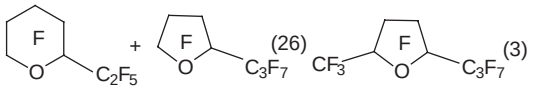
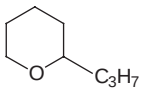
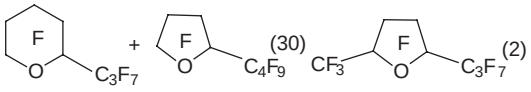
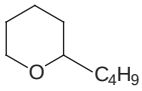
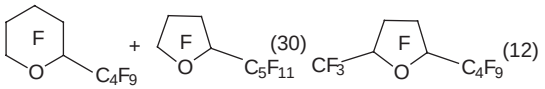
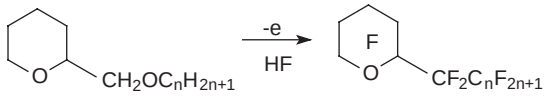
Substrate	Fluorination product	Yield (%)
		50
		16
		45
		36
		27
$[CF_3CHFCF_2CH(CH_3)]_2O$	$[CF_3CF_2CF_2CF(CF_3)]_2O$	8
$CH_2{=}CHCH_2CH_2OH$	 (14),	
$n\text{-}C_5H_{11}OH$	 (18),	 (4),
$n\text{-}C_6H_{13}OH$	 (18),	 (3),
	 (2),	 ,
$(CH_3)_3CCH_2CH_2OH$	 (10),	 (18),
	 (3),	

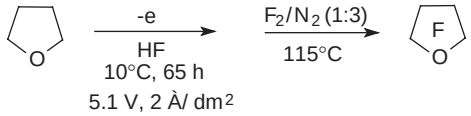
Table 20. Electrochemical fluorination of oxalanes (91USP5049670, 74JFC(4)387) and 2-alkyl derivatives (80JFC(15)353)

Substrate	Fluorinated Product (Yield, %)
	 R_F = F (42), n-C_4F_9 (41), c-C_6F_{11} (54)
	 n = 2 (42), 3 (39), 4 (42), 5 (19), 6 (9), 7 (3)
	 (16)
	 (28)  (2)
	
	 (3)
	
	$C_4F_9OC_3F_7$ (5)
	
	$C_4F_9OC_4F_9$ (2)
	
	$C_4F_9OC_5F_{11}$ (4)

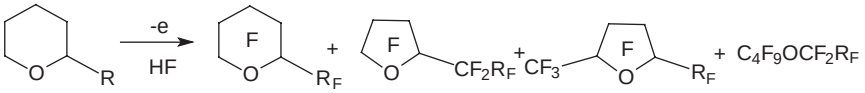
acid chlorides (e.g., caproic, enantyl, capryl, and capric acid chlorides) also form perfluoroacyl chlorides with low yields (11–15%), while the major products of these reactions are perfluorinated cyclic ethers (24–35%) (87JPP62-22756) (Scheme 56). In the ECF dicarboxylic acids, both six- and five-membered heterocycles may be formed (86JPP61-260047).



n = 2 (42 %), 3 (39 %), 4 (42 %),
5 (19 %), 6 (9 %), 7 (5 %)

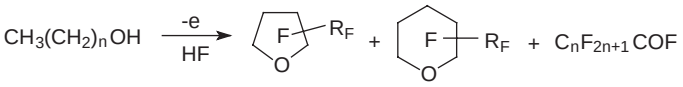


Scheme 53



R_F = CF_3, C_2F_5, n-C_3F_7, i-C_3F_7, n-C_4F_9, n-C_5F_{11}

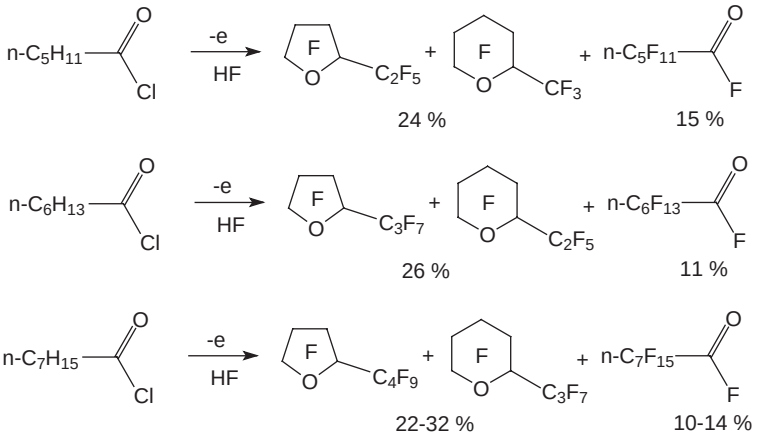
Scheme 54



n = 3, 7

R_F = CF_3, C_2F_5, n-C_3F_7, n-C_4F_9

Scheme 55



24 % 15 %

26 % 11 %

22-32 % 10-14 %

Scheme 56

Carboxylic esters subjected to ECF in anhydrous hydrogen fluoride are generally saponified to give the corresponding acyl fluorides as primary products, which undergo further fluorination. However, again perfluorinated heterocyclic compounds are formed (55USP2717871). Detailed study of this process indicated that substrates containing cycloalkyl groups as substituents give satisfactory yields of bicyclic esters and perfluorospiroesters (Table 21) (71M31, 65BRP1007288). Cyclic esters of this kind have two five-membered rings or one five- and one six-membered rings. The product yield is moderate. The reaction also gives small amounts of perfluorinated esters formed from acids and their transformation products (perfluoroparaffins and perfluorinated acyclic derivatives) (69USP3471484, 67DRP1077301).

A new cyclization process, involving the multiple bond and leading to heterocyclic derivatives, was found during the ECF of methyl 2-cyclohexylacetic ether and some other derivatives of carboxylic acids (58JA1889, 00USP6110976, 84JFC(25)419, 80JPP80-18539) (Tables 21–23). This is a general process for carbonyl compounds with multiple bonds in the β position, which is currently successfully used for the synthesis of perfluorobicyclic and perfluoromonospiro ethers (Scheme 57).

Perfluoro(alkoxycycloalkane)carbonyl fluorides where R is perfluoroalkyl C_1–C_4 ($n = 2$–5), are synthesized by ECF of the corresponding acyl chlorides (e.g., 3,4,5-$(MeO)_3C_6H_2COCl$) in the presence of 10% dimethyl disulfide in boiling anhydrous hydrogen fluoride at a pressure of 2000 Torr and a temperature of 50 °C (nickel anode). The product was 3,4,5-$(CF_3O)_3C_6F_8COF$ (yield 30%) (96JPC99). These compounds are surfactants, also used as film-forming foams (Scheme 58).

If the carboxylic acid has an *N*,*N*-dialkylamino substituent, the direction of the fluorination does not change, and the reaction forms both perfluoroacyl fluorides and heterocyclic compounds (87OC133, 88JPP63-208572, 88CE191, 90JFC(50)173, 75ZPK709).

In the case of dibasic thio alcohols and monoethanolamines, ECF leads not only to a heterocyclic compound with hexavalent sulfur (77BCJ2809, 83SERDU204, 86NKGSH202), but also to a linear perfluoroinated compound R_FSF_5 (86NKGSH202) (Scheme 59).

B. Nitrogen-Containing Heterocyclic Compounds

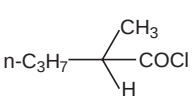
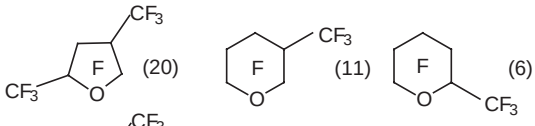
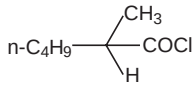
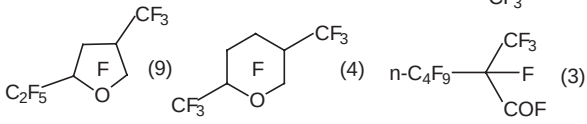
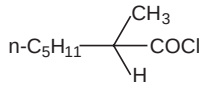
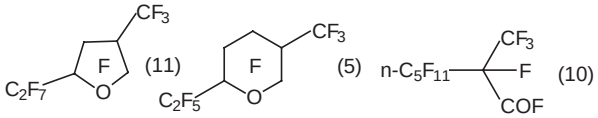
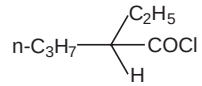
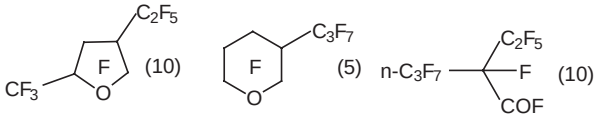
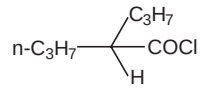
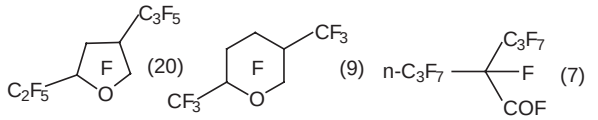
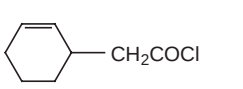
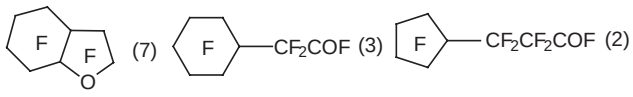
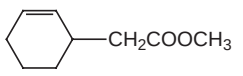
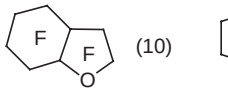
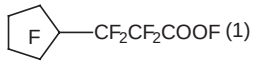
Many perfluorocylic amines are excellent blood substitutes that can serve as oxygen carriers for transfusion solutions and as media for conservation of organs. These compounds have naturally generated interest among researchers. Cyclic amines are highly soluble in hydrogen fluoride and give conducting solutions. When compounds of this type (e.g., RR^1NR, where NRR^1 is an unsubstituted or perfluoroalkyl-substituted five-, six-, or seven-membered heterocyclic radicals such as pyrrolidyl, cyclohexyl, cyclopentyl, or piperidyl) are subjected to ECF, perfluorinated nitrogen-containing heterocycles with an intact carbon skeleton are formed with high yields (Tables 24 and 25) (92JFC(58)187). However, ring cleavage takes place, leading to compounds in which the ring acquires or loses one carbon atom. The six-membered ring is thermodynamically most stable among the ring types (Scheme 60).

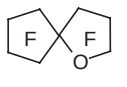
ECF of morpholines and piperidines yields the corresponding perfluorinated compounds. However, isomerization and fragmentation of the intermediate radical species can slightly decrease the efficiency of this process.

The nitrogen-containing functional group, present in the linear part of the alkane sulfoacid, does not markedly affect the ECF process (86JFC(32)89, 88M33, 69USP3476753, 92JFC(58)269) (Scheme 61).

Perfluorinated ethers containing a perfluorocycloalkyl fragment $R(CF_2)_mC(CF_3)_2O(CF_2)_nR^1$ (R and R^1 are perfluoroalkyls) (91GEP294514, 74JFC(4)383, 86USP4605786) or a dialkylamine fragment $R^1R^2N(AO)_nANR^3R^4$ gave a mixture of products among which were perfluorinated derivatives and partially fluorinated compounds $R'(CH_2)_mC(CF_3)_2OC(CH_2)_nR''$or $R^1_FR^2_FN(A_FO)$-

Table 21. Electrochemical fluorination of carboxylic acid derivatives (78JFC(12)1, 83JFC(23)123)

Compound	Reaction product (yield, %)
	
	
	
	
	
	
	
	



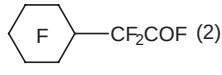
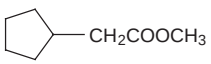
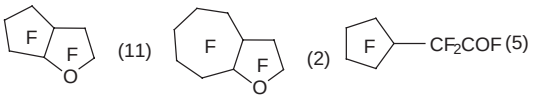
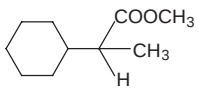
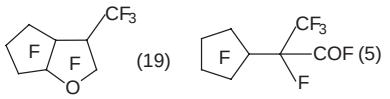
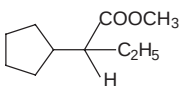
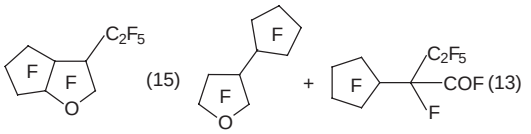
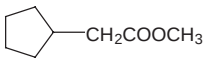
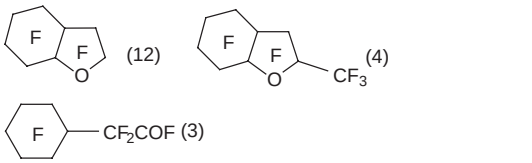
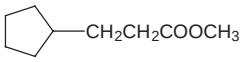
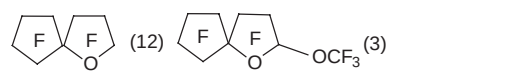
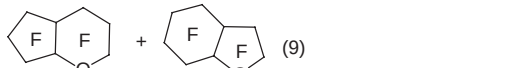
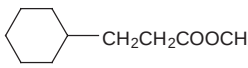
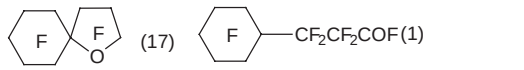


Table 21. Continued

Compound	Reaction product (yield, %)
	
	
	
	
	
	
	

$_nA_FNR^3{}_FR_F^4$ (current density 0.2–3 A/dm^2, temperature 3–10 °C, substrate concentration 0.1–0.3 mol, voltage 5–7 V, anhydrous HF) (Scheme 62).

If the molecule has two nitrogen atoms in the heterocycle, ECF affords perfluorinated derivatives of these heterocycles retaining the carbon skeleton of the molecule, but the yields are low (Tables 24–26).

Bicyclic amines give both perfluorinated derivatives with a preserved carbon skeleton and products of ring cleavage (one of the rings is opened, while the six-membered nitrogen-containing ring becomes five-membered). The five-membered ring is the main ring in these reactions; smaller rings were not obtained. The piperidine ring can be expanded into the seven-membered ring. For example, 1,2 -dimorpholinoethane gives perfluoro-1,2-dimorpholinoethane (yield 30%); 1,2-dipiperidinoethane affords perfluoro-1,2-dipiperidinoethane (yield 34%) and perfluoro-1-piperidino-1,2-(3-methylpyrrolidyl)ethane (yield 6%).

Piperazine-*N*,*N*′-di-α-propionic acid is converted into perfluorinated piperazine-*N*,*N*′-di-α-propionic acid fluoride (86JCS(JC)1249), and 1-ethyl-4-methoxycarbonylmethyl-1,4-diazepine gives perfluoro-1-ethyl-4-fluoro-carbonylmethyl-1,4-diazetine (03JAP(K)2003277367) (Scheme 63).

Analysis of the data in Table 26 indicates that the effect of the substituent at the nitrogen atom on the yield of the perfluorinated substance increases in the series

Table 22. Results of electrochemical fluorination of methyl carboxylic ethers containing cycloamino substituents (83JFC(23)123)

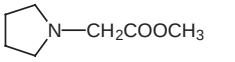
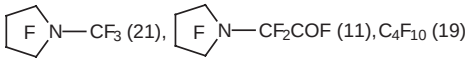
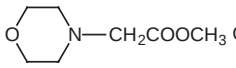
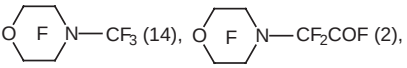
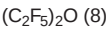
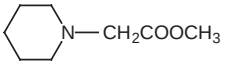
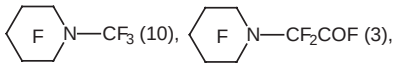
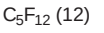
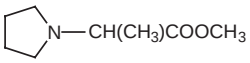
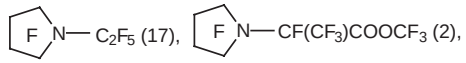
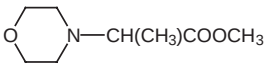
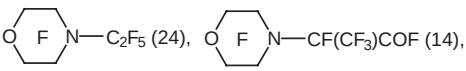
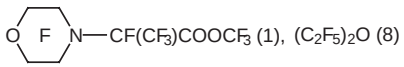
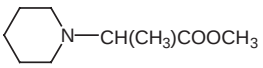
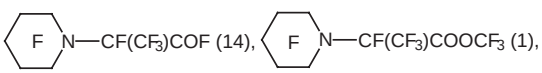
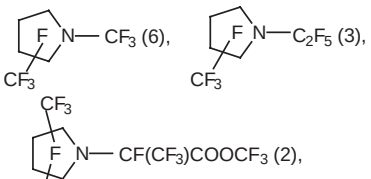
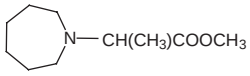
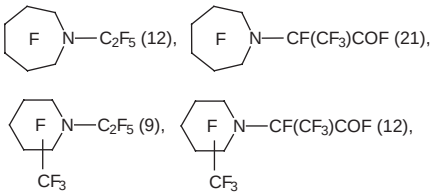
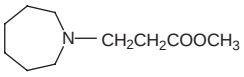
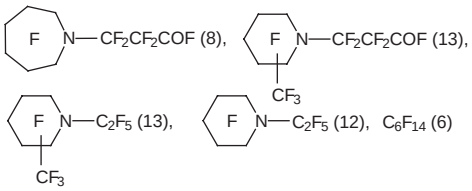
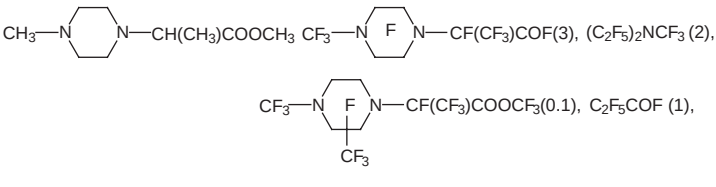
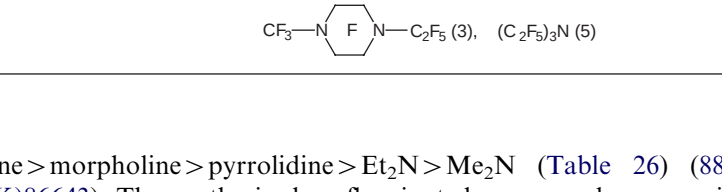
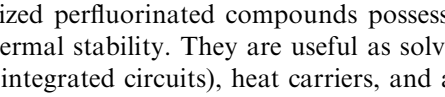
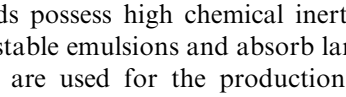
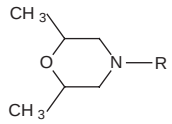
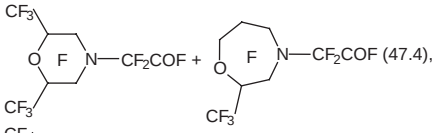
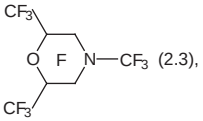
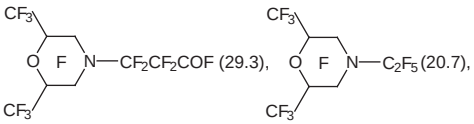
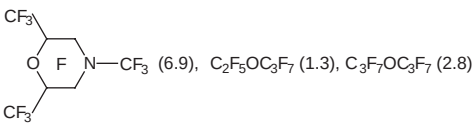
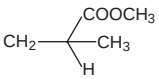
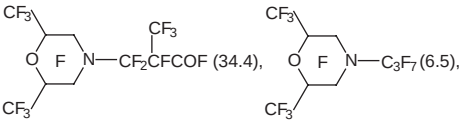
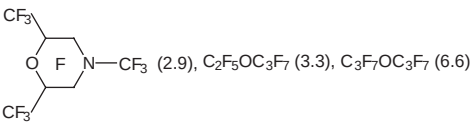
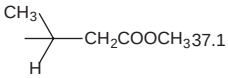
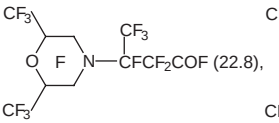
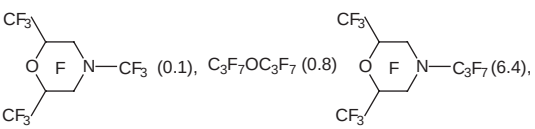
Substrate	Composition and yield (%) of fluorination products
	
	
	
	
	
	
	
	
	
	
	

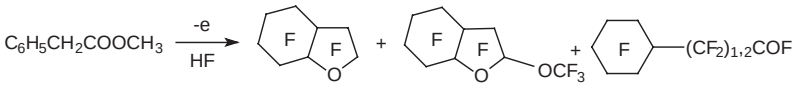
Table 22. Continued

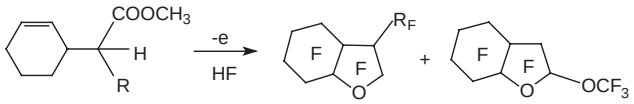
Substrate	Composition and yield (%) of fluorination products
	
	
	
	
	
	

piperidine > morpholine > pyrrolidine > Et_2N > Me_2N (Table 26) (88JFC(38)303, 00JAP(K)86643). The synthesized perfluorinated compounds possess improved dielectric properties and high thermal stability. They are useful as solvents, indicator liquids (for the production of integrated circuits), heat carriers, and artificial blood components. These compounds possess high chemical inertness and physiological compatibility. They can form stable emulsions and absorb large amounts of oxygen. Due to these properties they are used for the production of oxygen carriers in biology and medicine and for some technical purposes such as air enrichment with oxygen in blast-furnace production. Therefore, interest in such compounds has been steadily increasing, which is demonstrated by the increased number of publications in this field. These compounds also have excellent electrophysical characteristics exceeding those of mineral oils. They are used as impregnating liquids for textile, paper, and leather to make these materials incombustible and enhance their consumer utility. The synthesis of N-substituted perfluoropyridines (yield 31–53%) by ECF was reported in (65ZOB485, 75ZPK706) (current density 0.05–7 A/dm^2, voltage 4.5–9 V, temperature from −20 to 40 °C, substrate concentration in HF 0.5–40%, nickel electrodes) (Scheme 64).

Table 23. Results of electrochemical fluorination of methyl carboxylic ethers in anhydrous HF (current density 3.0 A/dm2, voltage 5.9–6.1 V, temperature 7–8 °C, 200–220 A/h) (98JFC(87)193)

 R	Yield crude products,%	Products of reaction (yield, %)
CH_2COOCH_3	42.3	$C_2F_5OC_2F_5$ (3.9), $C_2F_5OC_3F_7$ (3.3), $C_3F_7OC_3F_7$ (11.8),  
$CH_2CH_2COOCH_3$	56.9	 
	47.1	 
	37.1	 



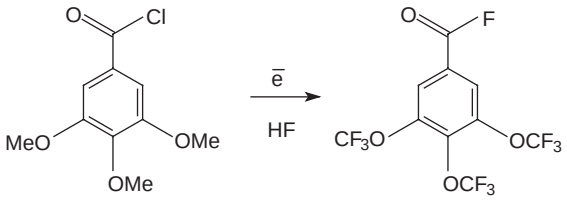


R = H, CH_3, C_2H_5, n-C_3H_7

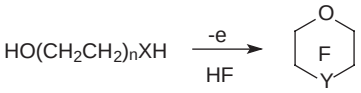
17-23 %

6-10 %

Scheme 57



Scheme 58



X = O, S, NH, NCH_3, NHC_2H_5

Y = CF_2, O, SF_4, NF, NCF_3, NC_2F_5

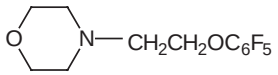
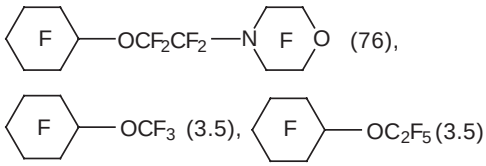
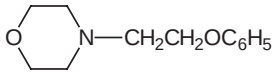
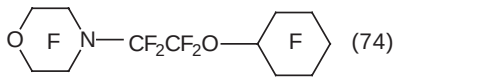
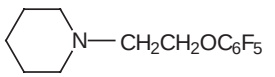
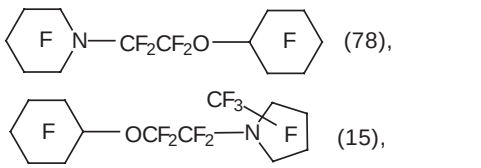
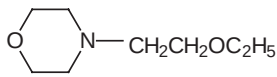
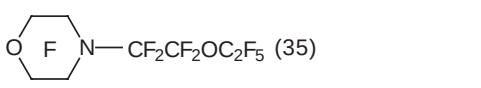
Scheme 59

Perfluorinated alkylmorpholine, piperidine, piperazine, and *N*-butylhexamethyleneimine were obtained in yields from 37% to 58% (00JAP(K)86643).

ECF of *N*-cycloalkylpyrrolidines and -piperidines gives a mixture of products (current density 5.4–6.2 A/dm^2, voltage 7–12 V, concentration 0.5–40%, time 0.2–2.1 h) in 79–87% yields (89JFC(43)67). The reactions take place with ring cleavage at the tertiary carbon atom. The six-membered carbo- and heterocycles are ring-contracted. These compounds are characterized by high chemical inertness and physiological compatibility; they form stable water emulsions and dissolve various gases and may be used as oxygen carriers.

ECF of *N*-morpholinines and *N*-piperidines forms perfluorinated compounds where the carbon skeleton remains intact, or cleavage of the heterocyclic ring takes place as a result of fragmentation in the course of electrolysis. For the synthesis of these perfluorinated compounds by ECF, appropriate bicyclic heterocycles with a tertiary nitrogen atom are the most promising substrates (Table 27) (69ZOB2716, 91JFC(51)53, 73BSJ2524, 83JFC(23)371, 77JFC(9)279). Analysis of Table 27

Table 24. Electrochemical fluorination of amino ethers (82JFC(19)427)

Amino ether	Composition and yield (%) of fluorination products
	
	
	
	

indicates that the ratio of products with an intact carbon skeleton to those with an opened heterocyclic ring is 1:1 (yield 55%).

ECF of *N*-methyl- and *N*-ethylcarbazole (current density 2.5–9.2 mA/dm^2, voltage 5.0–6.2 V, temperature from −2 to 5 °C, substrate concentration in anhydrous HF 5%) afforded perfluorinated derivatives with 10% and 17% yields, respectively (89DDRP2943133, 89JFC(45)93). The process occurs with cleavage of the benzene rings to form perfluorinated derivatives of tetrahydropyrrole (Scheme 65).

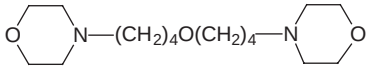
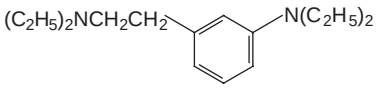
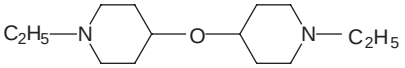
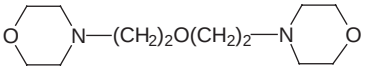
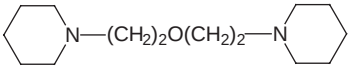
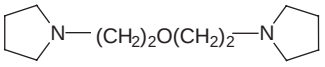
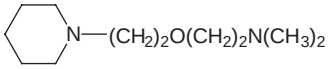
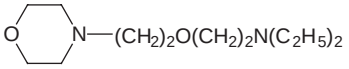
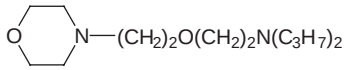
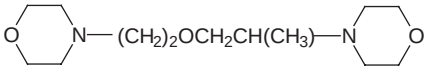
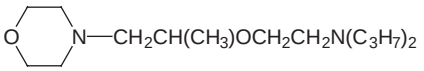
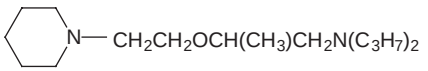
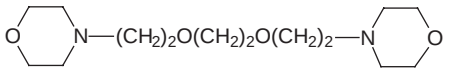
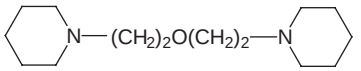
Many studies were devoted to ECF of cyclic amines, in particular, *N*-alkylpiperidines and *N*-alkylmorpholines (91JFC(54)216, 92JFC(59)351, 83IZV2561, 66ZOB1613, 66ZOB1619, 82JFC(19)427, 65JCS2720). ECF of cyclic amines are accompanied by ring expansion or contraction (83JFC(23)371, 65JCS2720, 85JFC(22)417) (Scheme 66).

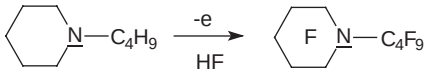
The carbon atom in the carbon chain may be preserved, or it may be replaced by fluorine. Also, products with rings extended or contracted by one carbon atom are formed in 7.6–14.8% yields. This behavior is common to all N-alkyl-substituted cyclic amines (85JFC(22)417) (Scheme 67).

The fluorination possibly follows Scheme 68.

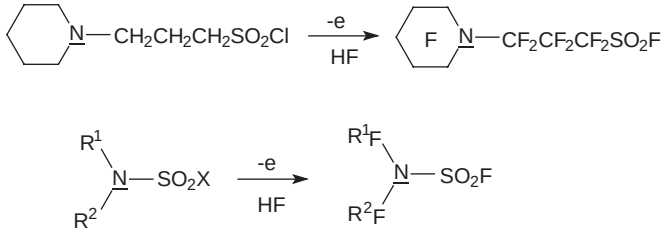
Ring cleavage and contraction also take place with heterocycles having two nitrogen atoms in the ring. Thus ECF of *N*-methylpiperazine gives perfluoro-1, 3-dimethyl-1,3-diazolidine and ring contraction products, as well as perfluorinated

Table 25. Electrochemical fluorination of dialkyl ethers containing a dialkylamino group (80JFC(15)353)

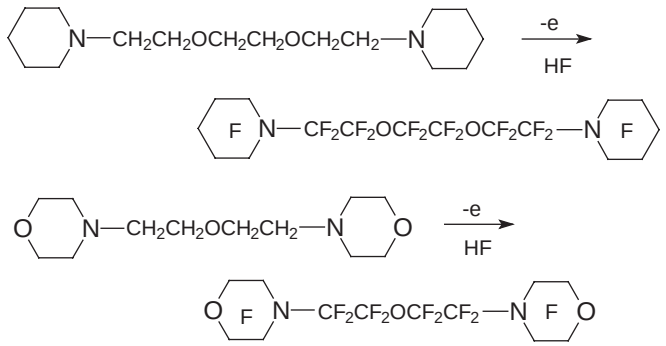
Substrate	Yield of perfluorinated analog, %
	23
	18
	5
	44
	45
	40
	6
	39
	42
	35
	38
	19
	15
	10



Scheme 60



Scheme 61



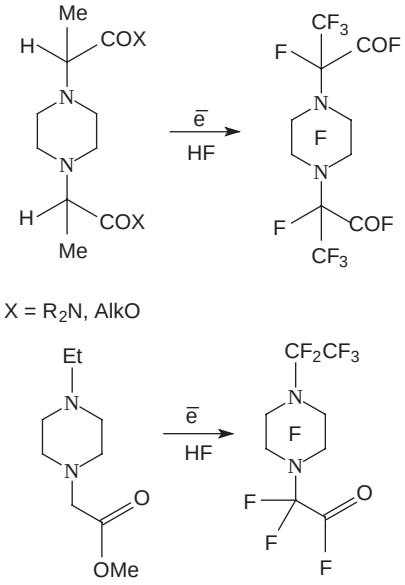
Scheme 62

trialkylamines (85JFC(22)417, 86JCSJC1249, 87JAP(K)62-22756, 86NKK1249) (Scheme 69).

It was shown (88DDRP254219) that perfluorinated compounds can be obtained by ECF of 1,4-dimethyl-1,4-homo-piperazine, methyl-4-ethylhomopiperazin-1-yl acetate, and 1,4-*bis*-(methoxycarbonylmethyl)-1,4-homopiperazine. However, the yields of perfluorinated products are very low.

Perfluorinated cycloaliphatic amino ethers are stable compounds. They were prepared by ECF of their hydrocarbon analogs using anhydrous HF at temperatures from −10 to 40 °C (86JCSJC1249, 87JAP(K)62-22756, 86NKK1249) (Scheme 70).

Bicyclic nitrogen-containing heterocyclic compounds were also fluorinated by ECF. ECF of *N*-methyl-decahydroquinoline forms a mixture of *cis*- and *trans*-isomeric perfluorinated derivatives. Ring contraction and formation of perfluorocyclohexanes are side processes. *Trans*-quinolizidine gives perfluoro-*trans*-quinolizidine (yield 16–23%) and a large amount of other compounds with unknown



Scheme 63

structures (87JAP(K)62-22756, 88JFC(38)303, 84JFC(26)485). *Trans,trans*-4-methylquinolizidine and its stereoisomers (*trans,cis:cis,trans* and *cis,cis*) lead to mixtures of *trans*- and *cis*-4-(trifluoromethyl)-perfluoroquinolizidine, 1-azabicyclo-[5,4,0]perfluoroundecane, and many unidentified compounds (conditions of electrolysis: voltage 5.2–6.0 V, temperature 7–19 °C, electrolysis time 58–87 h, amount of electricity passed 947–1091 A/h) (Scheme 71).

Alkyloctahydroquinolizidines behave in a similar way (87JPP62-54093, 83BEP895757, 87JPP62-54093, 84EP121614) (Scheme 72). Their perfluorinated derivatives are oxygen carriers; they also give stable emulsions and possess interesting pharmacodynamic properties.

When subjected to ECF, heterocyclic bicyclic compounds with rings of varying composition lead to perfluorinated cyclic compounds, which are useful as components of blood substitutes and as liquids for conservation of organs (85USP4526969, 81/82JAP(K)59204192, 85USP4534978) (Scheme 73).

However, the yield of the target materials is rather low, and the individual samples are not readily purified (83/84EUP121614, 84JPP59-27889, 84JPP57-115966, 84JPP57-137664, 84JPP57-137665, 59GEP1052369, 66DLRFBP66-65, 71ZAAC156, 81DK511, 70DK376, 59MC371, 69ZAAC62, 85USP453085, 90IZV1685). For example, ECF of 1-azatricyclo[6.2.1.0.2-7]undecane in anhydrous HF in a helium flow on a nickel anode gives only 9% of the perfluorinated derivative, while perfluoro-2-azatricyclo[5.3.1.$0^{2.6}$]undecane was obtained from 2-azatricyclo [5.3.1.$0^{2.6}$]undecane in 7% yield (83/84EUP121614) (Scheme 74).

If the substrate has fluorine atoms, then higher yields of perfluorinated products are obtained. Thus for partially fluorinated pyrrolizidines synthesized by the

Table 26. Electrochemical fluorination of bicyclic amines (69ZOB2716, 91JFC(51)53)

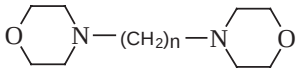
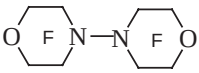
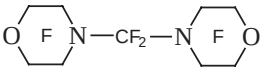
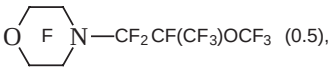
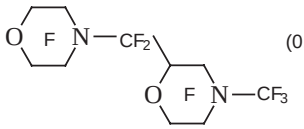
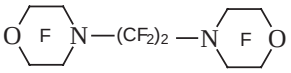
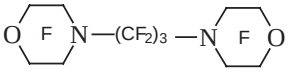
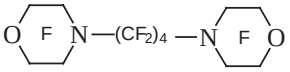
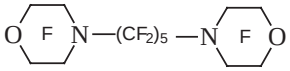
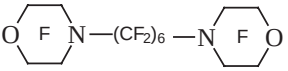
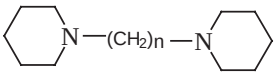
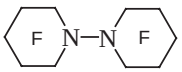
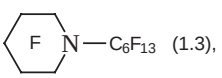
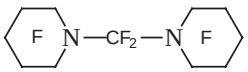
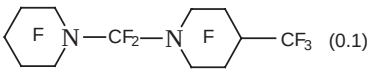
Substrate	Composition and content (%) of fluorinated products
 n = 1	 (0.4),  (0.1),  (0.5),  (0.4)
2	 (28.0)
3	 (25.0)
4	 (30.0)
5	 (26.0)
6	 (20.0)
 n = 1	 (0.1)  (1.3),  (0.1),  (0.1)

Table 26. Continued

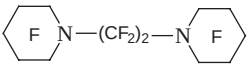
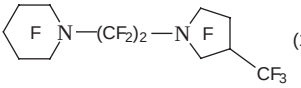
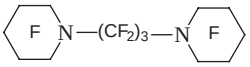
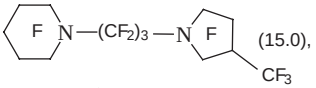
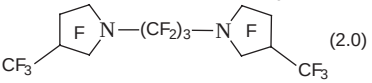
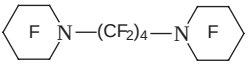
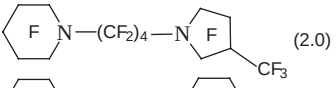
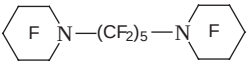
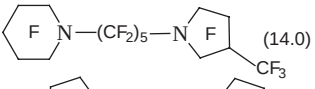
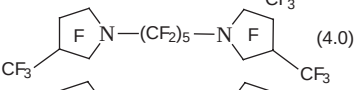
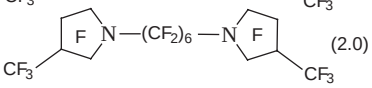
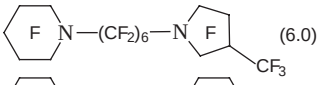
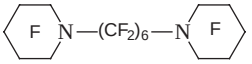
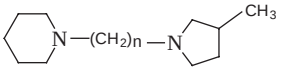
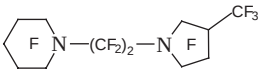
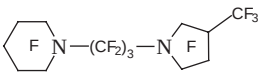
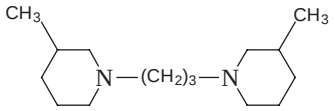
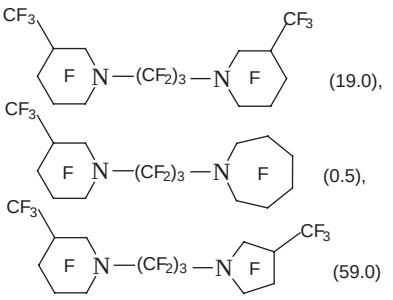
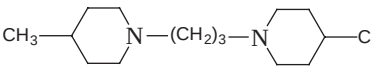
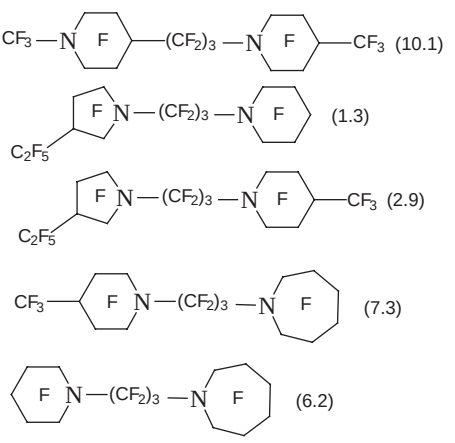
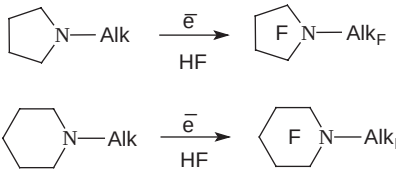
Substrate	Composition and content (%) of fluorinated products
2	 (25.0),  (1.0)
3	 (25.0),  (15.0),  (2.0)
4	 (20.0),  (2.0)
5	 (24.0),  (14.0),  (4.0)
6	 (2.0),  (6.0),  (8.0),
2	  (1.0)
3	 (15.0)

Table 26. Continued

Substrate	Composition and content (%) of fluorinated products
	
	



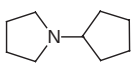
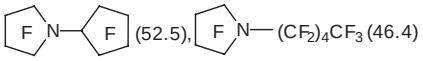
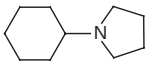
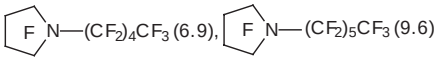
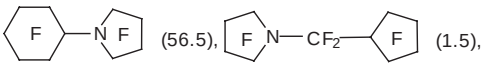
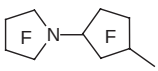
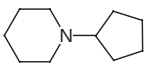
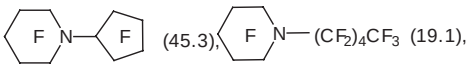
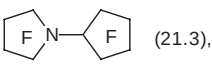
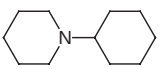
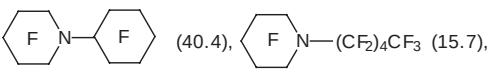
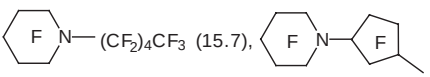
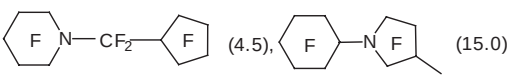
Alk = Me_2CH, Me_3C, Me_2CHCH_2, EtCHMe

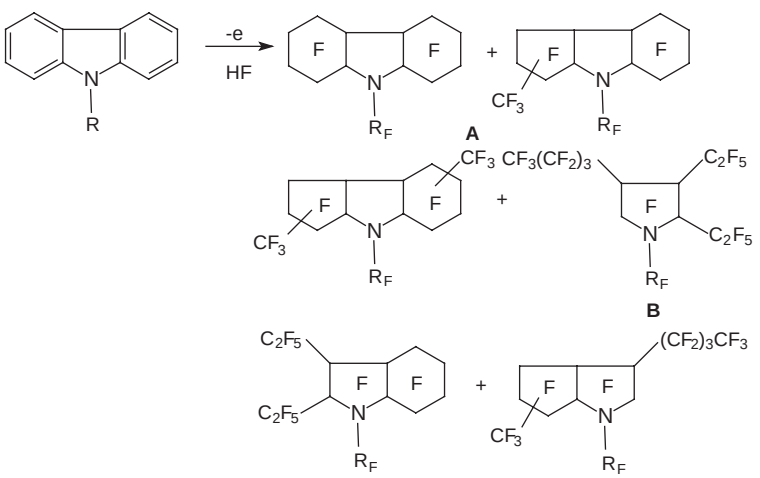
Alk_F = $(CF_3)_2CF$, $(CF_3)_3C$, $(CF_3)_2CFCF_2$, $CF_3CF_2CF(CF_3)$

Scheme 64

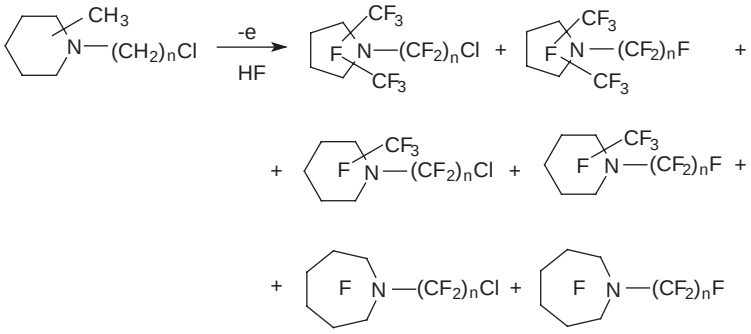
interaction between the hexafluoropropylene trimer and dimethylamine or cyclic amines (pyridine, morpholine, pyrrolizine) in the presence of triethylamine, perfluorinated bicyclic compounds are formed with very high yields (Table 28) (90IZV1685, 91JFC(52)305). This approach is illustrated in Scheme 75.

Table 27. Electrochemical fluorination of bicyclic amines (69ZOB2716, 91JFC(51)53)

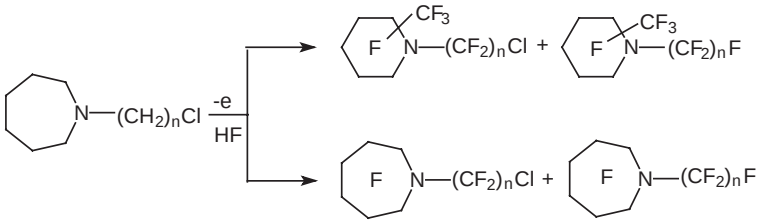
Substrate	Yield (crude product), %	Composition and content (%) of fluorinated products
	76(55)	
	76(53)	
		
		
	78(51)	
		
	76(52)	
		
		



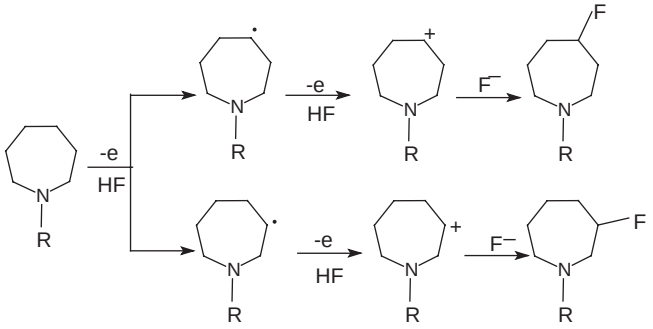
Scheme 65



Scheme 66



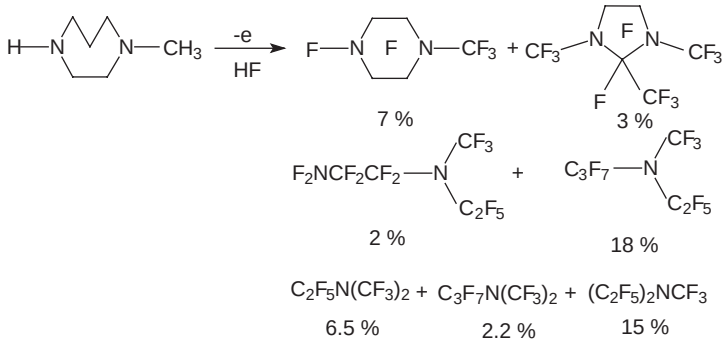
Scheme 67



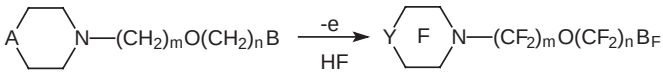
Scheme 68

The process is characterized by the following:

- no tar formation is observed at substrate concentrations up to 15–17% in anhydrous HF;
- no tar is formed at current densities up to 2.8 A/dm^2 and voltages of 6–7 V;
- the yields of perfluorinated heterocycles are very high for ECF processes.

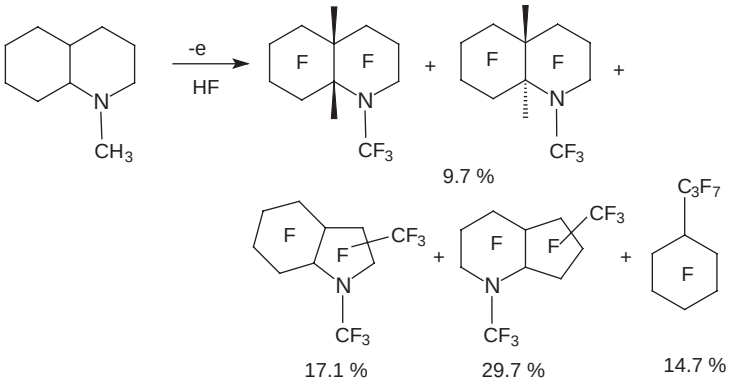


Scheme 69

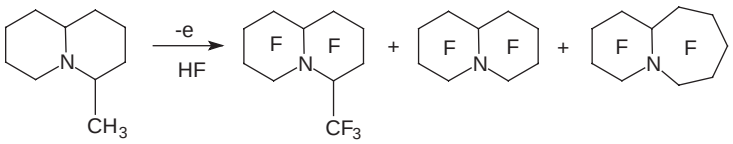


Y	m	n	B_F	Yield, %
0	20	c-C_5F_9		65
CF_2	2	0	c-C_6F_{11}	91
CF_2	2	0	c-C_5F_9	65
CF_2	2	0	c-C_6F_{11}	45
CF_2	2	0	4-CF_3-c-C_6F_{10}	89
CF_2	3	0	c-C_6F_{11}	55
O	2	0	4-CF_3-c-C_6F_{10}	60
O	3	0	c-C_6F_{11}	42

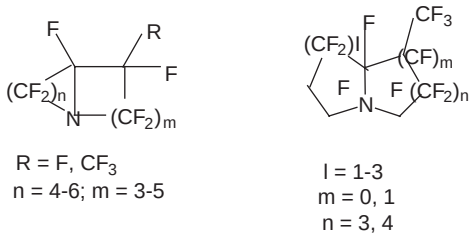
Scheme 70



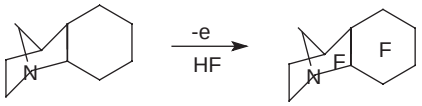
Scheme 71



Scheme 72

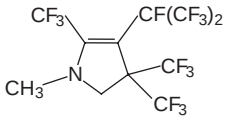
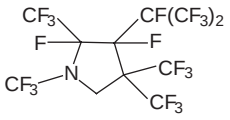
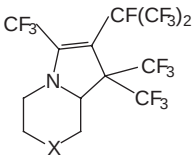
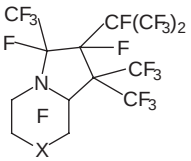


Scheme 73



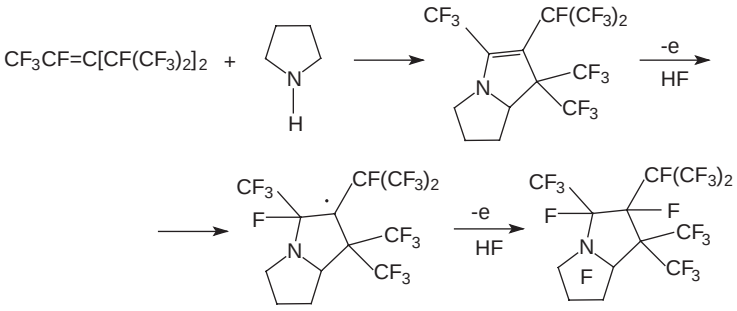
Scheme 74

Table 28. Electrochemical fluorination of nitrogen-containing bicyclic compounds (current density 2.8 A/dm2, temperature 20 °C, voltage 4–7 V, concentration 15–17% in HF) (91JFC(52)305)

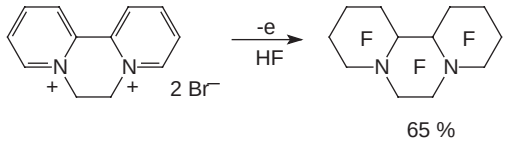
Heterocycle	Perfluorinated Compound		Yield, %
			75
		X = O	58
		X = CF_2	58

A new method for the production of perfluoroperhydro-7,10-diaza-phenanthrene by ECF of the appropriate salt is presented in (96IZV783) (Scheme 76).

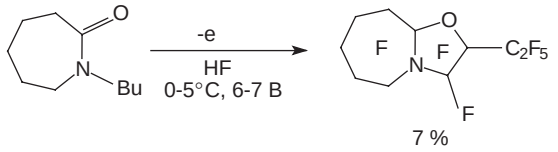
Perfluoro-1,3-oxazolidines were prepared by ECF of N-substituted caprolactam (90DDRP282715) (Scheme 77).



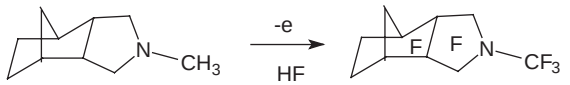
Scheme 75



Scheme 76



Scheme 77



Scheme 78

ECF of azabicycloalkanes in anhydrous HF forms perfluorinated derivatives, which are also potential components of blood substitutes. Thus perfluoro-*N*-methylazatricyclodecane was obtained in 8.6% yield (69ZAAC62) (Scheme 78).

Perfluorinated cyclic amines are formed from 2-azatricyclo-[4.2.2.1$^{2.5}$]undecane (current density 0.4–2 A/dm^2, 7–12 °C) with yields of 8% (90DDRP282715, 91JFC(54)221) and 9% (84JPP84-01484), respectively. 4-Azatricyclo[5.2.1.0$^{2.6}$]decane was converted by ECF into perfluoromethylazacyclodecane in 8.6% yield (87USP4654337, 84JPP59-27889). In general, 24 perfluorinated amines of this class were synthesized by ECF of 24 homologs of 2-azatricyclo[5.3.1.0$^{2.6}$]undecane and 44 perfluorinated amine homologs of 1-azatricyclo[6.3.0.0$^{2.6}$]-undecane. However, the yields of the target perfluorinated derivatives were low, and their practical applications are yet unknown.

Japanese chemists reported on syntheses of perfluorinated cyclic amines by ECF of the hydrocarbon analogs. They synthesized perfluoro-*N*-alkylperhydroindole, perfluorooctahydroindole, perfluoro-*N*-methyleneperfluoroquinoline, and perfluoro-*N*-cycloalkyl-pyrrolidine (83JPP83-144370, 82M33).

ECF of morpholines and piperidines affords the corresponding perfluorinated compounds. However, the intermediate radical species undergo isomerization and fragmentation, which slightly decreases the efficiency of fluorination (94M30, 74ZOR1215). Nevertheless, these compounds are useful as liquid dielectrics and impregnating liquids for fabric, paper, and leather, their electrophysical characteristics being even better than those of mineral oils.

Perfluoro[1-ethyl-4-fluorocarbonylmethyl-1,4-diazepine] was synthesized by ECF of 1-ethyl-4-(methoxycarbonylmethyl)hydro-1,4-diazepine in anhydrous hydrogen fluoride in good yield (03JAP(K)2003277367).

Thus ECF is an important method for the synthesis of perfluorinated organic compounds, whose potential has been steadily increasing. This led to considerable success in the synthesis of nitrogen- and oxygen-containing heterocyclic compounds. The synthesized materials have found wide use as hydraulic liquids, actuating fluids for turbines, heat carriers, and cooling components. In view of their important practical applications, elaborating production technologies has become a crucial problem stimulated by the technological demands. Further research will seek to elaborate various aspects of the electrochemical process and to innovative solutions and approaches. It seems important not only to define the behavior of organic substances during ECF in general, but also to try to reveal the specific features of the process and to define the behavior of perfluorinated compounds due to the presence of fluorine atoms. Another challenge is searching for new substrates, which would give high yields of target products and facilitate the ECF process. Here the task is to pass to partially fluorinated derivatives obtainable from basic perfluorinated compounds such as perfluoroolefins, polyfluorinated telomer alcohols, and polyfluoroaromatic compounds. These substrates are much more stable under the conditions of the ECF process and give much higher yields, facilitating the isolation of target products. Of great importance are studies aimed at changing the design or material or other characteristics of electrodes. The experimental conditions also need further perfection.

Conclusions

The material presented in this chapter indicates that the synthesis of fluorinated heterocyclic compounds has attracted considerable attention from the viewpoint of new methods and approaches; the specific features of perfluorinated organic compounds are extensively used to create new fluorinated materials with wide applications. Recent growth of fluoroorganic chemistry has led to the discovery of new fluorine-containing heterocyclic compounds with unique structures; many of these compounds exhibited specific biological activity and proved to be effective drugs and pesticides. It is hoped that more original methods for the synthesis of heterocyclic

structures will be developed, which will certainly enrich synthetic organic chemistry with new methodologies to synthesize the required structures and models.

Realization of the above ideas and one-electron transfer processes is of interest not only for fluoroorganic chemists, but also for specialists engaged in organic synthesis and technological design. Perfluorinated heterocyclic compounds are convenient and sometimes unique models for the design of new effective reagents and for solving some fundamental problems of theoretical organic chemistry. Therefore, they are expected to be of increasingly greater importance, although few compounds are currently known to be useful on an industrial scale.

Recent progress in studies of the potential of fluorinated heterocycles, therefore, is merely the starting point for the development of this extremely rich field of fluoroorganic chemistry. In view of the unique properties of fluorinated compounds, which cannot be achieved by incorporating other elements, fluorine applications in this direction are expected to be growing with attendant decrease in production costs. Thus effective methods for the transformation of organic compounds into valuable fluorine-containing products will lead to progress in organic syntheses in general.

It was not our aim to give a complete review of data available on fluorinated heterocyclic chemistry; however, the section highlights major directions in studies of fluorinated heterocyclic compounds and methods for direct representation of perfluorinated organic fragments. It is hoped that the review will prove useful not only for specialists in fluoroorganic chemistry, but also for other chemists engaged in synthetic organic chemistry in general.

References

50USP2500388 J. Simons, US Pat. 2500388 (1950).

50USP2519983 J. Simons, US Pat. 2519983 (1950).

53USP2631151 E. Kauck and J. Simons, US Pat. 2631151 (1953).

53USP2644823 E. A. Kauck and J. H. Simons, US Pat. 2644823 (1953).

55USP2717871 H. M. Scholberg and H. G. Bryce, US Patent 2717871 (1955).

56JA5183 E. Runner, C. Balog, and M. Kilpetrick, *J. Am. Chem. Soc.*, **78**, 5183 (1956).

56JA5187 M. Kilpetrick and T. J. Lewis, *J. Am. Chem. Soc.*, **78**, 5187 (1956).

58JA1889 J. A. Young and R. D. Dresdner, *J. Am. Chem. Soc.*, **80**, 1889 (1958).

59GEP1052369 M. Schmeisser and F. Huber, Ger. Pat. 1052369 (1959); [CA, **78**, 1245 (1961)].

59MC371 A. Engelbrecht and E. Nachbaur, *Monatsh-Chem.*, **90**, 371 (1959).

64M17 65BRPPat. 1007288, Br. Pat. 1007288 (1965).

65BRP1007288 Brit. Pat. 1007288 (1965).

65JCS2720 R. E. Banks, J. E. Burgess, and R. N. Haszeldine, *J. Chem. Soc.*, 2720 (1965).

65ZOB485 S. A. Mazalov, S. I Gerasimov, S. V. Sokolov, and V. L. Zolotavin, *Zh. Obshch. Khim.*, **35**, 485–489 (1965).

66DLRFBP66-65 E. W. Schmid, tDLR.FB Pat. 66–65 (1966); [CA, **68**, 45539 (1968)].

66ZOB1613 S. V. Sokolov, A. P. Stepanov, L. N. Pushkina, S. A. Mazalov, and O. K. Shabalina, *Zh. Obshch. Khim.*, **36**, 1613 (1966).

66ZOB1619 L. N. Pushkina, V. F. Kollegov, A. P. Stepanov, S. A. Mazalov, and S. V. Sokolov, *Zh. Obshch. Khim.*, **36**, 1619–1625 (1966).

67DRP1077301 Brit. Pat. 1077301 (1967).

67ZOB1229 N. A. Ryabinin, I. P. Kolenko, and B. N. Lundin, *Zh. Obshch. Khim.*, **37**, 1229 (1967).

69USP3471484 US Pat. 3471484 (1969).

69USP3476753 R. L. Hansen, US Pat. 3476753 (1969).

69ZAAC62 M. Schmeisser and F. Huber, *Z. Anorg. AlIg. Chem.*, **367**, 62 (1969).

69ZOB2716 N. A. Ryabinin, I. P. Kolenko, L. N. Pushkina, V. F. Kpllegov, and B. N. Lundin, *Zh. Obshch. Khim.*, **39**, 2716 (1969).

70DAK1322 I. N. Rozhkov, A. V. Bukhtiarov, N. D. Kuleshova, and I. L. Knunyants, *Dokl. Acad. Nauk SSSR*, **193**, 1322 (1970); [CA, **74**, 70878 (1971)].

70DK376 A. Tasaka, K. Nakanishi and N. Watanabe, *Denki Kagaku,* **38,** 376 (1970); [CA, **74**, 134113 (1971)].

70IZV1207 I. L. Knunyants, I. N. Rozhkov, A. V. Bukhtiarov, M. M. Gol'din, and R. V. Kudryatsev, *Izv. Acad. Nauk SSSR Ser. Khim.*, 1207–1208 (1970); [CA, **73**, 65752 (1970)].

71DAK369 I. N. Rozhkov, A. V. Bukhtiarov, E. G. Galpern, and I. L. Knunyants, *Dokl. Acad. Nauk*, **199**, 369 (1971).

71IZV1369 I. L. Knunyants, I. N. Rozhkov, and A. V. Bukhtiarov, *Izv. Acad. Nauk SSSR. Ser. Khim.*, 1369–1370 (1971); [CA, **75**, 83478 (1971)].

71M31 A. J. Rudge, *''Industrial Electrochemical Process''* (A. T. Kuhn, ed.), p. 77, Elsevier, Amsterdam (1971).

71ZAAC156 A. Tasaka and N. Watanabe, *Z. Anorg. AlIg. Chem.*, **385**, 156 (1971).

73BSJ2524 T. Abe, S. Nagase, and H. Baba, *Bull. Chem. Soc. Jpn.*, **46**, 2524–2527 (1973).

74GER2313862 S. Nagase, H. Baba, K. Kodaira, and K. Okazaki, Ger. Pat. 2313862 (1974); [CA, **80**, 82075 (1974)].

74JFC(4)383 K. Okazaki, S. Nagase, H. Baba, and K. Kodaira, *J. Fluorine Chem.*, **4**, 383 (1974).

74JFC(4)387 K. Okazaki, S. Nagase, H. Baba, and K. Kodaira, *J. Fluorine Chem.*, **4**, 387397 (1974).

74ZOR1215 V. S. Plashkin, L. N. Pushkina, and S. V. Sokolov, *Zh. Org. Khim.*, **10**, 1215 (1974); [CA, **81**, 105221 (1974)].

74ZOR2031 V. V. Berenblit, Yu. P. Dolnakov, V. P. Sass, L. N. Senyshov, and S. V. Sokolov, *Zh. Org. Khim.*, **10**, 2031 (1974).

74ZPK590 V. V. Berenblit, V. I. Grachev, I. M. Dolgopol'slii, and G. A. Davydov, *Zh. Prikl. Khim.*, **47**, 590 (1974).

75ZPK706 V. S. Plashkin, *Zh. Prikl. Khim.*, **48**, 706–709 (1975).

75ZPK709 V. V. Berenblit, B. A. Byzov, V. I. Grachev, I. M. Dolgopol'slii, and Yu. P. Dolnakov, *Zh. Prikl. Khim.*, **48**, 709 (1975); [CA, **82**, 161753 (1975)].

75ZPK2206 V. V. Berenblit, Yu. P. Dolnakov, G. A. Davydov, I. V. Grachev, and S. V. Sokolov, *Zh. Prikl. Khim.*, **48**, 2206–2210 (1975).

76BCS1888 T. Abe, S. Nagase, and H. Baba, *Bull. Chem. Soc. Jpn.*, **49**, 1888 (1976).

76UK1222 I. N. Rozhkov, *Uspechi Khimii*, **45**, 1222–1250 (1976).

76IZV1418 I. N. Rozhkov, I. Ya. Aliev, and I. L. Knunyants, *Izv. Acad. Nauk SSSR. Ser. Khim.*, 1418–1421 (1976).

77BCJ2809 H. Baba, K. Kodaira, S. Nagase, and T. Abe, *Bull. Chem. Soc. Jpn.*, **50**, 2809 (1977).

77JFC(9)279 K. Omori, S. Nagase, H. Baba, and K. Kodaira, *J. Fluorine Chem.*, **9**, 279–291 (1977).

77JHC1109 R. A. Henry and P. R. Hantmond, *J. Heterocycl. Chem.*, **14**, 1109 (1977).

77USP4026898 R. A. Henry, P. R. Peter, E. J. Schimitrischer, and J. A. Trias, US Pat. 4026898 (1977).

78JFC(12)1 T. Abe, K. Kodaira, H. Baba, and S. Nagase, *J. Fluorine Chem.*, **12**, 1–25 (1978).
78JFC(12)359 T. Abe and S. Nagase, *J. Fluorine Chem.*, **12**, 359–379 (1978).
78JOC1975 R. L. Alkins and D. E. Bliss, *J. Org. Chem.*, **43**, 1975–1980 (1978).
79JAE685 F. G. Drakesmith and D. A. Hughes, *J. Appl. Electrochem.*, **9**, 685 (1979).
79USP4146443 W. V. Childs, US Pat. 4146443 (1979); [CA, **90**, 194726t (1979).
80JFC(15)353 T. Abe, E. Hayashi, H. Baba, K. Kodaira, and S. Nagase, *J. Fluorine Chem.*, **15**, 353–380 (1980).
80JOC2283 E. R. Bissel, A. R. Mitchell, and R. E. Smith, *J. Org. Chem.*, **4**, 2283–2287 (1980).
80JPP80-18539 T. Abe and S. Nagase, Jpn. Pat. 80-18539 (1980); [CA, **93**, 8020 (1980)].
80NJC453 A. Bensadat, G. Bokennes, E. Laurent, and R. Tardivel, *Nouv. J. Chim.*, **4**, 453–460 (1980).
80ZPK858 V. V. Berenblit, Yu. P. Dolnakov, G. A. Davidov, and S. V. Sokolov, *Zh. Prikl. Khim.*, **53**, 858–861 (1980).
81DK511 A. Tasaka and N. Watanabe, *Denki Kagaku*, **49**, 511 (1981); [CA, **95**, 158699 (1981)].
81/82JAP(K)59204192 K.Yokoyama, Y. Inoue, Y. Arakawa, Y. Naito, and C. Fukaya, Jpn. Kokai, Tokkyo Koho JP, 59204192 (1981/82); [CA, **102**, 149127d (1985)].
82JFC(19)427 G. P. Gambaretto, M. Napoli, C. Franccaro, and L. Conte, *J. Fluorine Chem.*, **19**, 427–436 (1982).
82M1 D. S. L. Slinn and S. W. Green, *"In Preparation, properties and industrial applications of organic compounds"* (R. E. Banks, ed.), p. 45, Ellis Horwood, Chichester (1982).
82M8 R. Filler and Y. Kobayashi (eds.), *"Biomedicinal Aspects of Fluorine Chemistry"*, Kodansha & Elsevier Biomedical, Tokyo (1982).
82M29 T. Abe and S. Nagase, *"In Preparation, Properties and Industrual Application of Organofluorine Compounds"* (R. E. Banks, ed.), pp. 19–43, Ellis Horwood, Chichester (1982).
82M33 C. Fukaya, K. Yokoyama, T. Ono, Y. Inoue, Y. Arakawa, Y. Naito, T. Suyama, and R. Naito. *10th Inter. Symp. on Fluorine Chemistry*, Canada (1982).
83BEP895757 Belg. Pat. 895757 (1983); [CA, **99**, 122330 (1983)].
83/84EUP121614 K. Yokoyama, C. Fukaya, Y. Tsuda, T. Ono, Y. Arakawa, Y. Inoue, Y. Naito, and T. Suyama, Eur. Pat. 121614 (1983/84); [CA, **102**, 113282 (1985)].
83IZV2561 V. F. Snegirev, F. V. Zakharova, K. N. Makarov, and I. L. Knunyants, *Izv. Akad. Nauk SSSR. Ser. Khim.*, 2561 (1983).
83JES2170 J. F. Carpenter, L. H. Ekes, P. F. King, H. A. Mariani, M. M. Zadeh, R. F. O'Malley, and V. J. Roman, *J. Electrochem. Soc.*, **130**, 2170–2172 (1983); [CA, **100**, 14410 (1984)].
83JFC(23)123 T. Abe, H. Baba, E. Hayashi, and S. Nagase, *J. Fluorine Chem.*, **23**, 123–146 (1983).
83JFC(23)371 E. Hayashi, T. Abe, H. Baba, and S. Nagase, *J. Fluorine Chem.*, **23**, 371–381 (1983).
83JJC6 N. Ishikawa, *J. Jpn. Chem.*, **37**, 6–13 (1983); [РЖХим. 1983. 19Ж 362].
83JPP6429366 K. Makino and H. Yoshioka, Jpn. Pat. 6429366 (1989); [РЖХим, 1990, 6Н179П].
83JPP83-144370 Jpn. Pat. 83-144370 (1983).
83M22 I. N. Rozhkov, *"In Organic Electrochemistry"* (M. M. Baizer, M. Lundt, eds.), pp. 805–825, Marcel Dekker, New York (1983).

83SERDU204 A. Tasaka, M. Oguchi, M. Kawaguchi, R. Aki, and K. Kawabe, *Ski Eng. Rev. Doshisha Univ.*, **24**, 204 (1983).

84EP121614 K. Yokoyama, C. Fukaya, Y. Tsuda, T. Ono, Y. Arakawa, Y. Inoue, Y. Naito, and T. Suyama, Eur. Pat. Appl. EP 121614(1984); [CA, **102**, 113282m (1985)].

84JFC(25)419 T. Abe, E. Hayashi, H. Baba, and S. Nagase, *J. Fluorine Chem.*, **25**, 419–434 (1984).

84JFC(26)485 Y. Naito, Y. Inoue, T. Ono, Y. Arakawa, C. Fukaya, and K. Yokoyama, *J. Fluorine Chem.*, **26**, 485 (1984).

84JOC2803 R. F. King and R. F. O'Malley, *J. Org. Chem.*, **49**, 2803–2809 (1984).

84JPP57-115966 Jpn. Pat. 57-115966 (1984).

84JPP57-137664 Jpn. Pat. 57-137664 (1984).

84JPP57-137665 Jpn. Pat. 57-137665 (1984).

84JPP59-27889 Green Cross Corp., Jpn. Kokai Tokkyo Koho JP 59-27889 (1984); [CA, **101**, 54945j (1984)].

84JPP84-01484 Jpn. Pat. 84-01484 (1984).

84JSOC786 I. Kumadaki, *J. Synth. Org. Chem. Jpn.*, **42**, 786–793 (1984).

84M32 M. Enetani and T. Echmura, in *"Novoe in technology soedinernii ftora"* (N. Ishikawa ed.), pp. 289–446, Mir, Moscow (1984).

85EA1075 J. R. Ballinger and F. W. Teare, *Electrochim. Acta*, **30**, 1075 (1985).

85JES2424 E. J. M. O'Sullivan, F. W. Klinke, C. C. Liu, and E. B. Yeager, *J. Electrochem. Soc.*, **132**, 2424–2426 (1985).

85JFC(22)417 E. Hayashi, T. Abe, H. Baba, and S. Nagase, *J. Fluorine Chem.*, **22**, 417–436 (1985).

85USP453085 K. Yakoyama, C. Fukaya, Y. Tsuda, T. Ono, Y. Arakawa, Y. Inoue, Y. Naito, and T. Suyama, US Pat. 4535085 (1985); [CA, **103**, 215159q (1985)].

85USP4526969 K. Yokoyama, C. Fukaya, Y. Tsuda et al., US Pat. 4526969 (1985).

85USP4534978 K. Yokoyama, C. Fukaya, Y. Tsuda, T. Ono, Y. Arakawa, and T. Suyama, US Pat. 4534978 (1985); [CA, **104**, 75001a (1985)].

86BCJ3625 T. Umemoto and G. Tomizawa, *Bull. Chem. Soc. Jpn.*, **59**, 3625 (1986).

86CIT31 E. Hollitzer and P. Sartori, *Chem.-Ing. Techn.*, **58**, 31–38 (1986).

86JAP(K)183281 K. Sugasawa, N. Nakayama, H. Shimizu, and F. Nemoto, Jpn. Kokai. 61-183281 (1986); [CA, **106**, 33074 (1987)].

86JCS(JC)1249 H. Baba, T. Abe, and E. Hayashi, *J. Chem. Soc., Jpn. Chem. Ind. Chem.*, 1249–1251 (1986).

86JFC(31)231 T. Umemoto and Y. Goto, *J. Fluorine Chem.*, **31**, 231–236 (1986).

86JFC(32)77 F. W. Klink, F. Kucera, D. J. Wasser, and C. C. Liu, *J. Fluorine Chem.*, **32**, 77 (1986).

86JFC(32)89 F. W. Klink, D. J. Wasser, and C. C. Liu, *J. Fluorine Chem.*, **32**, 89–101 (1986).

86JFC(33)337 B. D. Joyner, *J. Fluorine Chem.*, **33**, 337 (1986).

86JPP61-260047 T. Abe and E. Hayashi, Jpn. Pat. 61-260047 (1986); [CA, **107**, 105032 (1987)].

86M4 A. I. Rakhimov, *"Khimia and Technology Fluoroorganic Compounds"* pp. 1–272, Mir, Moscow (1986).

86M337 B. D. Joyner, *"In Fluorine : The first 100 Years"* (R. E. Banks, D. W. A. Sharp and J. C. Tatlow, eds.), p. 337, Elsevier, New York (1986).

86NKGSH202 H. Baba, K. Kodaira, T. Abe, E. Hayashi, and S. Nagase, *Repts. Rov. Ind. Res. Inst. Nagoya*, **35**, 202 (1986); [CA, **106**, 24924 (1987)].

86NKK1249 H. Baba, T. Abe, and E. Hayashi, *Nippon Kagaku Kaishi*, 1249 (1986).

86USP4605786 K. Yokoyama, Y. Inoue, T. Ono, C. Fukaya, Y. Arakawa, Y. Naito, K. Yamauchi, and T. Suyama, US Pat. 4605786 (1986).
87JCP1119 J. G. Riess, *J. Chim. Physique*, **84**, 1119 (1987).
87JAP(K)62-22756 T. Abe, Jpn. Kokai. 62-22756 (1987); [CA, **107**, 77644 (1987)].
87JFC(35)557 D. J. Wasser, P. S. Johnson, F. W. Klink, F. Kucera, and C. -C. Liu, *J. Fluorine Chem.*, **35**, 557–569 (1987).
87JPP62-22756 T. Abe, Japan Pat. 62-22756 (1987); [CA, **107**, 77644 (1987)].
87JPP62-54093 S. Marikawa, M. Sasabe, and H. Matsuo, Jpn. Pat. 62-244 54093 (1987); [CA, **107**, 164115 (1987)].
87M28 P. Tarrant (ed.)Fluorine Chemistry Reviews, Vol. 1, p. 77, Marcel Dekker, Inc., New York (1987).
87OC133 W. Cao, W. Ge, and W. Huang, *Org. Chem.*, 133–137 (1987).
87TL2359 E. Laurent, B. Marquet, R. Tardivel, and H. Thilbault, *Tetrahedron Lett.*, **28**, 2359–2362 (1987).
88CE191 E. Hayashi, T. Abe, H. Baba, and S. Nagase, *Chem. Express*, **3**, 191–194 (1988).
88CL1887 T. Abe and E. Hayasi, *Chem. Lett.*, 1887 (1988).
88DDRP254219 S. Ruediger, V. E. Platonov, H. Meinert, N. V. Popkova, U. Jonethal, W. Radeck, and G. Zielinski, Ger (East) DD Pat. 142878 (1988); [CA, **109**, 179088 (1988)].
88EUP271272 M. Nishimura, N. Okada, Y. Munata, and Y. Hirai, Eur. 271272 (1988); [CA, **110**, 7191 (1989)].
88FRP2604189 E. Laurent, D. Marquet, and R. Nardivel, Fr. Pat. 2604189 (1988); [CA, **110**, 15128 m (1989)].
88JFC(38)303 Y. Inoue, Y. Arakawa, Y. Naito, T. Ono, C. Fukaya, K. Yamanouchi, and K. Yokoyama, *J. Fluorine Chem.*, **38**, 303–317 (1988).
88JFC(39)435 K. Makino and H. Yoshioka, *J. Fluorine Chem.*, **39**, 435–440 (1988).
88JFC(87)203 S. Higashiya, T. Sato, and T. Fuchigami, *J. Fluorine Chem.*, **87**, 203–208 (1988).
88JPP63-208572 K. Migami, Y. Ivau, N. Ivasita, and Y. Kotaka, Jpn. Pat. 63-208572 (1988).
88M33 R. Herkelmann and P. Sartori, *12th lnt. Symp. on Fluorine Chemistry*, p. 345, Santa Cruz, USA, August 7–13, 1988, Abstracts (1988).
89DDRP2943133 W. Radeck, St. Rudiger, and U. Jonethal, DDR Pat. 2943133 (1989).
89JAP(K)0129364 K. Makino and H. Yoshioka, Jpn. Kokai. 0129364, (1989); [CA, **111**, 78002 g (1989)].
89JFC(43)67 T. Ono, Y. Inoue, Y. Arakawa, Y. Naito, C. Fukaya, K. Yamanouchi, and K. Yokoyama, *J. Fluorine Chem.*, **43**, 67–85 (1989).
89JFC(45)93 H. Meinert, R. Fackler, J. Mader, and P. Reuter, *J. Fluorine Chem.*, **45**, 93 (1989).
89JPP09-29364 K. Makino and H. Yoshioka, Jpn. Pat. 09-29364 (1989); [CA, **111**, 78002 g (1989)].
89T4431 E. Laurent, B. Marquet, and R. Tardivel, *Tetrahedron*, **45**, 4431–4444 (1989).
90BE471 P. Sartori, *Bull. Electrochem.*, **6**, 471–477 (1990).
90DDRP282715 S. Schramn, W. Radeck, U. Gross, and St. Rudiger, DDR Pat. 282715 (1990).
90GC1749 G. Cerichelli, M. E. Creatoni, and S. Fornarini, *Gazz. Chim. Ital.*, **120**, 749 (1990).
90IZV1685 A. A. Kadyrov, L. L. Gervits, L. F. Komarova, and K. N. Makarov, *Izv. Akad. Nauk SSSR. Ser. Khim.*, 1685 (1990).
90JFC(49)409 R. D. Chambers, R. W. Fuss, and M. Jones, *J. Fluorine Chem.*, **49**, 409–419 (1990).

90JFC(50)173 T. Abe, E. Hayashi, H. Fukaya, and H. Baba, *J. Fluorine Chem.*, **50**, 173–196 (1990).

90JOC6074 T. Fuchigami, M. Shimojo, A. Konno, and K. Nakagawa, *J. Org. Chem.*, **55**, 6074–6075 (1990).

90TL3137 L. Kabore, S. Chebli, R. Faure, E. Laurent, and D. Marquet, *Tetrahedron Lett.*, **31**, 3137–3140 (1990).

90USP4929317 M. Nishimura, N. Okada, Y. Murata et al., US Pat. 4929317 (1990).

91AA31 M. J. Silverster, *Aldrichim. Acta*, **24**, 31–38 (1991).

91GEP294514 S. Rudiger and A. W. Dimitrov, Ger. Pat. 294514 (1991).

91JCS(CC)1027 A. N. Konno, K. Nakagawa, and T. Fuchigami, *J. Chem. Soc., Chem., Commun.*, 1027–1029 (1991).

91JFC(51)53 H. Meinert, R. Fackler, J. Mader, P. Renter, and W. Rohlke, *J. Fluorine Chem.*, **51**, 53–73 (1991).

91JFC(54)216 H. Meinert, R. Fackler, J. Mader, P. Reuter, and W. Rohlke, *J. Fluorine Chem.,* **54** 216 (1991). *J. Fluorine Chem.*, **59**, 351–365 (1992).

91JFC(54)221 K. N. Makarov and L. F. Komarova, *J. Fluorine Chem.*, **54**, 221 (1991).

91JFC(52)305 L. L. Gervits, A. A. Kadyrov, K. N. Makarov, L. F. Komarova, B. L. Tumanskii, A. Dimitrov, U. Gross, and St. Rudiger, *J. Fluorine Chem.*, **52**, 305 (1991).

91M10 J. T. Welch and S. Eswarakrishnan (eds.), *"Fluorine in Bioorganic Chemistry"*, Wiley, New York (1991).

91M11 J. T. Welch and S. Eswarakrishnan, Fluorine in Bioorganic Chemistry, Wiley, New York (1991).

91M16 J. T. Welch (ed.), *"Selective Fluorination of Organic and Bioorganic Chemistry"*, ACS Books, Washington, DC (1991).

91M26 J. T. Welch (ed.), *"Selective Fluorination in Organic and Bioorganic Chemistry American Chemical Society"*, Washington, DC (1991).

91M27 W. V. Childs, L. Christensen, F. W. Klink, and C. F. Kolpin, *"Organic Electrochemistry"* (H. Lunt and M. M. Baizer, eds.), 3rd edn., pp. 1103–1127, Marcel Dekker, New York (1991).

91T705 J. H. H. Meurs and W. Eilenberg, *Tetrahedron*, **47**, 705–717 (1991).

91T3969 E. Laurent, B. Marquet, and R. Tardivel, *Tetrahedron*, **47**, 3969–3980 (1991).

91USP4983747 M. Nishimura, N. Okada, Y. Murata, and Y. Hirai, US Pat. 4983747 (1991).

91USP5049670 G. G. I. Moore and J. C. Hansen, US Pat. 5049670 (1991).

92CL1995 T. Yoshiyama and T. Fuchigami, *Chem. Lett.*, 1995–1998 (1992); [CA, **118**, 6677 (1993)].

92JFC(58)187 D. D. Moldavsky, T. V. Kovalenko, T. V. Mikhailova, and G. G. Furin, *J. Fluorine Chem.*, **58**, 187 (1992).

92JFC(58)269 W. Radeck, A. Dimitrov, St. Rudiger, et al., *J. Fluorine Chem.*, **58**, 269 (1992).

92JFC(59)351 H. Meinert, R. Fackler, J. Mader, P. Reuter, and W. Rohlke, *J. Fluorine Chem.*, **59**, 351–365 (1992).

92JOC3755 T. Fuchigami, S. Narizuka, and A. Konno, *J. Org. Chem.*, **57**, 3755–3757 (1992).

92JOC6074 T. Fuchigami, S. Narizuka, and A. Konno, *J. Org. Chem.*, **57**, 6074 (1992).

92M9 R. Filler, Y. Kobayashi and L. M. Yagupolskii (eds.), *"Organo Fluorine Compounds in Medicinal and Biomedicinal Applications"*, Elsevier, Amsterdam (1992).

92TL7017 A. Konno, W. Naito, and T. Fuchigami, *Tetrahedron Lett.*, **33**, 7017–7020 (1992).

93CJC122 X. -M. Shen and C. -M. Hu, *Youji Huaxue (Chin. J. Chem.)*, **13**, 122 (1993).

93EA619 K. Momota, M. Morita, and Y. Matsuda, *Electrochim. Acta*, **38**, 619–624 (1993).

93EA1123 K. Momota, M. Morita, and Y. Matsuda, *Electrochim. Acta*, **38**, 1123–1130 (1993).

93JES858 S. Narizuka, A. Konno, H. Matsuyama, and T. Fuchigami, *J. Electrochem. Soc. Jpn.*, **61**, 858 (1993).

93JOC4200 S. Narizuka and T. Fuchigami, *J. Org. Chem.*, **58**, 4200 (1993).

94AHC1 K. Burger, U. Wucherpfenning, and E. Brunner, *Adv. Heterocycl.*, **60**, 1–64 (1994).

94JOC7190 T. Fuchigami and T. Fujita, *J. Org. Chem.*, **59**, 7190–7192 (1994).

94JSOC1063 T. Fuchigami, *J. Synth. Org. Chem. Jpn.*, **52**, 1063 (1994).

94M3 R. E. Banks, B. E. Smart and J. C. Tatlow (eds.), *"Organofluorine chemistry, principles and commercial applications"*, Plenum, New York (1994).

94M18 T. Fuchigami, in *"Topics in Current Chemistry. 170. Electrochemistry"* (E. Steckhan, ed.), Vol. 5, pp. 1–37, Springer, Berlin (1994); [CA, **125**, 85795 (1997)].

94M30 T. A. Bispen, T. V. Mikhailova, D. D. Moldavsky, and G. G. Furin, *1st International Conference: "Chemistry, Technology and Application of Fluorocompounds in Industry"*, p. 155, May 30–June 3, 1994, St. Petersburg, Russia, Abstracts, L4–9 (1994).

94M35 Y. W. Alsmeyer, W. V. Childs, R. M. Flynn, G. G. I. Moore, and J. C. Smeltzer, in *"Organofluorine Chemistry"* (R. E. Banks, J. C. Smart, and J. C. Tatlow, eds.), Plenum Press, New York, pp. 121–142 (1994).

94RHC155 T. Fuchigami, *Rev. Heteroatom. Chem.*, **10**, 155–172 (1994).

94TL7245 A. W. Erian, A. Konno, and T. Fuchigami, *Tetrahedron Lett.*, **35**, 7245–7248 (1994).

94TL9237 M. Sono, N. Toyoda, Y. Shizuri, and M. Tori, *Tetrahedron Lett.*, **35**, 9237–9238 (1994).

94USP5322597 W. V. Childs, F. W. Klink, J. C. Smelizer, and J. C. Spangler, US Pat. 5322597 (1994).

95BMCL1293 S. Narizuka and T. Fuchigami, *Bioorg. Med. Chem. Lett.*, **5**, 1293 (1995).

95JCS(PI)1327 K. Suda, K. Hotoga, M. Aoyagi, and T. Takanami, *J. Chem. Soc. Perkin Trans. I*, 1327–1329 (1995).

95JFC(73)121 S. Narizuka, H. Koshiyama, A. Konno, and T. Fuchigami, *J. Fluorine Chem.*, **73**, 121 (1995).

95JOC6563 T. Umemoto and G. Tomizawa, *J. Org. Chem.*, **60**, 6563–6570 (1995).

95JOC7654 A. W. Erian, A. Konno, and T. Fuchigami, *J. Org. Chem.*, **60**, 7654–7659 (1995).

95M1 M. Hydlicky and A. E. Pavlath (eds.), *"Chemistry of Organic Fluorine Compound"* Vol. II, (ACS Monography, N 187), pp. 1–1296, American Chemical Society, Washington, DC, (1995).

95M27 K. Kato and K. Momota, *The 18th Symposium on Electroorganic Chemistry*, p. 101, Nagoya, Japan, 1995. Abstracts (1995).

95RUP2026889 V. I. Gribel, E. V. Stryuk, V. Yu. Muchin, I. N. Rozhkov, K. G. Kornilov, V. A. Brenaizer, E. B. Kononova, and V. I. Petrova, RU Pat. 2026889 (1995).

95TL6511 S. Hara, S. -Q. Chen, T. Hatakeyama, T. Fukuhara, M. Sekiguchi, and N. Yoneda, *Tetrahedron Lett.*, **36**, 6511–6514 (1995).

96IZV783 K. N. Makarov, O. A. Popova, L. T. Lantseva, V. Yu. Mukhin, and E. I. Mysov, *Izv. Akad. Nauk. Ser. Khim.*, 783 (1996).

96JFC(77)65 S. M. Lee, J. M. Roseman, W. J. Zartman, E. P. Morrison, S. J. Harrison, C. A. Stankiewicz, and W. J. Middleton, *J. Fluorine Chem.*, **77**, 65 (1996).

96JFC(79)71 P. Sartori and C. Junger, *J. Fluorine Chem.*, **79**, 71–75 (1996).

96JPC99 T. Haufe, *J. Prakt. Chem.*, **338**, 99 (1996).

96M14 G. G. Furin and G. P. Gambaretto, Direct fluorination of organic compounds, CLEUP, cooperativa Libraria Editrice Universita di Padova, Italy (1996).

96YOKK7 K. Momota, *Yoyuen Oyobi Koon Kagaku*, **39**, 7 (1996); [CA, **125**, 12520953v (1996)].

97JES626 T. Fuchigami and S. Nishiyama, *Denki Kagaku (J. Electrochem. Soc., Jpn.)*, **65**, 626–630 (1997).

97JES841 P. Baroux, R. Tardivel, and J. Simonet, *J. Electrochem. Soc.*, **144**, 841–846 (1997); [CA, **126**, 348759 (1998)].

97JFC(83)31 M. Noel, V. Suryanarayanan, and S. Chellammal, *J. Fluorine Chem.*, **83**, 31–40 (1997).

97JOC8579 A. Konno and T. Fuchigami, *J. Org. Chem.*, **62**, 8579–8581 (1997).

97JOC8773 Y. Hou, S. Higashiya, and T. Fuchigami, *J. Org. Chem.*, **62**, 8773–8776 (1997).

97JOC9173 Y. Hou, S. Higashiya, and T. Fuchigami, *J. Org. Chem.*, **62**, 9173–9176 (1997).

97JSOC301 T. Fuchigami and A. Konno, *J. Synth. Org. Chem. Jpn.*, **55**, 301–312 (1997); [CA, **126**, 330223 (1998)].

97M23 W. V. Childs and T. Fuchigami (eds.), *"Electrochemistry in the Preparation of Fluorine and its Compounds"*, The Electrochemical Society, Inc., Pennington (1997).

97M34 T. Fuchigami, in *"Topic in Current Chemistry 170. Electrochemistry"* (E. Steckhan, ed.), Springer, Berlin, **5**, 1–37 (1994); [CA, **125**, 85795 (1997)].

97PES65 T. Fuchigami, *Proc.- Electrochem. Soc.*, **97–15**, 65–73 (1997); [CA, **127**, 254429 (1998).

97PES74 K. Momoto, *Proc. Electrochem. Soc.*, **97–15**, 74–82 (1997); [CA, **127**, 254430 (1998)].

97SL655 Y. Hou, S. Higashiya, and T. Fuchigami, *Synlett*, 655–656 (1997); [CA, **127**, 176334 (1998)].

98EA(43)1985 T. Fuchigami, S. Narizuka, A. Konno, and K. Momota, *Electrochim. Acta*, **43**, 1985–1989 (1998); [CA, **129**, 141845y (1999)].

98EA(43)2503 K. Momota, K. Mukai, K. Kato, and M. Morita, *Electrochim. Acta*, **43**, 2503–2514 (1998); [CA, 129, 181319 (1999)].

98F1118 T. Fuchigami, *Farumashia*, **34**, 1118–1122 (1998); [CA, **129**, 343125z (1999)].

98JFC(87)137 A. Konno, M. Shimojo, and T. Fuchigami, *J. Fluorine Chem.*, **87**, 137–140 (1998).

98JFC(87)193 T. Abe, H. Fukaya, T. Ono, E. Hayashi, I. Soloshonok, and K. Okuhara, *J. Fluorine Chem.*, **87**, 193–202 (1998).

98JFC(87)215 E. Laurent, B. Marquet, C. Roze, and F. Ventalon, *J. Fluorine Chem.*, **87**, 215–220 (1998).

98JFC(91)153 V. Suryanarayanan and M. Noel, *J. Fluorine Chem.*, **91**, 153–157 (1998).

98JFC(92)177 V. Suryanarayanon and M. Neol, *J. Fluorine Chem.*, **92**, 177–180 (1998).

98PJ1118 T. Fuchigami, *Pharmacia (Jpn.)*, **34**, 1118 (1998).

98RHC67 T. Fuchigami, S. Higashiya, Y. Hou, and K. M. Dawood, *Rev. Heteroat. Chem.*, **19**, 67–78 (1998); [CA, **130**, 338029 (1999)].

98SL973 Y. Hou, S. Higashiya, and T. Fuchigami, *Synlett*, 973–974 (1998); [CA, **129**, 302460 m (1999)].

99ACS887 A. Konno, W. Naito, and T. Fuchigami, *Acta Chem. Scand.*, **53**, 887–891 (1999); [CA, **132**, 22923z (2000)].

99EC445 Y. Hou and T. Fuchigami, *Electrochem. Commun.*, **1**, 445–448 (1999); [CA, **131**, 357298 (1999)].

99IJC151 M. Sawaguchi, S. Hara, T. Fukuhara, and N. Yoneda, *Isr. J. Chem.*, **39**, 151–154 (1999); [CA, **131**, 286337k (1999)].

99JFC(93)159 K. M. Dawood, S. Higashiya, Y. Hou, and T. Fuchigami, *J. Fluorine Chem.*, **93**, 159–164 (1999).

99JFC(99)189 S. Higashiya, K. M. Dawood, and T. Fuchigami, *J. Fluorine Chem.*, **99**, 189–195 (1999).

99JOC133 S. Higashiya, S. Narizuka, A. Konno, T. Maeda, K. Momota, and T. Fuchigami, *J. Org. Chem.*, **64**, 133–137 (1999).

99JOC138 K. M. Dawood and T. Fuchigami, *J. Org. Chem.*, **64**, 138–143 (1999).

99JOC3346 Y. Hou, S. Higashiya, and T. Fuchigami, *J. Org. Chem.*, **64**, 3346–3349 (1999).

99JOC7935 K. M. Dawood, S. Higashiya, Y. Hou, and T. Fuchigami, *J. Org. Chem.*, **64**, 7935–7939 (1999).

99M12 T. Fuchigami, in *"Advances in Electron Transfer Chemistry"* (P. S. Mariano, ed.), JAI Press, CT, USA (1999).

99M20 T. Fuchigami, in "Advances in Electron-Transfer Chemistry" (P. S. Mariano, ed.), Vol. 6, pp. 41–130, JAI Press, Greenwich, CT (1999); [CA, **130**, 324748 (1999)].

99RHC1 K. Uneyama, *Rev. Heteroatom. Chem.*, **20**, 1–27 (1999).

99TL7819 Y. Hou and T. Fuchigami, *Tetrahedron Lett.*, **40**, 7819–7822 (1999); [CA, **132**, 49739 (2000)].

00JAP(K)160382 N. Okada, H. Yoshimatsu, Y. Tanaka, M. Yoshinaga, and T. Ikeda, Jpn. Kokai. 160382 (2000); [CA, **133**, 23722r (2000)].

00JAP(K)204492 F. Okino, H. Tohara, and R. Hyakuta, Jpn. Kokai. 204492 (2000); [CA, **133**, 95982c (2000)].

00JAP(K)86643 T. Abe and K. Okuhara, Jpn. Kokai. 86643 (2000); [CA, **132**, 222554s (2000)].

00JCS(CC)1617 H. Ishii, N. Yamada, and T. Fuchigami, *J. Chem. Soc. Chem. Commun.*, 1617–1618 (2000); [CA, **133**, 350158y (2000)].

00JFC(105)181 T. Abe, *J. Fluorine Chem.*, **105**, 181 (2000).

00JOC3920 F. C. Gozzo, D. R. Ifa, and M. N. Eberlin, *J. Org. Chem.*, **65**, 3920 (2000).

00JOC8685 M. R. Shaaban, H. Ishii, and T. Fuchigami, *J. Org. Chem.*, **65**, 8685–8689 (2000).

00M7 B. Baasner, H. Hagemann and J. C. Tatlow (eds.), *"Houben Weyl Organofluorine Compounds"*, p. E10, Thieme, Stuttgart (2000).

00M15 G. G. Furin and A. A. Fainzilberg, *"Sovremenie methodi ftorirovaniy organicheskich soedinenii"*, Moscow, Nauka, pp. 1–239 (2000).

00PES2000 T. Fuchigami and Y. Hou, *Proc. Electrochem. Soc.*, 2000–2015 (2000); [CA, **135**, 210737c (2001)].

00SL999 M. Sawaguchi, S. Ayuda, Y. Nakamura, T. Fukuhara, S. Hara, and N. Yonerda, *Synlett*, 999–1000 (2000); [CA, **133**, 251864u (2000)].

00T8877 H. Ishii, Y. Hou, and T. Fuchigami, *Tetrahedron*, **56**, 8877–8881 (2000); [CA, **134**, 131240 (2001)].

00TL273 M. R. Shaaban and T. Fuchigami, *Tetrahedron Lett.*, **43**, 273–276 (2000).

00USP6110976 J. C. Hansen, G. G. I. Moore, S. D. Polson, P. M. Sowu, and R. M. Stern, US Pat. 6110976 (2000).

01EC467 T. Tajima, H. Ishii, and T. Fuchigami, *Electrochem. Commun.*, **3**, 467–471 (2001); [CA, 135, 303741q (2001)].

01JFC(1 1 1)21 T. Abe, H. Dada, K. Okuhara, and H. Fukaya, *J. Fluorine Chem.*, **111**, 115–128 (2001).

01JOC5633 M. R. Shaaban, H. Ishii, and T. Fuchigami, *J. Org. Chem.*, **66**, 5633–5636 (2001).

01JOC7020 D. Baba, H. Ishii, S. Higashiya, K. Fujisawa, and T. Fuchigami, *J. Org. Chem.*, **66**, 7020–7024 (2001).

01JOC7030 K. M. Dawood, H. Ishii, and T. Fuchigami, *J. Org. Chem.*, **66**, 7030–7034 (2001).

01JOC7691 K. M. Dawood and T. Fuchigami, *J. Org. Chem.*, **66**, 7691–7695 (2001).

01M13 G. G. Furin, *"Fluorine-Containing Heterocyclic Compounds. Synthesis and Application"*, Nauka, Novosibirsk, pp. 1–304 (2001).

01M19 T. Fuchigami, *"Organic Electrochemistry"* (H. Lund and O. Hammerich, eds.), 4th edn., Chapter 26, pp. 1035–1050, Marcel Dekker, New York (2001); [CA, **134**, 358728 (2001)].

01M23 T. Fuchigami, in *"Organic Electrochemistry"* (H. Lund and O. Hammerich, eds.), 4th edn., Chapter 26, Marcel Dekker, New York (2001).

01M25 T. Nonaka and T. Fuchigami, *"Organic Electrochem"* (H. Lund and O. Hammerrich, eds.), 4th edn., pp. 1051–1102, Marcel Dekker, Inc., New York, NY (2001); [CA, **134**, 352990 (2001)].

01PES25 M. Sawaguchi, T. Fukuhara, S. Hara, and N. Yoneda, *Proceedings of Electrochemical Society*, pp. 25–28 (2001-14); [CA, **136**, 385701 (2003)].

01PES33 T. Fuchigami, D. Baba, and H. Ishii, *Proc. Electrochem. Soc.*, **14**, 33–36 (2001); [CA, **136**, 369643 (2003)].

01SL1269 T. Fuchigami, M. Tetsu, T. Tajima, and H. Ishii, *Synlett*, 1269–1271 (2001); [CA, **135**, 318361 (2001)].

01SL1644 M. R. Shaaban and T. Fuchigami, *Synlett*, 1644–1646 (2001); [CA, **136**, 167339 (2003)].

01SL1938 S. Kobayashi, M. Sawaguchi, S. Ayuba, T. Fukuhara, and S. Hara, *Synlett*, 1938–1940 (2001).

01T8817 S. M. Riyadh, H. Ishii, and T. Fuchigami, *Tetrahedron*, **57**, 8817–8821 (2001); *Tetrahedron*, **58**(45). 9273–9278 (2002).

01T9067 H. Ishii, N. Yamada, and T. Fuchigami, *Tetrahedron*, **57**, 9067–9072 (2001).

01TL2513 K. M. Dawood and T. Fuchigami, *Tetrahedron Lett.*, **42**, 2513–2515 (2001).

01TL4857 T. Tajima, H. Ishii, and T. Fuchigami, *Tetrahedron Lett.*, **42**, 4857–4860 (2001).

01TL4861 K. Suzuki, H. Ishii, and T. Fuchigami, *Tetrahedron Lett.*, **42**, 4861–4863 (2001).

02JFC(115)21 D. Velayutham, K. Jayaraman, M. Noel, S. Krishnamoorthy, and P. Sartori, *J. Fluorine Chem.*, **115**, 21–26 (2002).

02JOC9379 S. M. Riyadh and T. Fuchigami, *J. Org. Chem.*, **67**, 9379–9383 (2002).

02H623 N. Iwayasu, M. R. Shaaban, and T. Fuchigami, *Heterocycles*, **54**, 623–629 (2002); [CA, **137**, 207757 (2003)].

02S2597 T. Tajima and T. Fuchigami, *Synthesis*, 2597–2600 (2002); [CA, **138**, 304117 (2003)].

02T9273 S. M. Riyadh, H. Ishii, and T. Fuchigami, *Tetrahedron*, **58**, 9273–9278 (2002).
02TL1503 M. Hasegawa, H. Ishii, and T. Fuchigami, *Tetrahedron Lett.*, **43**, 1503–1505 (2002).
02TL4805 D. Baba and T. Fuchigami, *Tetrahedron Lett*, **43**, 4805–4808 (2002).
02YOKK42 K. Momota, *Yoyuen Oyobi Koon Kagaku*, **45**, 42–60 (2002); [CA, **136**, 408044 (2003)].
03FN G. G. Furin, *Fluorine Notes*. 2003. Vol. 26 (online computer file); [CA, **139**, 139895 (2003)].
03GC512 M. Hasegawa, H. Ishii, and T. Fuchigami, *Green Chem.*, **5**, 512–515 (2003).
03H15 S. M. Riyadh and T. Fuchigami, *Heterocycles*, **60**, 15–22 (2003); [CA, **138**, 401644 (2003)].
03JAP(K)073874 R. Udagawa, Jpn. Kokai. 2003073874 (2003); [CA, **138**, 211893 (2003)].
03JAP(K)2003277367 T. Abe and H. Fukaya, Jpn. Kokai. 2003277367 (2003); [CA, **139**, 261332 (2003)].
03JAP(K)3137867 A. Udagawa, Jpn. Kokai. 2003137867 (2003); [CA, **138**, 368673 (2003)].
03JFC(121)93 D. Baba, Y. -J. Yang, B. -J. Uang, and T. Fuchigami, *J. Fluorine Chem.*, **121**, 93–96 (2003).
04JFC(125)7 N. Yoneda, *J. Fluorine Chem.*, **125**, 7–17 (2004).
04JFC(125)139 L. Conte and G. Gambaretto, *J. Fluorine Chem.*, **125**, 139–144 (2004).
04JOC1276 K. Suzuki and T. Fuchigami, *J. Org. Chem.*, **69**, 1276–1282 (2004).

Cumulative Index of Authors, Volumes 1–90

Cumulative Index of Titles, Volumes 1–90

A

B

C

D

E

F

G

H

I

L

M

N

O

P

Q

R

S

T

U

V

Subject Index of Volume 90