Synthesis of aromatic heterocycles

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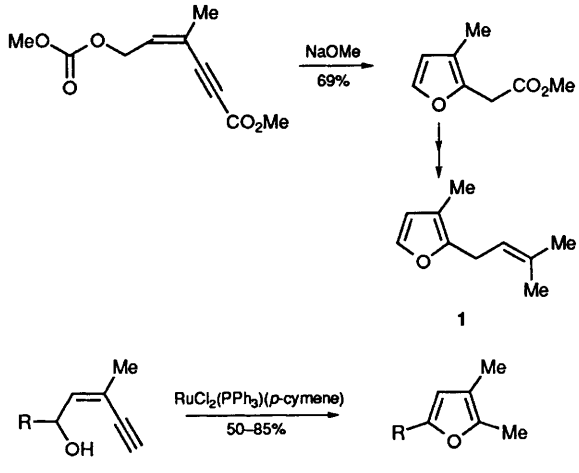
Reviewing the literature published between July 1993 and February 1995
Continuing the coverage in *Contemporary Organic Synthesis*, 1994, **1**, 205

1 Introduction

This is the second general survey in *Contemporary Organic Synthesis* of new and improved methods for the preparation of aromatic heterocycles. The first review[1] covered only five-membered aromatic heterocycles but this one also includes six-membered ring systems. As before, the methods discussed are those in which aromatic rings are produced from acyclic precursors or by ring interconversion; syntheses which involve functional group transformations on the existing ring system are excluded. Only the more common monocyclic and bicyclic ring systems are discussed systematically.

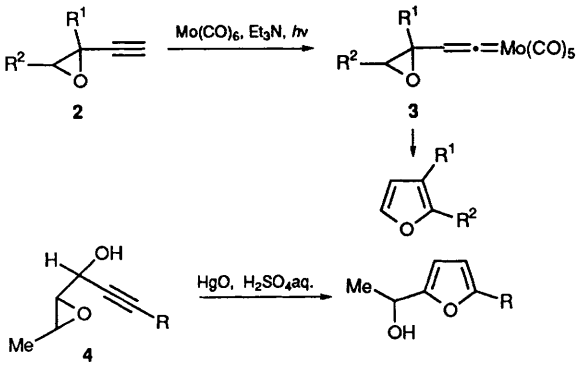
2 Furans and benzofurans

There have been further examples of the synthesis of furans by the intramolecular addition of an alkoxide anion to a carbon–carbon triple bond.[2–5] Marshall and co-workers have described a synthesis of 2,3-disubstituted furans by this method: an example is shown in **Scheme 1**.[2] This method provided a route to rosefuran (**1**). The related ruthenium-catalysed cyclization shown in **Scheme 1** is restricted to terminal alkynes. An intramolecular nucleophilic addition to a coordinated triple bond was proposed.[5]

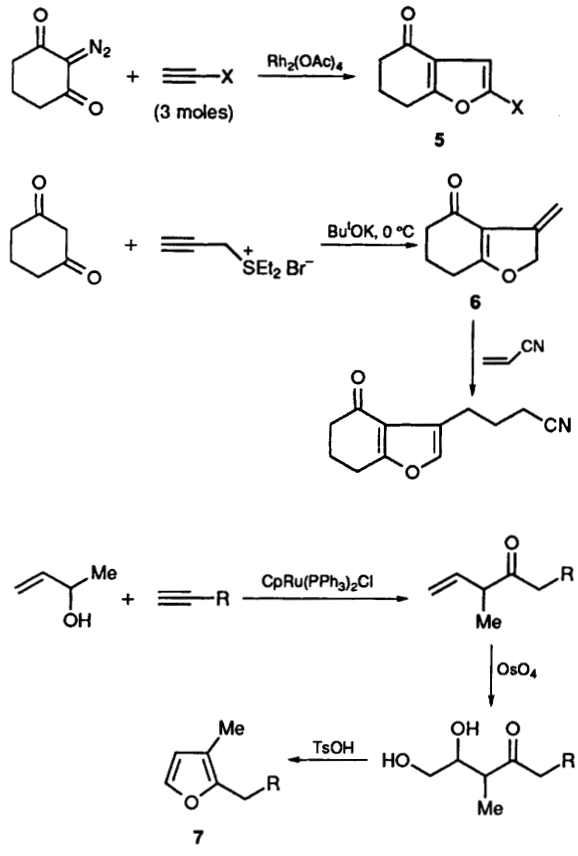


Scheme 1

The ring expansion of alkynyloxiranes **2** to 2,3-disubstituted furans has been achieved by irradiation in the presence of molybdenum hexacarbonyl and triethylamine; the molybdenum complex **3** has been suggested as an intermediate (**Scheme 2**).[6] The mercury(II)-catalysed hydration of the triple bond of the oxiranes **4** provides a new synthesis of 2,5-disubstituted furans.[7]



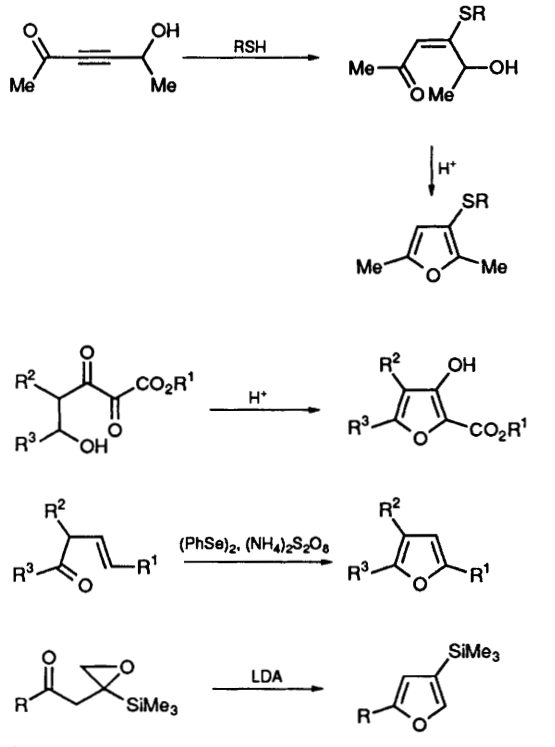
Scheme 2



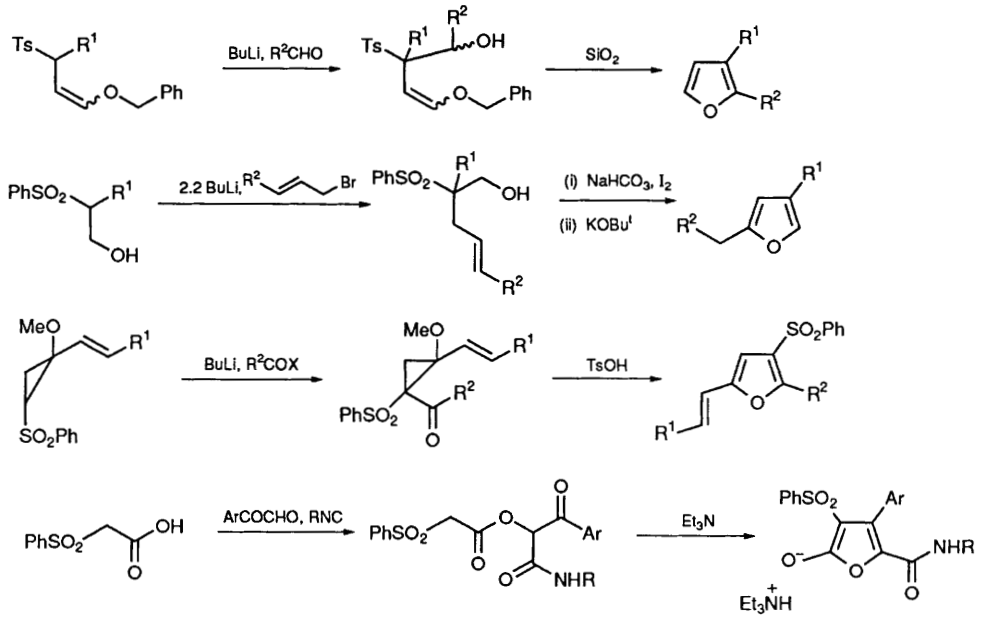
Scheme 3

Several useful furan syntheses which involve intermolecular addition reactions of alkynes are illustrated in **Scheme 3**. The rhodium carbenoid derived from 2-diazocyclohexane-1,3-dione reacts with a range of acetylenes (X = OEt, $SiMe_3$, CO_2Me, COMe, 1-pyrrolyl) to give the furans **5** in moderate to good yield.[8] Cyclohexane-1,3-dione is used as the precursor to the 3-methylene-dihydrofuran **6**, which can be isolated but which reacts readily with enophiles such as acrylonitrile (as shown) and diethyl azodicarboxylate to give 3-substituted furans.[9] The synthetic method for 2-alkyl-3-methylfurans **7** shown was also used as a route to rosefuran (**1**).[10]

The new furan syntheses shown in **Scheme 4** all make use of the arenesulfonyl group to activate an adjacent C–H bond and thereby to provide a route to an intermediate suitable for cyclization.[11–14] New



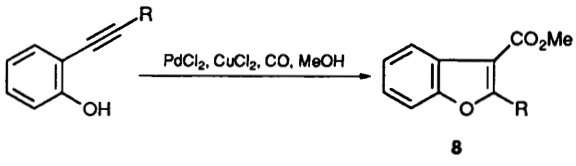
Scheme 5



Scheme 4

methods for the construction of hydroxyenones suitable for cyclization to furans[15,16] include the addition of sulfur nucleophiles to 5-hydroxyhex-3-yn-2-one (**Scheme 5**).[16] Three other cyclization reactions which lead to the formation of furans in good yield are also shown in **Scheme 5**.[17–19] A short and efficient synthesis of furan-3-carboxaldehyde from (*Z*)-but-2-ene-1,4-diol has been described[20] and 3,4-bis(trimethylsilyl)furan has been prepared in good yield by cycloaddition of bis(trimethylsilyl)-acetylene to 4-phenyloxazole.[21]

The *endo* cyclization of 2-alkynylphenols is an established route to benzofurans, but some new variants of the method have been described.[22,23] The carbonylative cyclization illustrated in **Scheme 6** leads to methyl benzofuran-3-carboxylates **8**,[23] the same method has been used to prepare the analogous indole esters.



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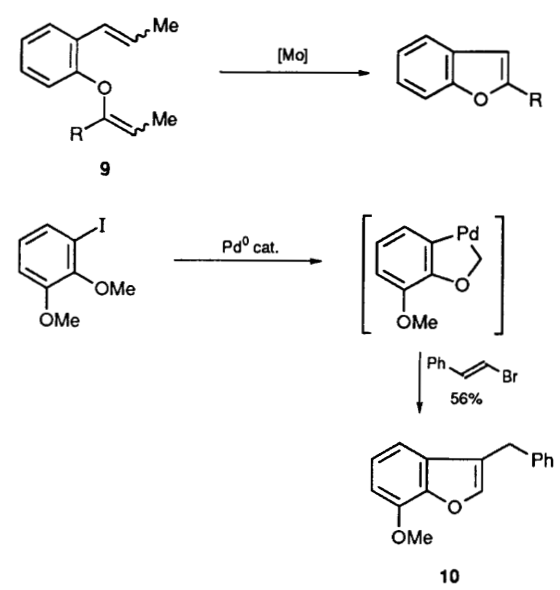
Scheme 6

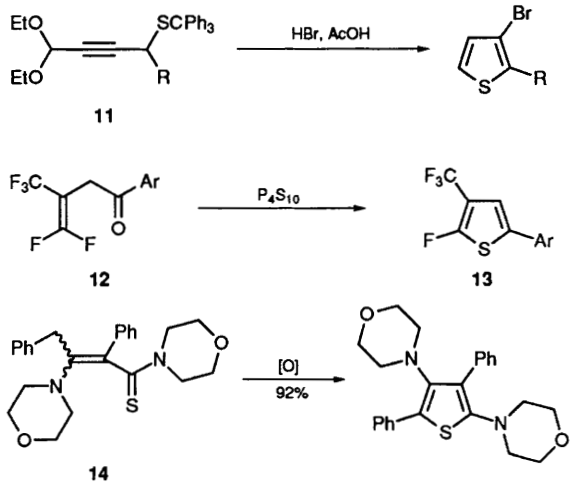
An unusual method for the preparation of benzofurans is the metathesis of aryl enol ethers **9** in the presence of a molybdenum alkylidene complex (**Scheme 7**).[24] 2-Benzylbenzofuran and 2-arylbenzofurans were prepared in high yield in this way. Another mechanistically interesting route, also illustrated in **Scheme 7**, is based on the palladium(0)-catalysed activation of methoxy groups. Thus, 3-benzyl-7-methoxybenzofuran **10** was prepared (56%) from 2,3-dimethoxyiodobenzene and β-bromostyrene.[25]



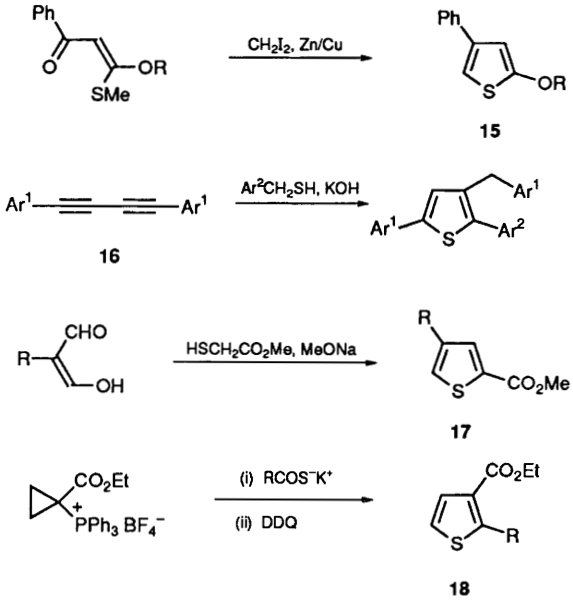
Scheme 7

3 Thiophenes and benzothiophenes

There are several new methods for the preparation of thiophenes bearing specific substituents, and in which the five-membered ring is constructed from an acyclic precursor by the formation of a C–S bond (**Scheme 8**). A range of 3-bromothiophenes has been prepared by the addition of hydrogen bromide and deprotection of trityl sulfides such as **11**.[26] The ketones **12**, which are prepared from hexafluoroacetone, react with phosphorus pentasulfide to give the thiophenes **13**. The 2-fluoro substituent can be displaced by nucleophiles, thus providing a route to other 3-trifluoromethyl-thiophenes.[27] 2,4-Dimorpholino-3,5-diphenylthiophene, a rare example of a 2,4-diaminothiophene, was prepared in high yield by oxidation of the thioacrylmorpholide **14**.[28]



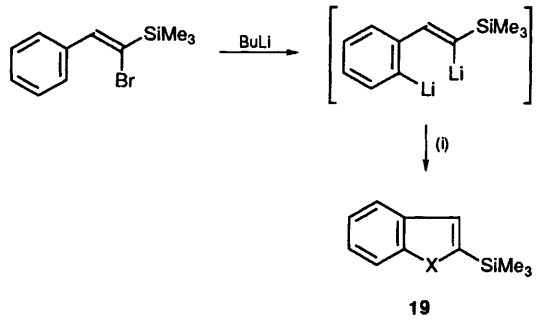
Scheme 8



Scheme 9

Some examples of the preparation of thiophenes by carbon–carbon bond formation are shown in **Scheme 9**. 2-Alkoxythiophenes and 2-aryloxythiophenes **15** have been prepared from acylketene *O,S*-acetals by reaction with diiodomethane and zinc–copper couple.[29] The addition of benzylthiols to diaryldiynes **16** has been used to prepare terthiophenes and other 2,5-diarylthiophenes.[30] Methods for the preparation of esters **17** and **18** of thiophene-2- and 3-carboxylic acids are also illustrated.[31,32]

A general method has been described for the synthesis of 2-trimethylsilylbenzothiophene **19** (X = S) and other benzo fused heterocycles, including those with X = Se and X = Te. The method, outlined in **Scheme 10**, is based on a directed *ortho* lithiation reaction.[33] Benzothiophenes have also been constructed from halobenzenes by palladium(0)-catalysed cyclization[34] and by generation and cyclization of aryl radicals[35] (**Scheme 11**). A synthesis of 3-chlorobenzothiophenes has been described starting from alkynylbenzenes; their 1:1 adducts with phthalimidosulfenyl chloride are cyclized by reaction with aluminium chloride.[36]



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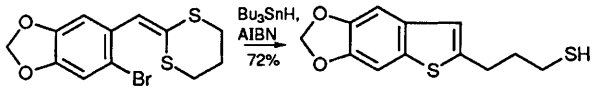
Reagent: (i) X = S; $(PhSO_2)_2S$ (62%); X = Se; red Se (67%)

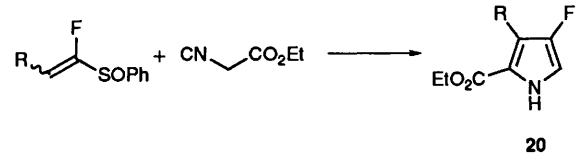
Scheme 10



Scheme 11

4 Pyrroles

Activated isocyanides are useful starting materials for the preparation of pyrroles with specific substitution patterns. There are several new examples of the synthesis of pyrroles by conjugate addition of carbanions, derived from isocyanides, to conjugated alkenes.[37–39] The reaction between ethyl isocyanoacetate and α-fluorovinyl sulfoxides, which leads to β-fluoropyrroles **20** in moderate yield, is shown in **Scheme 12**.[39] This is one of several methods of pyrrole ring synthesis which have been applied to the preparation of β-fluoropyrroles,[40–42] and which include the first synthesis of 3,4-difluoropyrrole.[41]



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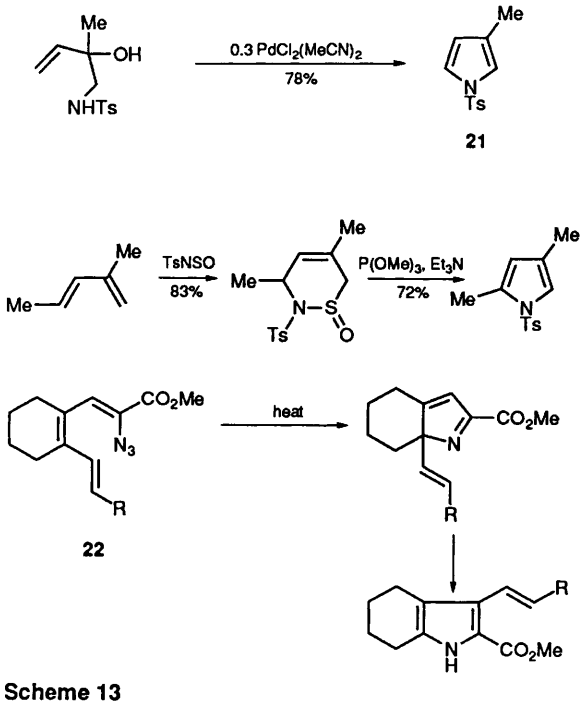
Scheme 12

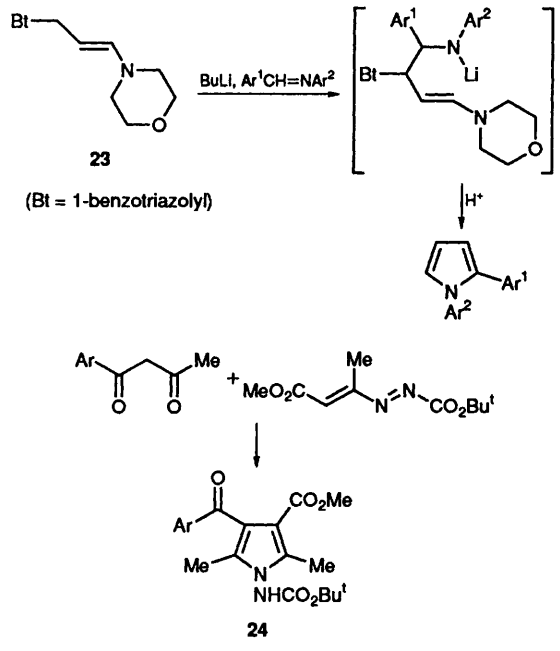
Cyclization reactions which lead to pyrroles by formation of a nitrogen to carbon bond are illustrated in **Scheme 13**. The palladium-catalysed cyclization leading to 3-methyl-1-tosylpyrrole **21** and to other *N*-tosylpyrroles is initiated by coordination of palladium(II) to the double bond.[43] *N*-Tosylpyrroles can also be prepared by the cycloaddition of dienes to *N*-tosylsufinylamine followed by base-catalysed ring contraction of the cycloadduct; the efficiency of the ring contraction step is significantly improved by using trimethyl phosphite as a co-reagent.[44] The cyclization of the 2-azidoacrylates **22** resembles the well established route to indole-2-carboxylic esters from alkyl α-azidocinnamates.[45]



Scheme 13

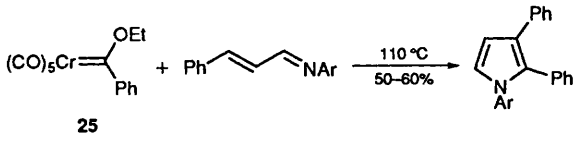
Further examples of the preparation of pyrroles by formation of C–N bonds are illustrated in **Scheme 14**. 1-Substituted benzotriazoles are proving to be useful starting materials for the preparation of a variety of aromatic heterocycles. Examples of their use for the preparation of 2-arylpyrroles[46] and of 1,2-diarylpyrroles[47] have been described. The route to 1,2-diarylpyrroles from the enamine **23** (which is prepared from benzotriazole, acrolein, and morpholine) is shown in **Scheme 14**. There are also

further examples of the preparation of *N*-aminopyrroles from azoalkenes by the addition of activated methylene compounds;[48,49] a route to benzoylpyrroles **24** is shown.[49] The useful method of synthesis of pyrroles from ketoximes and alkynes, which proceeds by a [3,3]-sigmatropic rearrangement of *O*-vinylketoximes followed by cyclization, has been reviewed.[50]

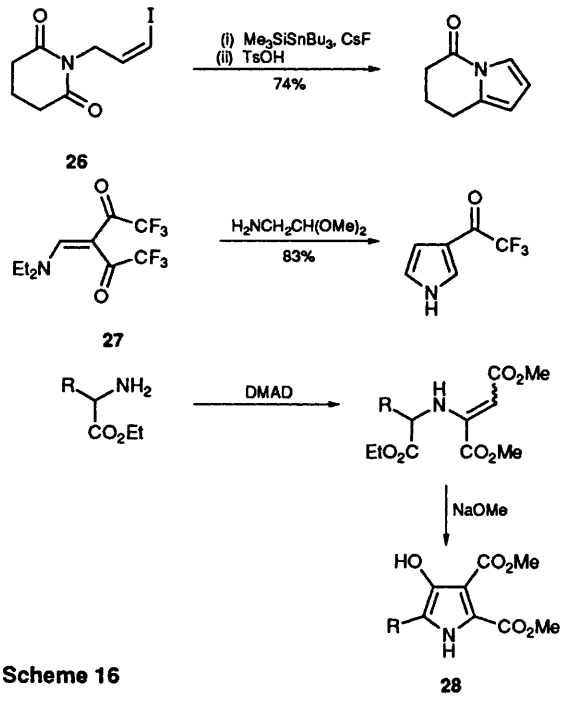


Scheme 14

Pentacarbonylchromium carbene complexes have been used as starting materials for the preparation of several 1,2-diarylpyrroles.[51,52] The preparation of 1-aryl-2,3-triphenylpyrroles from the complex **25** and Schiff bases of cinnamaldehyde is shown in **Scheme 15**.[52] Some cyclization reactions which provide efficient routes to pyrroles of specific types are illustrated in **Scheme 16**. The cyclization of the imide **26** (and of its five-membered ring analogue) is brought about by reaction with tributyltrimethylsilylstannane and caesium fluoride, which in effect provide a source of the tributylstannyl anion.[53] The enaminoketone **27** has proved to be a useful reagent for the preparation of a variety of aromatic heterocycles; its reaction with aminoacetaldehyde dimethyl acetal provided a good route to 3-trifluoroacetylpyrrole.[54] The diesters **28** were prepared in good yield from α-amino carboxylic esters and DMAD.[55] 2-Hydroxypyrroles have been prepared from phenylglyoxal by a reaction sequence analogous to that shown for hydroxyfurans in **Scheme 4**.[56]

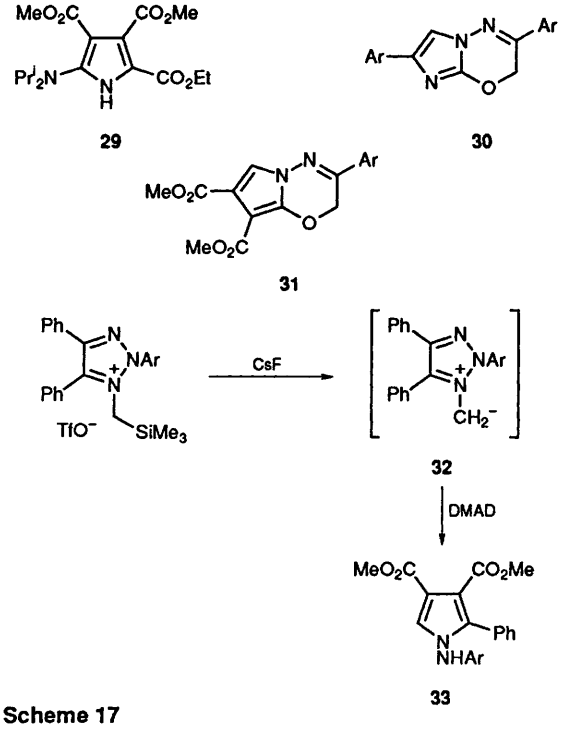


Scheme 15



Scheme 16

Dimethyl pyrrole-3,4-dicarboxylates are often most readily prepared from DMAD by Diels–Alder reaction with oxazoles or by a 1,3-dipolar cycloaddition reaction. The former method has been used to prepare the aminopyrrole **29** by the interception of a transient oxazole in solution.[57] Analogous cycloaddition reactions of imidazoles are much more difficult to achieve but the bicyclic imidazoles **30** have been shown to give the pyrroles **31** in high yield with DMAD.[58] The transient



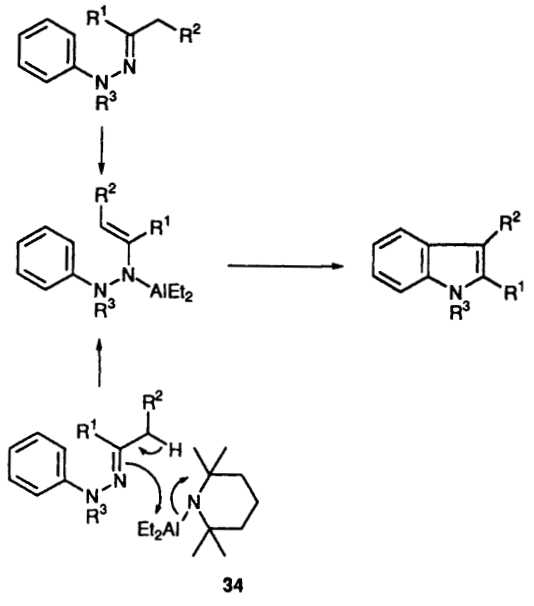
Scheme 17

triazolium ylides **32**, which are generated as shown in **Scheme 17**, react with DMAD to give the pyrrole diesters **33**.[59]

5 Indoles

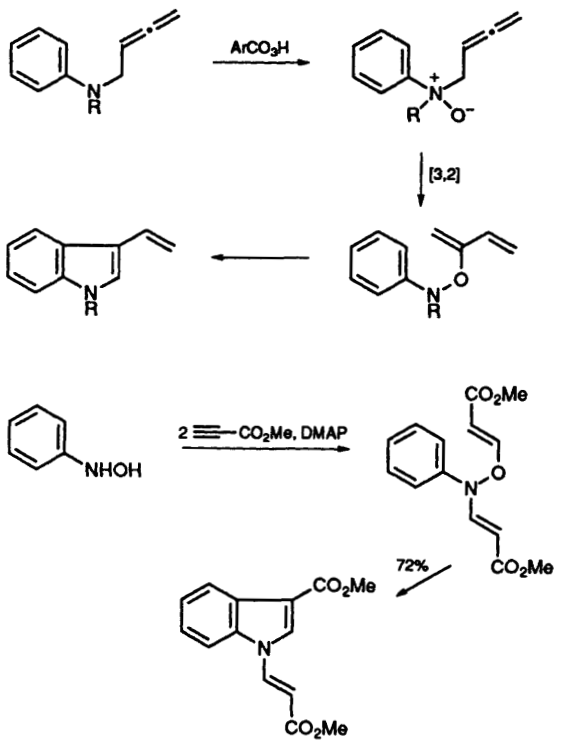
Methods for the synthesis of indoles have been reviewed separately in this journal.[60]

The Fischer indole synthesis still represents the best method for the preparation of many indole derivatives. Recent progress in the use of the method has been reviewed[61] and the reaction has been used to prepare *N,N*-dimethyltryptamines[62] and analogues of sumatriptan, used in the treatment of migraine.[63] Organoaluminium amides such as **34** are effective catalysts for the Fischer indole synthesis and they enable indoles to be prepared regioselectively from ketone arylhydrazones.[64] These catalysts control the regioselectivity by abstracting a proton from an α-methylene group *anti* to the hydrazone, as shown in **Scheme 18**. The stereochemistry of the starting hydrazone thus controls which indole will be formed when two are possible.



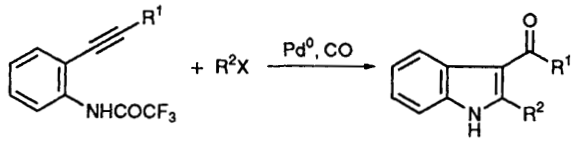
Scheme 18

Two related indole syntheses, which are postulated to go by sigmatropic rearrangement of *N*-aryl-*O*-vinylhydroxylamines, are shown in **Scheme 19**.[65,66] Further examples of the construction of indoles from ketone *N*-arylimines by way of aryne intermediates have been described[67] and details have been published[68] of the zirconium-catalysed cyclization of 2-bromo-*N*-allylanilines, which provides a useful route to 3,4-disubstituted indoles.[60]

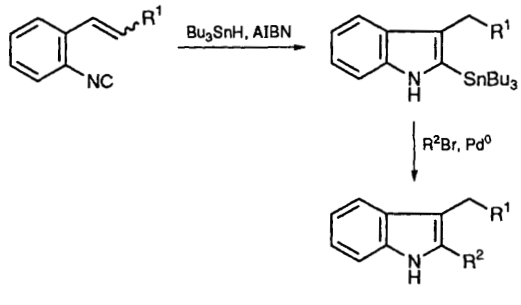


Scheme 19

The Heck reaction of 2-iodoaniline derivatives and alkenes or alkynes provides a good route to 3-substituted indoles. Recent examples of the method include the synthesis of indole-3-acetic acid derivatives,[69] tryptophan esters,[70] and 3-alkylindoles.[71] Palladium-catalysed carbonylative cyclizations of 2-alkynylaniline derivatives have been used for the preparation of 2-substituted 3-acylindoles, as shown in **Scheme 20**,[72] and 2-substituted indole-3-carboxylic esters by a reaction sequence analogous to that shown in **Scheme 6** for



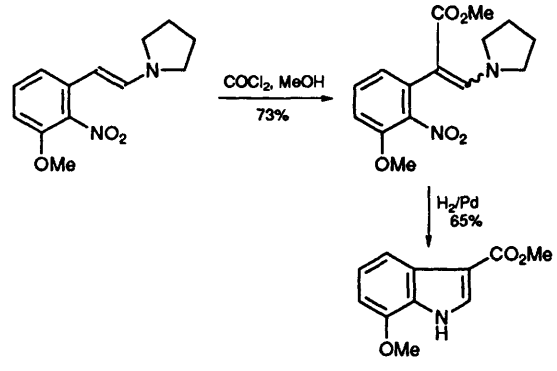
Scheme 20



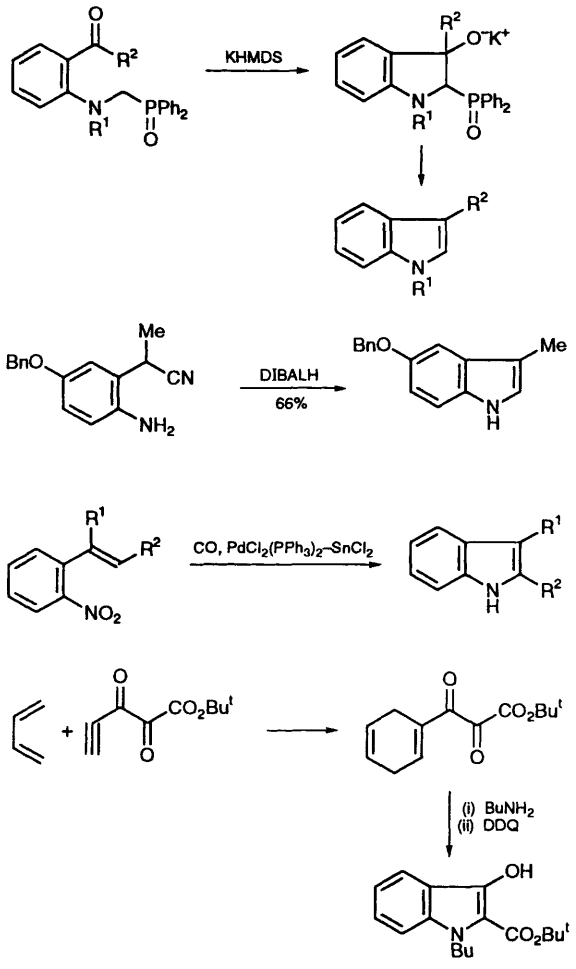
Scheme 21

the corresponding benzofurans.[23] A radical cyclization and palladium coupling sequence which leads to 2,3-disubstituted indoles is shown in **Scheme 21**.[73] The 2-tributylstannylindoles formed by cyclization are used as partners in a palladium(0) coupling reactions to provide the final products in good yield.

The intramolecular McMurry coupling procedure for the preparation of 2,3-disubstituted indoles which was described in the previous review[1] has been extended and the yields have been improved by using an active titanium catalyst prepared *in situ*.[74] The Leimgruber–Batcho indole synthesis has also been extended by methoxycarbonylation of the enamine precursor before reductive ring closure (**Scheme 22**).[75]



Scheme 22

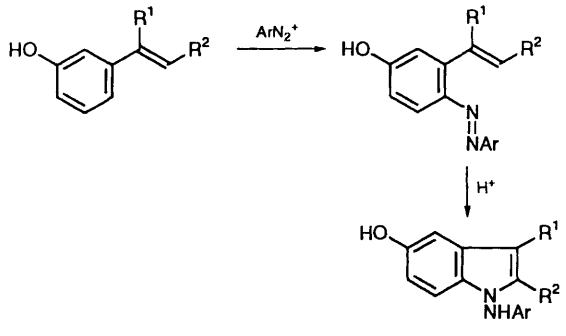


Scheme 23

Some other cyclization routes to indoles are outlined in **Scheme 23**. An intramolecular Horner–Wittig method has been described for the preparation of *N*-alkylindoles with substituents at the 3-position.[76] Marino and Hurt have shown that diisobutylaluminium hydride acts both as a selective method for the reduction of a cyano group to an imine and as a Lewis acid in a preparation of 5-alkoxy-3-methylindoles.[77] The catalyst $PdCl_2(PPh_3)_2$–$SnCl_2$ allows the reductive cyclization of 2-nitrostyrenes to indoles to be carried out in relatively mild conditions.[78] A new indole synthesis makes use of a Diels–Alder reaction to construct the six-membered ring and a cyclization of a vicinal tricarbonyl compound to produce the five-membered ring.[79]

A route to 5-hydroxyindoles has been described starting from 3-hydroxystyrenes;[80,81] they react with arenediazonium salts and cyclize to give 1-arylamino-5-hydroxyindoles **35** in good yield (**Scheme 24**). The arylamino group can be removed by reduction using Raney nickel.

The cycloaddition of the osmium complexed 3-isopropenylpyrrole **36** to *N*-phenylmaleimide proceeds in good yield and the indole **37** is isolated after oxidation of the intermediate cycloadduct.[82] Moody and co-workers have provided further



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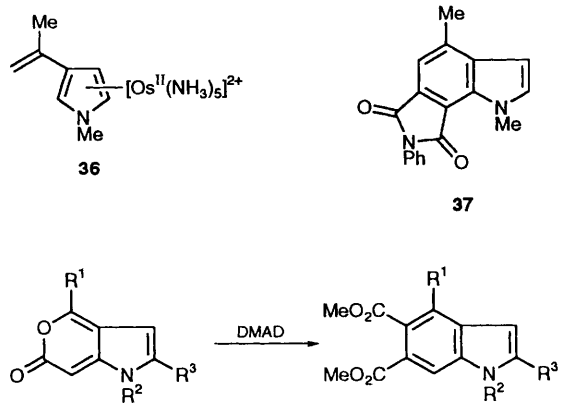
Scheme 24

examples of the synthesis of indoles by cycloaddition of activated acetylenes to pyranopyrrolones (**Scheme 25**).[83]

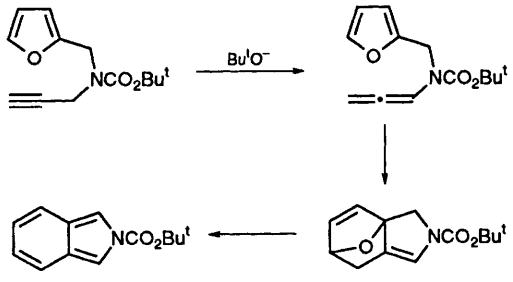
6 Other fused pyrroles

A new method for the generation of *N*-t-butoxycarbonylisoindole **38** by intramolecular



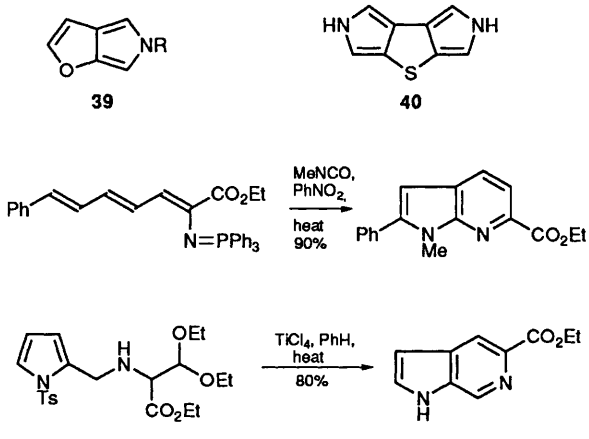
Scheme 25

cycloaddition is outlined in **Scheme 26**.[84] The isoindole was intercepted by Diels–Alder cycloaddition to *N*-phenylmaleimide and to other dienophiles.



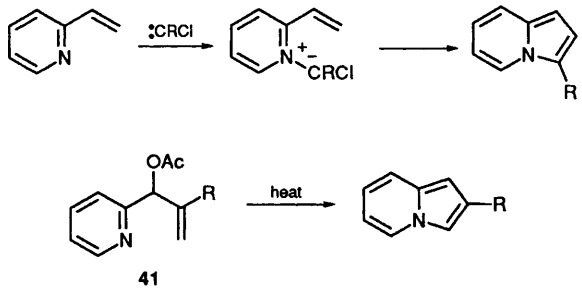
Scheme 26

Details of the preparation of *N*-substituted furo[2,3-*c*]pyrroles **39**[85] and of thieno[2,3-*c*:4,5-*c'*]dipyrrole **40**[86] from furan and thiophene precursors have been published. Two high yielding preparations of pyrrolopyridines are outlined in **Scheme 27**.[87,88]



Scheme 27

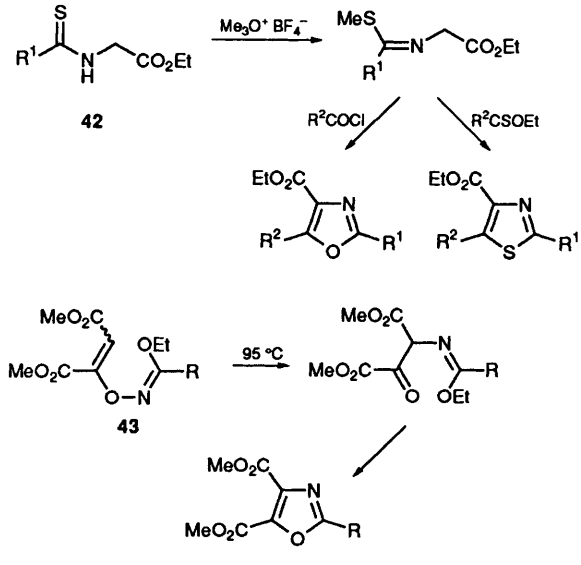
3-Substituted indolizines have been prepared by the generation of chlorocarbenes in the presence of 2-vinylpyridine. The reaction is envisaged to proceed by cyclization of intermediate pyridinium ylides followed by dehydrochlorination (**Scheme 28**).[89] Indolizines are more commonly prepared by intermolecular cycloaddition of pyridinium ylides to olefinic dipolarophiles followed by oxidation of the adducts. It has been found that indolizines are obtained in good yield if the cycloaddition is carried out in the presence of the oxidant tetrapyridine-cobalt(II) dichromate.[90] The generality of a previously reported preparation of indolizines by thermal cyclization of 2-substituted pyridines **41** has been investigated.[91]



Scheme 28

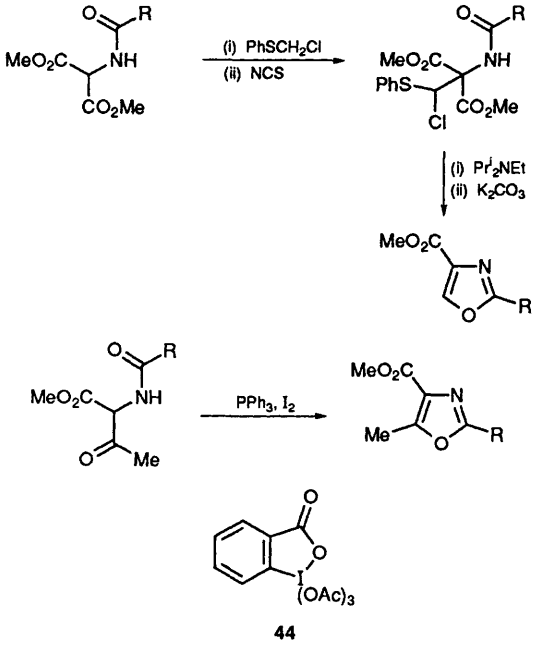
7 Oxazoles, thiazoles, benzoxazoles, and benzothiazoles

A synthesis of oxazole-and thiazole-4-carboxylic acid esters in good yield from the thioamide **42** is shown in **Scheme 29**.[92] 2-Substituted oxazole-4,5-dicarboxylic esters have been prepared by thermal rearrangement of the imidates **43**.[93]



Scheme 29

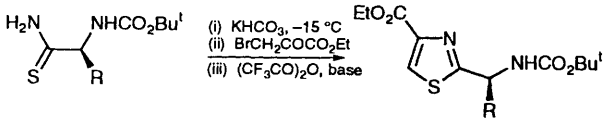
Two methods for the preparation of oxazoles based on the use of acylaminomalonate esters[94] or acylamino-β-ketoesters[95] are illustrated in **Scheme 30**. The latter were generated by oxidation of the corresponding β-hydroxyamides and the Dess–Martin periodinane **44** was found to be the most efficient oxidant for this purpose. Further examples of the preparation of oxazoles by the rhodium(II)-catalysed reaction of diazocarbonyl compounds with nitriles have been reported.[57,96,97]



44

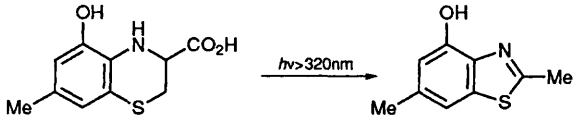
Scheme 30

2,4-Disubstituted 4,5-dihydrooxazoles can be prepared in high yield by sodium iodide catalysed ring expansion of *N*-acylaziridines; the dihydrooxazoles can be aromatized by oxidation using nickel perodixe.[98] The oxidation of dihydrooxazoles and dihydrothiazoles bearing chiral substituents at C-2 by t-butyl perbenzoate and copper(I) bromide proceeds in good yield when copper(II)acetate is added as co-catalyst.[99] The conditions have also been defined which enable thiazoles with chiral substituents at C-2 to be synthesized by a modified Hantzsch procedure without racemization (**Scheme 31**).[100]



Scheme 31

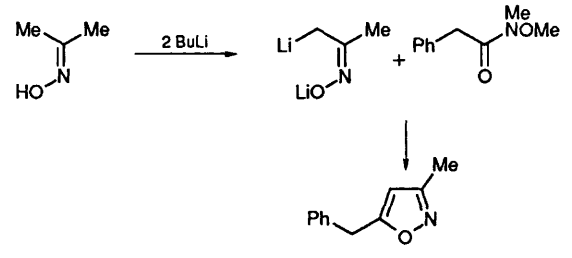
2-Arylbenzothiazoles have been prepared in one pot from 2-aminothiophenol by reaction with sodium hydride (4 moles) and an aromatic nitrile[101] and by reaction with an aryl iodide and carbon monoxide in the presence of a palladium(0) catalyst.[102] Benzothiazoles have also been produced in good yield by photochemical ring contraction of dihydrobenzothiazine-3-carboxylic acids: an example is shown in **Scheme 32**.[103]



Scheme 32

8 Isoxazoles, isothiazoles, isoselenazoles, and fused analogues

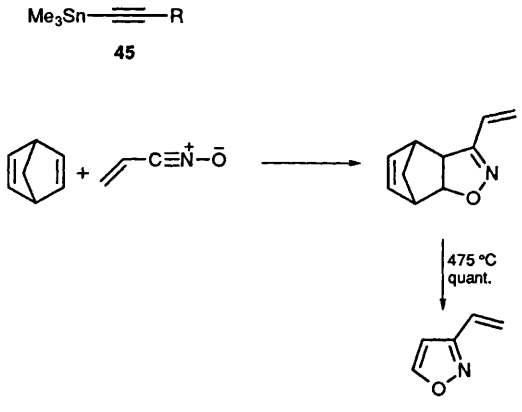
The acylation of oxime dianions, already known as a method for the preparation of 5-arylisoxazoles, has now been applied to the preparation of 5-alkylisoxazoles. Both *N*-methoxy-*N*-alkylamides and aliphatic carboxylic esters have been used as the acylating agents. Most of the preparations reported started from either acetone oxime or cyclohexanone oxime; an example of a preparation from acetone oxime is shown in **Scheme 33**.[104]



Scheme 33

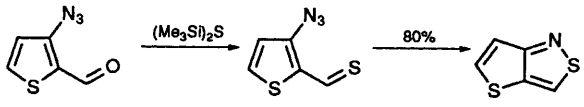
The diplar cycloaddition of trimethylstannyl-acetylenes **45** to nitrile oxides gives 4-trimethyl-stannylisoxazoles, with the exception of ethynyltrimethylstannane which gives 5-trimethyl-stannylisoxazoles.[105] The regiochemistry is consistent with the predictions of FMO theory. A route to 3-vinylisoxazole which is based on a dipolar cycloaddition and retro Diels–Alder reaction sequence is outlined in **Scheme 34**.[106]

3-Bromoisoxazoles can be prepared by dipolar cycloaddition of bromonitrile oxide to alkynes and it has now been shown that even unactivated alkynes will give isoxazoles in acceptable yield, but with little regioselectivity, if the reaction is carried out in the presence of potassium fluoride dihydrate.[107] A pH below 5 is maintained during the reaction and this seems to be necessary for the cycloaddition to take place. The cyclization of *ortho*-substituted aromatic azides provides a useful route to several fused five-membered heterocycles. The reaction has now been



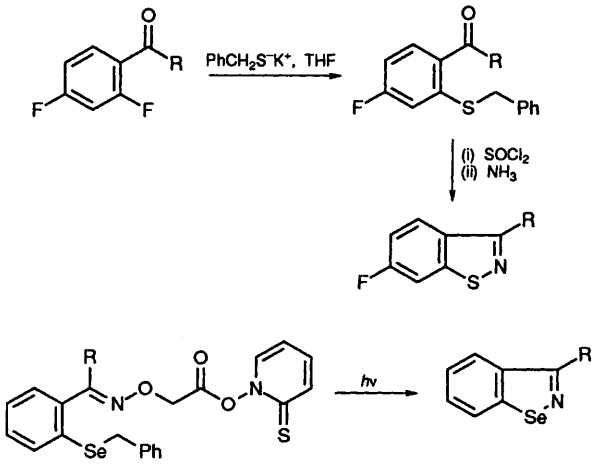
Scheme 34

used for the preparation of thieno[3,2-*c*]-isothiazole (**Scheme 35**);[108] several other fused isothiazoles were synthesized in a similar way.



Scheme 35

New routes to 6-fluorobenzisothiazoles[109] and to benzisoselenazoles[110] are shown in **Scheme 36**; the radical cyclization leading to benzisoselenazoles is claimed to be an effective alternative to existing methods for the preparation of this ring system.

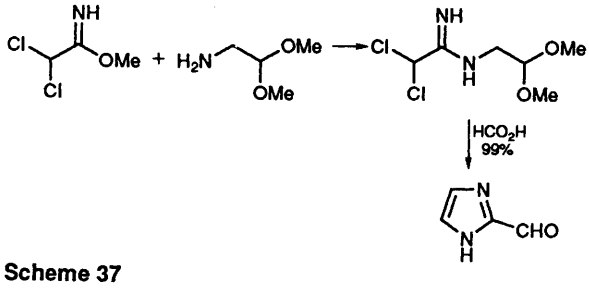


Scheme 36

9 Imidazoles and benzimidazoles

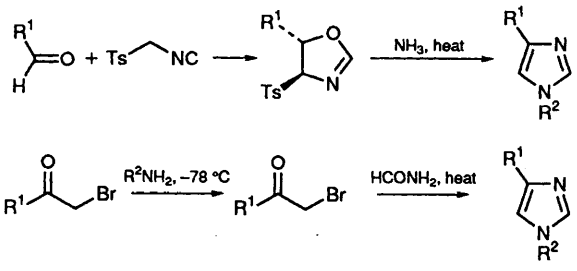
An improved procedure for the synthesis of imidazole from glyoxal, formaldehyde, and ammonium chloride has been described.[111] The pH of the reaction medium is 0–1 and this is an essential feature of the procedure.

1-Alkylimidazoles were prepared in moderate yield by an analogous method from the corresponding alkylamines. Several other new or improved procedures for the preparation of specifically substituted imidazoles have been described. An improved route to imidazole-2-carboxaldehyde is shown in **Scheme 37** and similar procedures were used to prepare imidazole-2-carboxylic acid and its ethyl ester in good yield.[112]

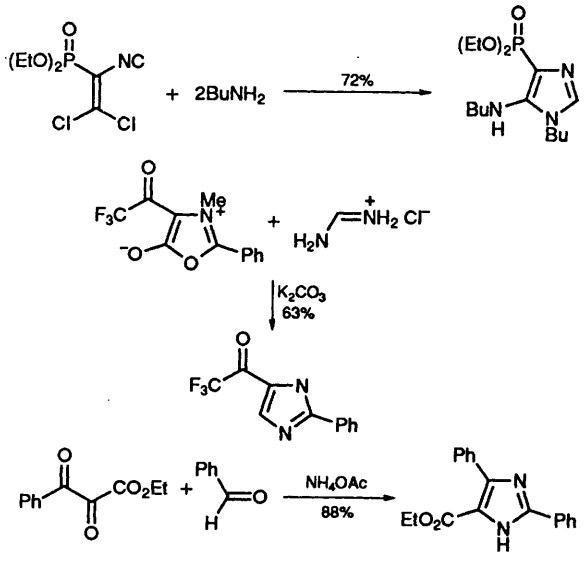


Scheme 37

Two methods for the preparation of 1,4-disubstituted imidazoles are illustrated in **Scheme 38**;[113,114] both procedures can also be used for the synthesis of 4-alkylimidazoles. A new procedure related to the second method of **Scheme 38** has been described for the preparation of 2-aminoimidazoles; this involves the condensation of α-haloketones with *N*-acetylguanidine.[115]

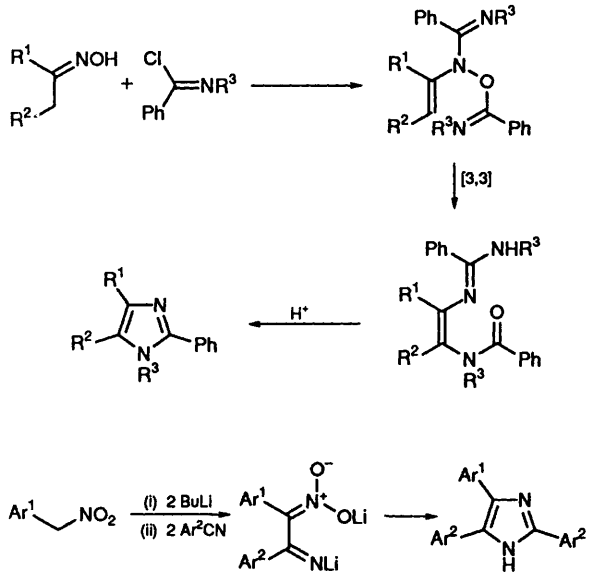


Scheme 38



Scheme 39

Isocyanides are useful for the preparation of several types of imidazole unsubstituted at C-2 and a new example is shown in **Scheme 39**.[116] New routes to imidazoles from mesoionic 1,3-oxazolium-5-olates[117] and from vicinal tricarbonyl compounds[118] are also illustrated. The latter method represents the first use of vicinal tricarbonyl compounds for the preparation of imidazoles; ethyl imidazole-5-carboxylates with propyl or phenyl groups at C-2 and C-5 were isolated in good yield. Two unusual procedures for the preparation of arylimidazoles, shown in **Scheme 40**, involve a hetero Cope rearrangement[119] and the substitution of arylnitromethanes.[120]



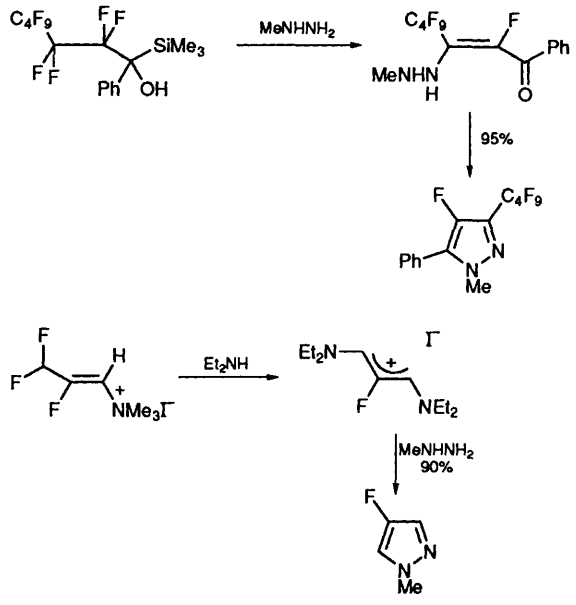
Scheme 40

The palladium-catalysed carbonylation of aryl iodides as a route to 2-arylbenzothiazoles was described in Section 7; an analogous method has been used to prepare 2-arylbenzimidazoles from *o*-phenylenediamine.[121] Several new syntheses of benzimidazoles being methoxy and other electron releasing groups at specific positions in the benzene ring have been described.[122–124]

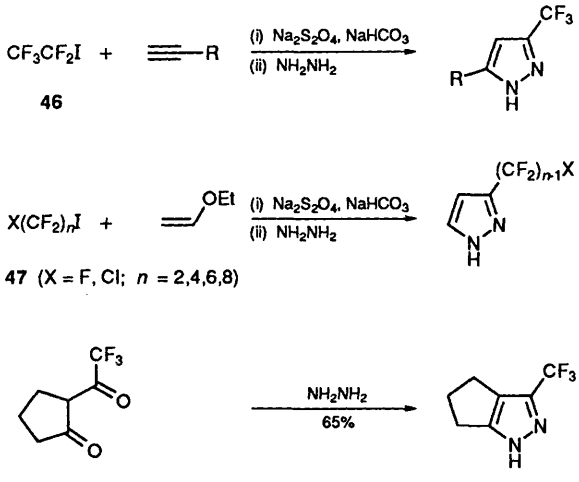
10 Pyrazoles and indazoles

Two new methods of preparation of 4-fluoro-pyrazoles are illustrated in **Scheme 41**.[125,126] 3-(Fluoroalkyl)pyrazoles have also been prepared from a variety of fluorinated precursors by cyclization with hydrazine. The fluorinated iodoalkanes **46**[127] and **47**[128] and 2-(trifluoroacetyl)ketones such as **48**[129] are suitable starting materials (**Scheme 42**). The enaminoketone **27** (shown in **Scheme 16**) also reacts with hydrazine to give 4-trifluoroacetyl-3-trifluoromethylpyrazole in high yield.[54]

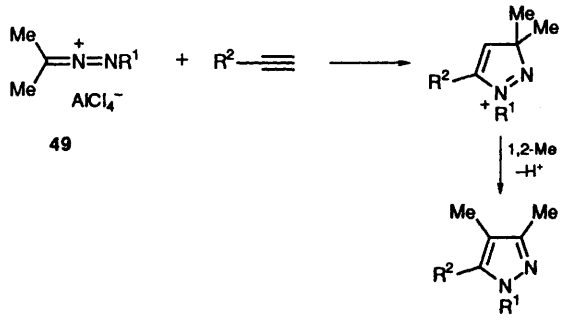
A route to tetrasubstituted pyrazoles is provided by the reaction of the salts **49** (which are generated from α-chloroazoalkanes and aluminium chloride) with monosubstituted alkynes (**Scheme 43**).[130]



Scheme 41



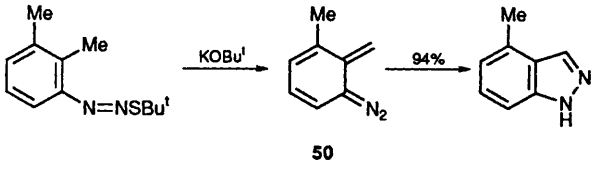
Scheme 42



Scheme 43

Disubstituted alkynes also react with the salts but give pentasubstituted pyrazolium salts. A simple procedure for the preparation of a variety of substituted indazoles is illustrated by the synthesis

of 4-methylindazole shown in **Scheme 44**; the diazo compound **50** is probably an intermediate in the reaction.[131] In a method analogous to that used for the preparation of indoles from 2-nitrostyrenes and illustrated in **Scheme 23**, 2-nitrobenzaldimines have been catalytically reduced to 2*H*-indazoles. This is the first example of a transition metal catalysed synthesis of a 2*H*-indazole.[78]

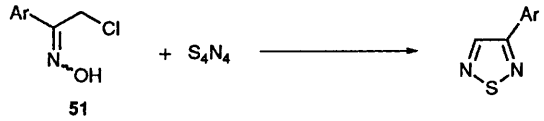


50

Scheme 44

11 Thiadiazoles

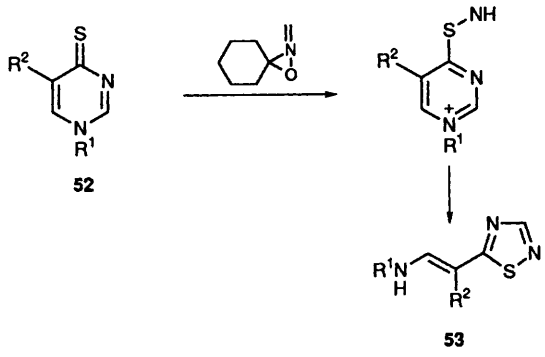
3-Aryl-1,2-5-thiadiazoles are produced in good yield when chloroketoximes **51** are heated with tetrasulfur tetranitride (S_4N_4) in dioxan (**Scheme 45**).[132] α,α-Dibromoacetophenone derivatives have also been used in related syntheses.[133] 3,4-Disubstituted-1,2,5-thiadiazoles have also been prepared in moderate yield from alkyl aryl ketoximes and S_4N_4.[134]



51

Scheme 45

The ring contraction of pyrimidinethiones **52** to the 1,2,4-thiadiazoles **53** (**Scheme 46**) is analogous to a previously reported preparation of thiazoles from **52** in which phenacyl halides were used as co-reagents.[135].

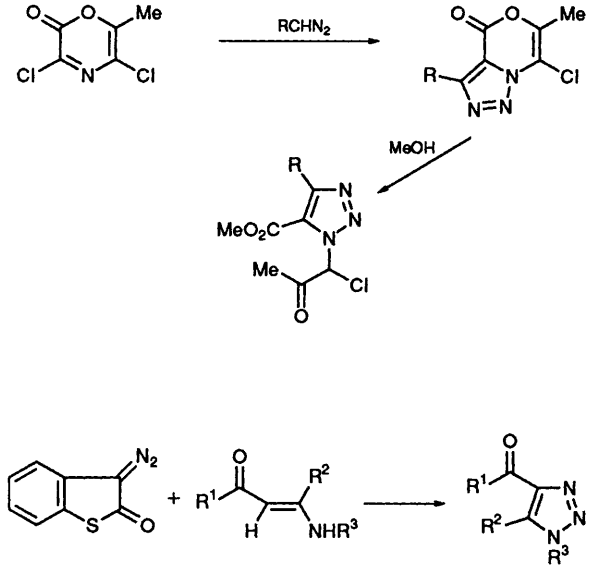


52 53

Scheme 46

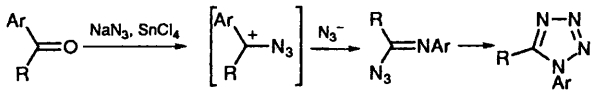
12 Triazoles and tetrazoles

3,5-Dichloro-2*H*-1,4-oxazin-2-ones, which are readily prepared from aldehyde cyanohydrins and oxalyl chloride, can be converted into 1,2,3-triazoles by sequential reaction with diazoalkanes and alcohols (**Scheme 47**).[136] Analogous reactions with sodium azide give the corresponding tetrazoles. Another new route to 1,2,3-triazoles is also illustrated in **Scheme 47**; this involves an unusual diazo transfer reaction.[137]



Scheme 47

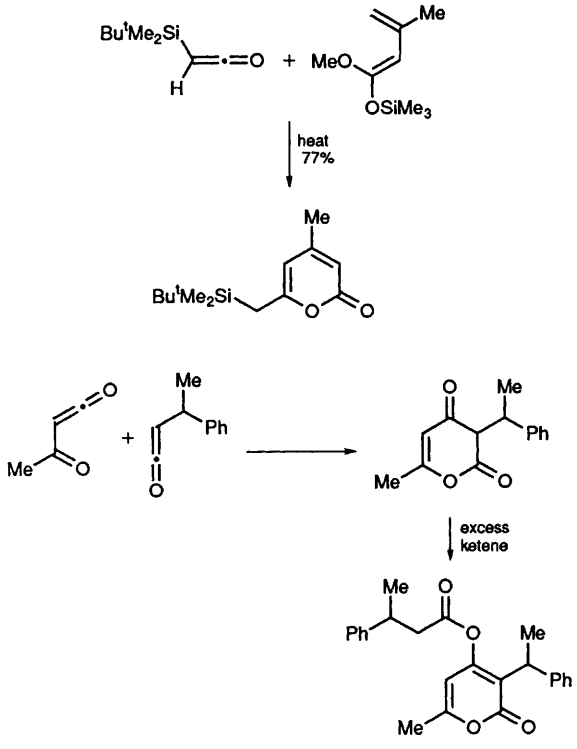
Several new or improved methods have been reported for the preparation of tetrazoles. The preparation of 5-substituted tetrazoles from nitriles and trimethylsilyl azide is improved either by adding an equimolar amount of trimethylaluminium (which may simply act as a Lewis acid)[138] or by using two moles of trimethylsilyl azide with a catalytic amount of dimethyltin oxide [the active reagent in this case probably being $Me_2Sn(OSiMe_3)N_3$].[139] Secondary amides can be activated by reaction with triflic anhydride and the resulting imidates are then converted into 1,5-disubstituted tetrazoles in a one-pot reaction.[140] Analogous routes have been described from secondary thioamides, tin(IV) chloride, and trimethylsilyl azide[141] and, more directly, by the reaction of aryl ketones with an excess of sodium azide in the presence of tin(IV) chloride (**Scheme 48**).[142] For example, 1,5-diphenyltetrazole was prepared from benzophenone in 93% yield by this method. A one-pot synthesis of 5-halo-1-phenyltetrazoles has been achieved from phenyl isocyanide, sodium azide, and the appropriate *N*-halosuccinimide in the presence of a phase transfer catalyst. This is analogous to the known synthesis from isocyanide dihalides but avoids the need to isolate these reactive halides.[143]



Scheme 48

13 Pyrones, coumarins, and chromones

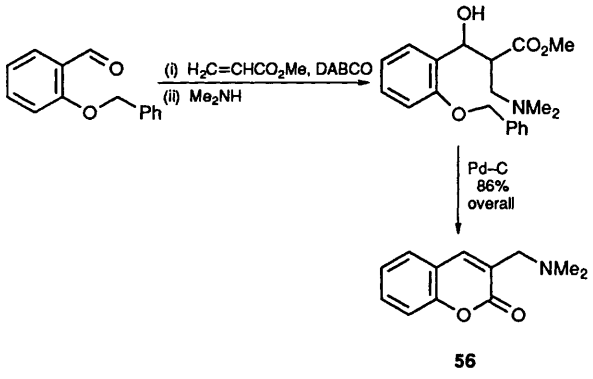
The first examples have been reported of the synthesis of α-pyrones by the cycloaddition of trialkylsilylketenes to dienes[144] and the ring system has also been produced by the cycloaddition of ketenes to α-oxoketenes.[145] These methods are exemplified in **Scheme 49**. Other new methods of forming this ring system include the aluminium chloride catalysed cyclization of carboxylic acid chlorides RCH_2COCl, which leads to the formation of the pyrones **54** from three moles of the acid chloride[146] and the conjugate addition of Meldrum's acid derivatives to but-3-yn-2-one.[147]



Scheme 49

4-Methylcoumarin has been produced from phenol and acetic anhydride in up to 75% yield by passing the vapours over a zeolite catalyst at 380 °C.[148] A new palladium-catalysed route to 4-methylcoumarin from the ester **55** has also been described.[149] Coumarins are most often formed from salicylaldehyde derivatives; several new examples of this type of preparation make use of phosphonium ylides, $Ph_3P{=}CRCO_2Et$, to produce the second ring.[150–152] An efficient synthesis of the coumarin **56** from the benzyl ether of salicyladehyde is illustrated in **Scheme 50**.[153]

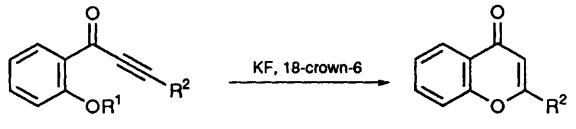
7,8-Dimethoxycoumarin has been prepared in good overall yield from 2,3,4-trimethoxybenzaldehyde by condensation with Meldrum's acid, cyclization, and decarboxylation.[154]



56

Scheme 50

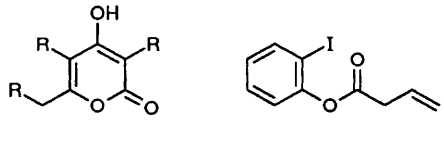
2-Substituted chromones are formed in high yield from alkynones **57** (R^1 = t-butyldimethylsilyl) by 6-*endo* cyclization (**Scheme 51**); anhydrous conditions are essential, otherwise products of 5-*exo* cyclization are also isolated.[155] In the absence of a proton source the *exo* cyclization is reversible and the products come only from the *endo* process. A related synthesis has been described in which the intermediates **57** (R^1 = H) are produced *in situ* from 2-iodophenols and alkynes by palladium-catalysed carbonylation.[156]



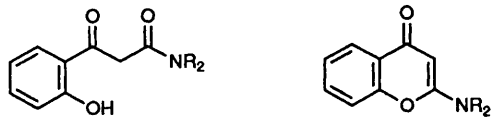
57

Scheme 51

The cyclization of *N*,*N*-dialkylsalicylylacetamides **58** in acidic or basic conditions is known to give 4-hydroxycoumarins, but when triflic anhydride is used as the cyclizing agent the products are 2-dialkylaminochromones **59**.[157] A one-pot synthesis of flavonols in water from 2-hydroxyacetophenone derivatives and benzaldehyde has been described.[158]



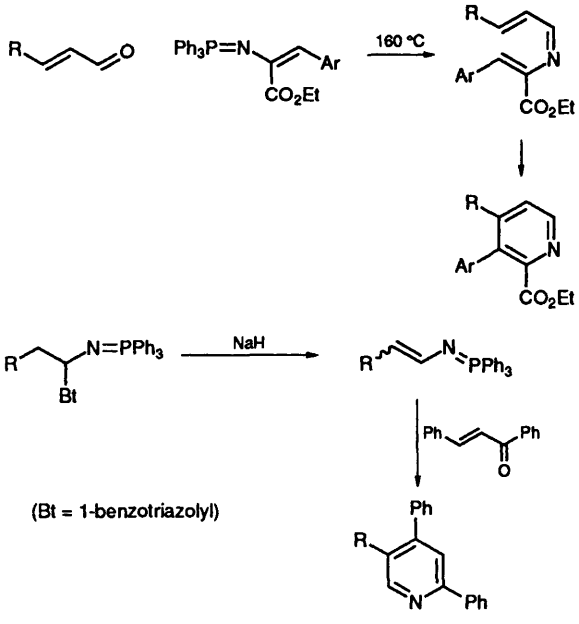
54 **55**



58 **59**

14 Pyridines

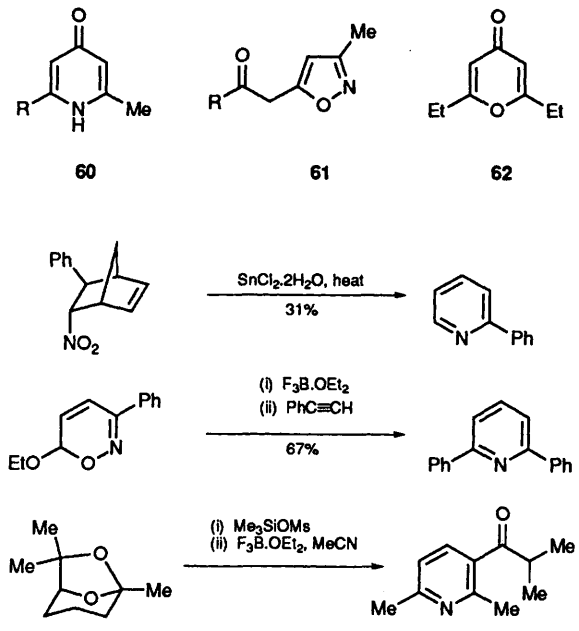
The electrocyclic ring closure of 2-azatrienes, produced *in situ* from iminophosphoranes and α,β-unsaturated aldehydes or ketones, provides a good method for the preparation of a variety of substituted pyridines. Molina and his co-workers have developed this as a synthetic method and have reviewed the use of iminophosphoranes in the preparation of pyridines and other nitrogen heterocycles.[159] Two examples of the synthesis of monocyclic pyridines by this method are given in **Scheme 52**;[160,161] the second, by Katritzky and his colleagues, [161] illustrates a new way of producing unsaturated iminophosphoranes by using benzotriazole as a leaving group.



Scheme 52

Because of the stability of the ring system, pyridines are often the final end products of complex reaction sequences. Three such processes, in which the reaction pathway is not obvious, are shown in **Scheme 53**. The discoverers of the first reaction have suggested that the initial steps are the reduction of the nitro to a nitroso group and a [3,3]-sigmatropic rearrangement;[162] the second may involve the Diels–Alder cycloaddition of phenylacetylene to a 1,2-oxazinium cation.[163] The third[164] seems likely to be initiated by activation by the electrophile of the acetal which is then cleaved by nucleophilic attack of the nitrile.

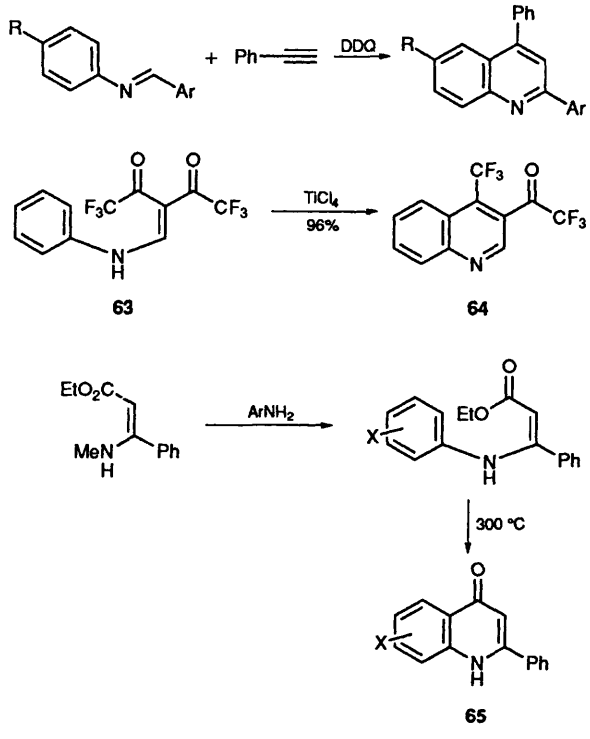
4-Pyridones **60** have been isolated in moderate to good yield from the reductive cleavage of isoxazoles **61** by molybdenum hexacarbonyl.[165] A one stage synthesis of 4-amino-2,6-diethylpyridine from the corresponding 4-pyrone **62** has been achieved using tosyl isocyanate and ammonia.[166]



Scheme 53

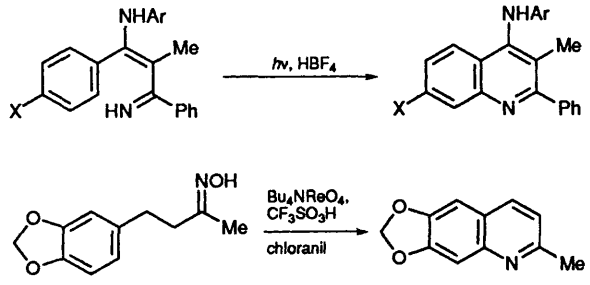
15 Quinolines and isoquinolines

Some new examples of the construction of quinolines by cyclization of aniline derivatives with a free *ortho* position are shown in **Scheme 54**. The reaction of Schiff bases of aromatic aldehydes with alkenes or alkynes is formally a Diels–Alder reaction, although there is evidence for a stepwise mechanism.[167] The enaminone **63**, which is prepared



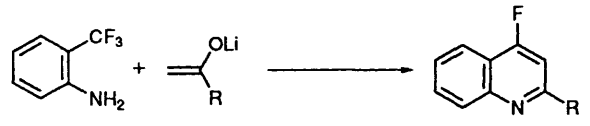
Scheme 54

from compound **27** (shown in **Scheme 16**) and aniline, is converted into the quinoline **64** in high yield by titanium(IV) chloride.[54] A similar exchange of an aromatic for an aliphatic amino group is used to construct the precursors for 2-arylquinolin-4-ones **65**.[168] Two cyclization processes in which a carbon–nitrogen bond is formed are shown in **Scheme 55**.[169,170]

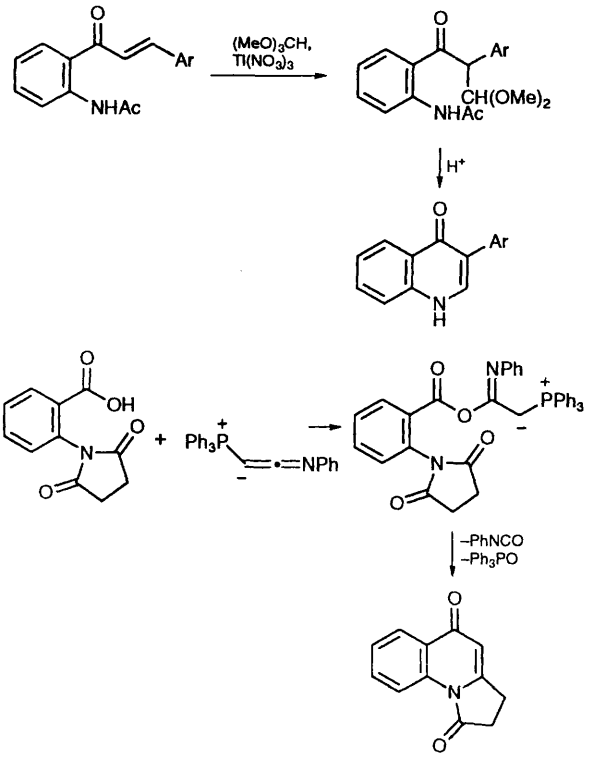


Scheme 55

2-Trifluoromethylaniline has been shown to react with lithium enolates derived from methyl ketones to give 4-fluoroquinolines in moderate yield (**Scheme 56**).[171,172] The Pfitzinger quinoline



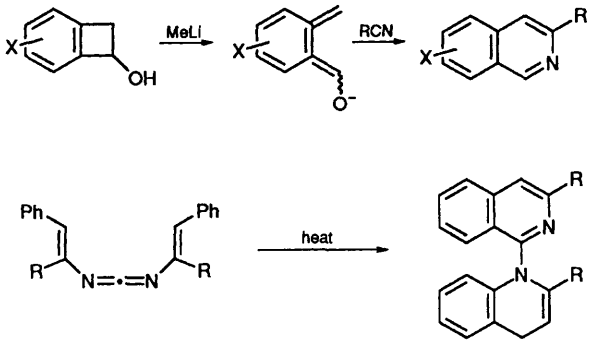
Scheme 56



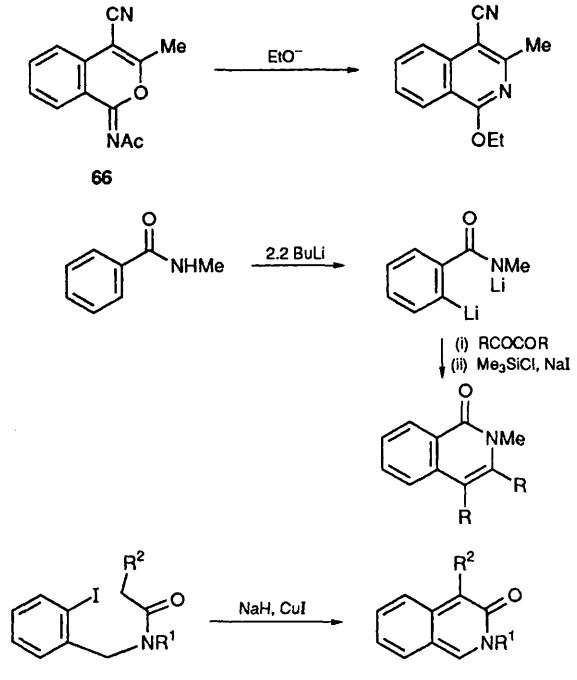
Scheme 57

synthesis (in which the ring system is constructed from isatin and a ketone) has been shown to go with fewer side-reactions when performed in an acidic medium.[173] Two procedures for constructing functionalized 4-quinolones are illustrated in **Scheme 57**.[174,175] Other methods reported include the ruthenium-catalysed reductive cyclization of 2-nitrochalcones[176] and a route from 2-iodoanilines, alkynes, and carbon monoxide analogous to that used for chromones (Section 13).[156]

A convenient new route to 3-substituted isoquinolines has been described starting from benzocyclobutenols and nitriles (**Scheme 58**)[177] and the ring system has also been produced by cyclization of divinylcarbodiimides, as illustrated.[178] Isoquinoline has been prepared (55%) from phthalaldehyde by reaction with the iminophosphorane $(EtO)_2POCH(Li)N{=}PPh_3$.[179]



Scheme 58



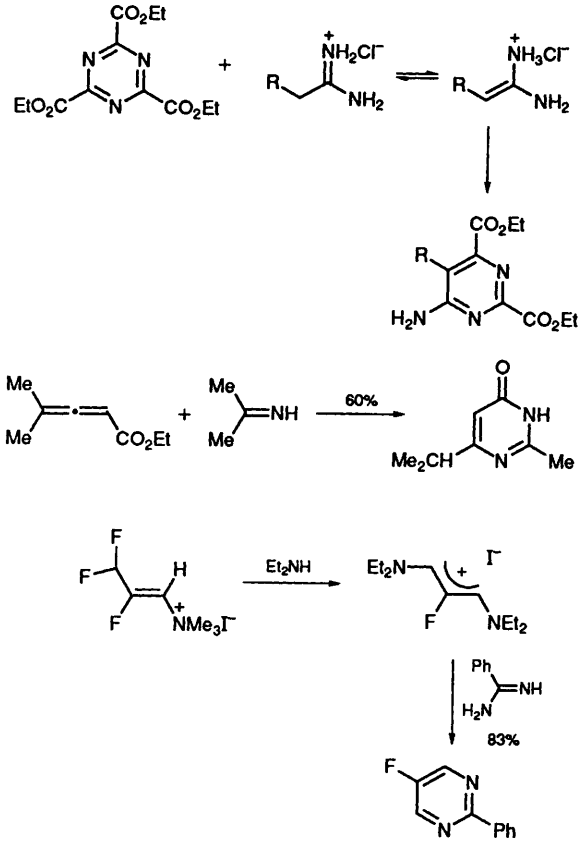
Scheme 59

The product of acetylation of 2-cyanophenylacetonitrile has been identified as the isocoumarin **66**.[180] This compound reacts with a variety of

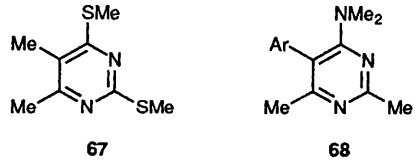
nucleophiles to give isoquinolines or isoquinolones. An example of this reaction, and of other recent methods for the preparation of isoquinolones, are shown in **Scheme 59**.[181,182]

16 Pyrimidines and quinazolines

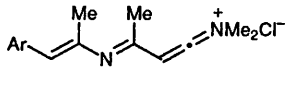
A cycloaddition–cycloreversion sequence has been described for the preparation of pyrimidine diesters (**Scheme 60**).[183] Two other methods in which amidines are used to construct the ring system are also illustrated.[126,184] The pyrimidine **67** and related bis(methylthio)pyrimidines have been prepared in good yield from aliphatic ketones, methyl thiocyanate, and triflic anhydride.[185] 4-Dimethylaminopyrimidines **68** are formed by thermal cyclization of the iminium salts **69**.[186] The ring system has also been produced by ring expansion of imidazolinones.[187]



Scheme 60

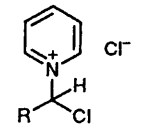


67 **68**

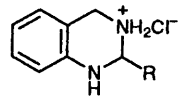


69

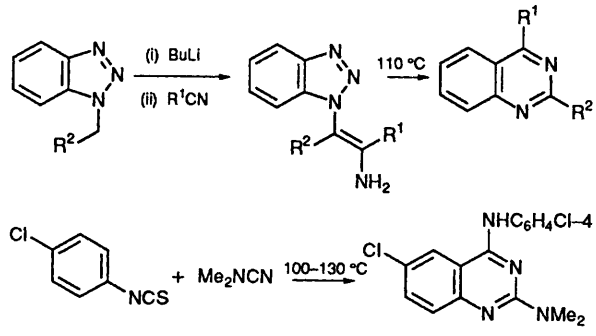
The pyridinium salts **70**, which are produced *in situ* from aldehydes, thionyl chloride, and pyridine, are proving to be useful electrophilic components in heterocyclic synthesis. An example is their reaction with 2-aminobenzylamine to give tetrahydroquinazoline salts **71** in high yield.[188] These compounds can then be oxidized to quinazolines. Two other recent methods for the preparation of quinazolines are outlined in **Scheme 61**.[189,190]



70



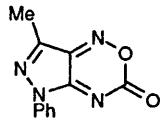
71



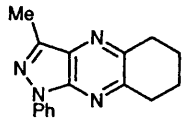
Scheme 61

17 Pyrazines, cinnolines, and triazines

A new cycloaddition–cycloreversion method for the construction of pyrazines has been explored with compound **72** as a precursor. This reacted readily with enamines at low temperature; for example, the fused pyrazine **73** was isolated in high yield from a reaction with pyrrolidinocyclohexene.[191]



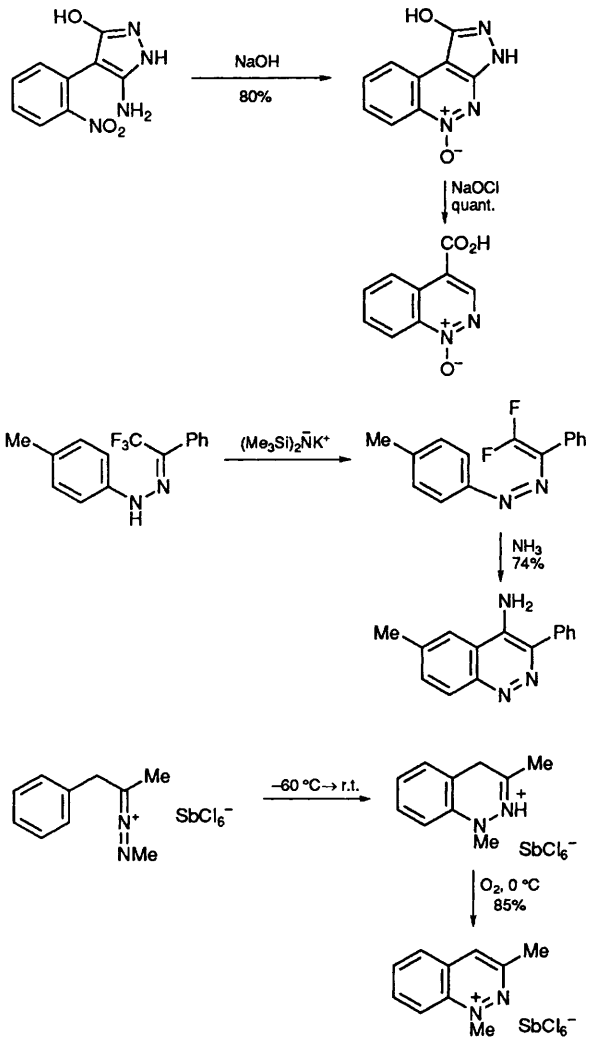
72



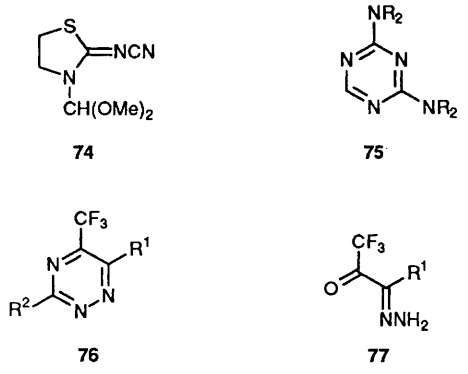
73

Some new routes to cinnoline 1-oxides from aromatic nitro compounds have been described; an example, shown in **Scheme 62**, provides a route to the previously unknown 1-oxides of cinnoline-4-carboxylic acids.[192,193] New routes to 4-aminocinnolines[194] and to 1-methylcinnolinium salts[195] are also illustrated in **Scheme 62**.

The (*N*-cyanoimino)thiazolidine **74** reacts with secondary amines to give the 1,3,5-triazines **75** in good yield.[196] A synthesis of 5-trifluoromethyl-1,2,4-triazines **76** has been described from the hydrazones **77**, aldehydes, and ammonia.[197]



Scheme 62



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