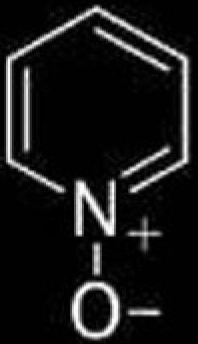
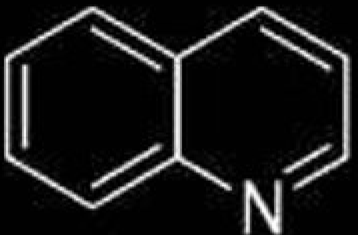
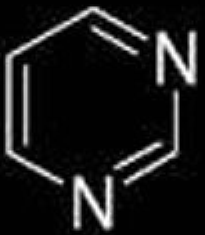
Advances in HETEROCYCLIC CHEMISTRY







VOLUMES 99, 100, AND 101 ARE ALL PUBLISHED IN 2010 TO MARK THE SERIES REACHING 100 VOLUMES.

Volume 99

Advances in
HETEROCYCLIC CHEMISTRY

VOLUME 99

Editor

ALAN R. KATRITZKY, FRS
Kenan Professor of Chemistry
Department of Chemistry
University of Florida
Gainesville, Florida

ELSEVIER
Amsterdam • Boston • Heidelberg • London
New York • Oxford • Paris • San Diego
San Francisco • Singapore • Sydney • Tokyo
Academic Press is an imprint of Elsevier

Academic Press is an imprint of Elsevier
Linacre House, Jordan Hill, Oxford OX2 8DP, UK
84 Theobald's Road, London WC1X 8RR, UK
Radarweg 29, PO Box 211, 1000 AE Amsterdam, The Netherlands
30 Corporate Drive, Suite 400, Burlington, MA 01803, USA
525 B Street, Suite 1900, San Diego, CA 92101-4495, USA

First edition 2010

Copyright © 2010 Elsevier Inc. All rights reserved

No part of this publication may be reproduced, stored in a retrieval system or transmitted in any form or by any means electronic, mechanical, photocopying, recording or otherwise without the prior written permission of the publisher.

Permissions may be sought directly from Elsevier's Science & Technology Rights Department in Oxford, UK: phone (+44) (0) 1865 843830; fax (+44) (0) 1865 853333; email: permissions@elsevier.com. Alternatively you can submit your request online by visiting the Elsevier web site at http://www.elsevier.com/locate/permissions, and selecting *Obtaining permission to use Elsevier material.*

Notice
No responsibility is assumed by the publisher for any injury and/or damage to persons or property as a matter of products liability, negligence or otherwise, or from any use or operation of any methods, products, instructions or ideas contained in the material herein. Because of rapid advances in the medical sciences, in particular, independent verification of diagnoses and drug dosages should be made

ISBN: 978-0-12-380934-6
ISSN: 0065-2725

For information on all Academic Press publications
visit our website at www.elsevierdirect.com

Printed and bound in USA

10 11 12 13 14 10 9 8 7 6 5 4 3 2 1

Working together to grow
libraries in developing countries

www.elsevier.com | www.bookaid.org | www.sabre.org

ELSEVIER BOOK AID International Sabre Foundation

CONTRIBUTORS

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

Edgars Abele (107)
Latvian Institute of Organic Synthesis, 21 Aizkraukles, Riga, LV-1006, Latvia

Nuzhat Arshad (33)
Institute of Chemistry, Karl-Franzens University Graz, Heinrichstrasse 28, A-8010 Graz, Austria

Alexandru T. Balaban (61)
Texas A&M University at Galveston, 5007 Ave, U. Galveston, TX 77551, USA

Luba Ignatovich (107)
Latvian Institute of Organic Synthesis, 21 Aizkraukles, Riga, LV-1006, Latvia

C. Oliver Kappe (33)
Institute of Chemistry, Karl-Franzens University Graz, Heinrichstrasse 28, A-8010 Graz, Austria

L.I. Belen'Kii (143)
N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, Moscow, Russia

Edmunds Lukevics (107)
Latvian Institute of Organic Synthesis, 21 Aizkraukles, Riga, LV-1006, Latvia

A. I. Mikhaleva (209)
A. E. Favorsky Irkutsk Institute of Chemistry, Siberian Branch of the Russian Academy of Sciences, 1 Favorsky Str., Irkutsk 664033, Russian Federation

Albert Padwa (1)
Emory University, Department of Chemistry, Atlanta, GA 30322, USA

J. Schantl (185)
Institut für Organische Chemie, Universität Innsbruck, Innrain 52a, A-6020 Innsbruck, Austria

E. Yu. Schmidt (209)
A. E. Favorsky Irkutsk Institute of Chemistry, Siberian Branch of the Russian Academy of Sciences, 1 Favorsky Str., Irkutsk 664033, Russian Federation

L. N. Sobenina (209)
A. E. Favorsky Irkutsk Institute of Chemistry, Siberian Branch of the Russian Academy of Sciences, 1 Favorsky Str., Irkutsk 664033, Russian Federation

B.A. Trofimov (209)
A. E. Favorsky Irkutsk Institute of Chemistry, Siberian Branch of the Russian Academy of Sciences, 1 Favorsky Str., Irkutsk 664033, Russian Federation

MILESTONE OF 100 VOLUMES OF ADVANCES IN HETEROCYCLIC CHEMISTRY MARKED BY THE PUBLICATION OF VOLUMES 99, 100, AND 101 AS A CELEBRATORY SET

It is hard to believe that it is now 50 years since I conceived the concept of periodical volumes of these ''Advances'' that would record progress in Heterocyclic Chemistry. In 1960, heterocyclic chemistry was slowly emerging from the dark ages; chemists still depicted purines by the archaic structural designation introduced (was it by Emil Fischer?) 50 years before that. Together with Jeanne Lagowski I had published in 1959 a modern text on heterocyclic chemistry, the first that treated this subject in terms of structure and mechanism and attempted to logically cover significant methods of preparation and reactions of heterocyclic compounds as a whole, all in terms of reactivity.

The first two volumes of Advances contained extensive chapters on the tautomerism of various classes of heterocycles. Despite the great influence the precise structure of heterocyclic compounds has on chemical and biological properties (we only have to remember base pairing of nucleotides to illustrate this), at that time the literature was replete with incorrectly depicted tautomers. The basis for the position of tautomeric equilibria was usually completely misunderstood. Although great progress has been made in the last 50 years, there still exist holdouts even among otherwise reputable chemists who persist in depicting 2-pyridone as ''2-hydroxypyridine'' which is a very minor component of the tautomeric equilibrium under almost all conditions.

Over the years Advances in Heterocyclic Chemistry has indeed monitored many of the advances in the subject: the series is now boosted by ''Comprehensive Heterocyclic Chemistry'' of which the first edition was published in 1984 in 8 volumes, followed by the second edition in 1996 in 11 volumes and the third in 2008 in 15 volumes. Heterocyclic chemistry has now taken its place as one of the major branches (by several criteria the most important) of Organic Chemistry.

Chemistry has rapidly become the universal language of molecular interactions; it has essentially taken over biochemistry and is rapidly gaining dominance in zoology, botany, physiology and indeed in many branches of medicine.

Chemical structural formulae are quite basic to this progress and have enabled us to rationalize many natural phenomenon and countless reactions both simple and exotic discovered in the laboratory.

Now we have reached the milestone of 100 volumes of the series. In place of a single volume we are offering the three volume set 99, 100 and 101 which contain a fascinating variety of reviews covering exciting topics in heterocyclic chemistry.

Alan R. Katritzky
Gainesville, Florida

PREFACE TO VOLUME 99

Dr. Albert Padwa (Emory University) starts the volume with a fascinating chapter on the cycloaddition and cyclization chemistry of 2H-azirines, an area in which he has been closely connected with some of the most interesting developments. Dr. Nuzhat Arshad and Dr. Oliver Kappe of the University of Graz (Austria) update our knowledge of heterocyclic BINAP analogues, important ligands for asymmetric synthesis.

Professor Alexandru Balaban (Texas A&M University) has contributed a focused account of monocycle hetarenes possessing a π-electron aromatic sextet; this illustrates the wide variety of possible systems, many of which remain unknown or little explored. Professor Edmund Lukevics, with Drs Abele and Ignatovich, reviews the chemistry of biologically active silacyclanes covering some lesser known aspects of silicon chemistry and the evidently very wide range of possible structures here.

Professor Leonid Belen'kii (Zelinsky Institute, Moscow) has rationalized the orientation of substitution in furan, thiophene, and pyrrole. Professor Joachim Schantl of University of Innsbruck (Austria) surveys the chemistry of cyclic azomethine imines derived from azo compounds, illustrating the diversity of their possible [3+2] cycloaddition reactions.

Finally, Professor Boris Trofimov, together with three colleagues from the Irkutsk Institute of the Russian Academy of Sciences, gives an account recent advances in the chemistry of *N*-vinylpyrroles obtained from ketones and acetylenes.

Alan R. Katritzky
Gainesville, Florida

CHAPTER 1

Cycloaddition and Cyclization Chemistry of 2*H*-Azirines

Albert Padwa

Contents

1. INTRODUCTION

Azirines can be regarded as one of the most simple of all heterocyclic systems, one which is characterized by the presence of two carbon atoms and one nitrogen atom in a three-membered ring containing a π-bond.

Emory University, Department of Chemistry, Atlanta, GA 30322, USA

Advances in Heterocyclic Chemistry, Volume 99
ISSN 0065-2725, DOI 10.1016/S0065-2725(10)09901-0

While numerous members of the 2*H*-azirine (**1**) ring systems are known and have been fully characterized, derivatives of the 1*H*-azirine ring system (**2**) are known only as transient intermediates. Interest in these nitrogen-containing small rings is due to the general influence of ring strain upon chemical reactivity, to the degree to which the 1*H*-azirine ring, for example, is destabilized by conjugation of the nitrogen lone pair electrons with the π-bond, and to the potential of derivatives of these compounds to act as precursors to more elaborate heterocyclic molecules. The stabilities and overall profiles of chemical reactivity of these heterocycles are attributable not only to the combined effects of bond shortening and angle compression, but also to the presence of the electron-rich nitrogen atom. With 1*H*-azirines, cyclic delocalization of the lone pair electrons is believed to destabilize the ring to an extent which precludes isolation but not detection of the 4π-electron containing antiaromatic ring system. Polarization toward the more electronegative nitrogen atom of the 2*H*-azirine ring results in a shorter C–N bond and a longer C–C bond, consistent with the dimensions of 2*H*-azirines found by single crystal X-ray data (97CEJ1757). The stability of the 2*H*-azirine ring can be attributed not only to the combined effects of bond shortening and angle compression, but also to the presence of the electron-rich nitrogen atom. The strain energy associated with these heterocycles is principally due to deformation of the normal bond angles between the atoms of the ring. The total ring-strain energy of 2*H*-azirine has been estimated at 48 kcal mol^{-1} (91AG238, 02EJOC1750) although lower values of 44.6 and 46.7 kcal mol^{-1} have been reported using *ab initio* calculations at the MP2/6-31G* and B3LYP/6-31G* levels of theory (98JCC912). The chemistry of 2*H*-azirines is dominated by processes in which the strain of the three-ring system is relieved. They readily participate in cycloaddition reactions as 2π-components and undergo ring cleavage on photochemical excitation to give nitrile ylides. These dipoles then undergo a subsequent 1,3-dipolar cycloaddition reaction with a variety of π-bonds. Thermal ring cleavage produces vinyl nitrenes by cleavage of the N–C_2 bond, which then undergo ring expansion reactions. The theoretical, biological applications, and the synthetic chemistry of 2*H*-azirines have been extensively explored and a number of general reviews have appeared (01EJOC2401, 02OPP219) (Figure 1).

1; 2*H*-Azirine **2**; 1*H*-Azirine

Figure 1 Isomeric azirine ring system.

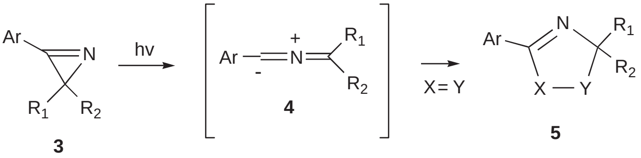
A major and characteristic reaction of the 2*H*-azirine ring is its reactivity toward a wide variety of reagents, an effect undoubtedly resulting from the necessary compression of bond angles in the three-membered ring. Thus, this system is extremely susceptible toward ring cleavage because of the favorable release of strain energy involved. For this reason, 2*H*-azirines have been converted to a wide variety of functionalized compounds. 2*H*-Azirines are capable of acting in reactions as nucleophiles and electrophiles, as 2π-components in thermal cycloadditions, and as 4π-components in photochemical cycloadditions. These reactions can be regarded in general terms as involving the participation of the C=N, C–C and C–N bonds of the 2*H*-azirine ring. The cycloaddition and cyclization reactions of 2*H*-azirines have invoked considerable interest in recent years. In this chapter, some of the more important "*cyclo*" transformations of this unique heterocyclic system are described.

2. PHOTOCYCLOADDITION REACTIONS OF 2*H*-AZIRINES

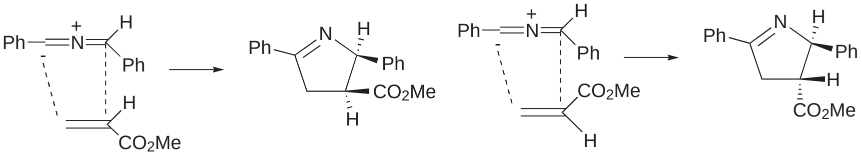
2.1 Bimolecular [1,3]-dipolar cycloadditions

2*H*-Azirines undergo irreversible ring opening on electronic excitation to give nitrile ylides **4** as reactive intermediates (Scheme 1) (76ACR371, 77H143, 73JA1954). Nitrile ylides may be classified as nitrilium betaines, a class of 1,3-dipoles containing a central nitrogen atom and a π-bond orthogonal to the 4π-allyl system. They can be intercepted with a wide variety of dipolarophiles to form five-membered heterocyclic rings (e.g., **5**).

The photocycloaddition of arylazirines with electron deficient alkenes to produce Δ^1-pyrrolines (73JA1954) exhibits all the characteristics of a concerted reaction, including stereospecificity and regioselectivity. 1,3-Dipolar additions proceed *via* a "two-plane" orientation complex where the dipole and dipolarophile approach each other in parallel planes (Scheme 2) (68JOC2291). For the case of diphenylazirine and methyl acrylate, two possible orientation complexes (**6** or **8**) exist. The interaction of substituent groups in the *syn* complex **6** can be of an attractive (π-overlap, dipole–dipole interaction) or a repulsive nature (van der Waals' strain). Both effects are negligible in the *anti* complex **8**. The ratio of the products obtained gives insight into the interplay of steric and



Scheme 1

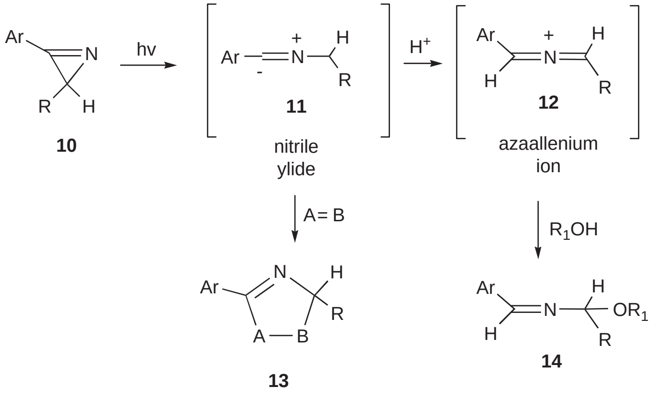


Scheme 2

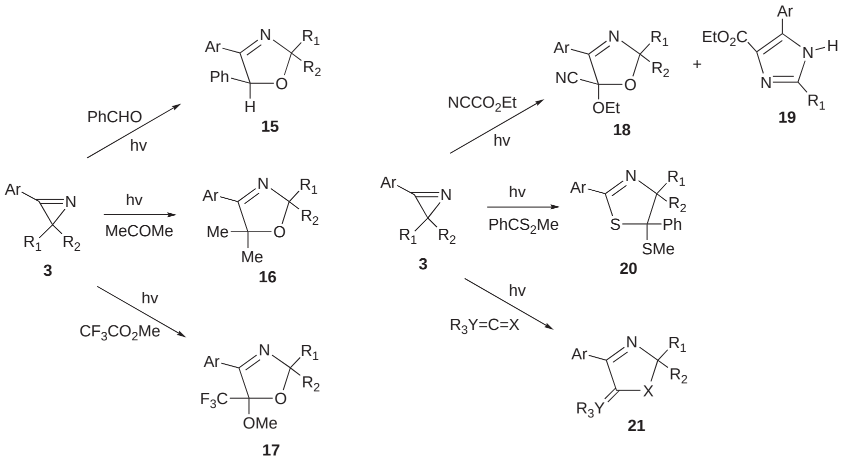
electronic substituent effects in the transition state of 1,3-dipolar addition and emphasizes the important role these effects have in controlling the stereochemical distribution of the products obtained.

Frontier molecular orbital theory correctly rationalizes the regioselectivity of most 1,3-dipolar cycloadditions (73JA7287). When nitrile ylides are used as 1,3-dipoles, the dipole highest occupied (HOMO) and dipolarophile lowest unoccupied (LUMO) orbital interaction importantly stabilizes the transition state. The favored cycloadduct is that formed by union of the atoms with the largest coefficient in the dipole HOMO and dipolarophile LUMO. An electron deficient alkene has the largest coefficient on the unsubstituted carbon in the LUMO. In order to predict regioselectivity in the photocycloaddition of arylazirines, the relative magnitudes of the coefficients in the HOMO of the nitrile ylide must be known. The photoconversion of arylazirines to alkoxyimines **14** indicates that in the HOMO of the nitrile ylide the electron density at the disubstituted carbon is greater than at the trisubstituted carbon atom. With this conclusion, all the regiochemical data found in the photoaddition of arylazirines with dipolarophiles can be explained. In alcohols as solvents, the nitrile ylides are protonated to yield azallenium cations **12** which are then trapped by the alcohol to furnish alkoxyimines **14**. The protonation rate of the ylide in alcohol increases with the acidity of the alcohol. On the basis of a large kinetic isotope effect ($k_H/k_D = 5.5$) for protonation of the ylide, the transition state for the nitrile ylide protonation was concluded to be linear (97JA11605). Cycloaddition of the 2*H*-azirine ring to give pentagonal heterocycles **13** by photochemical activation has become a well known reaction of this heterocyclic system (Scheme 3) (95HCA935).

The photochemistry of 3-methyl-2-(1-naphthyl)-2*H*-azirine has been investigated by the direct observation of reactive intermediates in Ar matrixes and by the characterization of reaction products in solution (05JA2628). Interestingly, the irradiation of this particular 2*H*-azirine with long-wavelength light resulted in selective cleavage of the C–N bond. On the other hand, products derived from C–C bond cleavage were obtained when the irradiation was carried out with short-wavelength light. On the basis of MO calculations using the INDO/S method, it was proposed that C–N bond cleavage occurs from an excited triplet state having an electronic character of a localized π–π^* excitation on the naphthyl moiety.

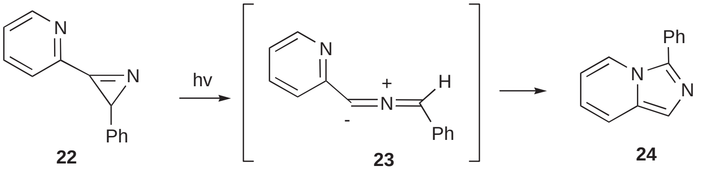


Scheme 3



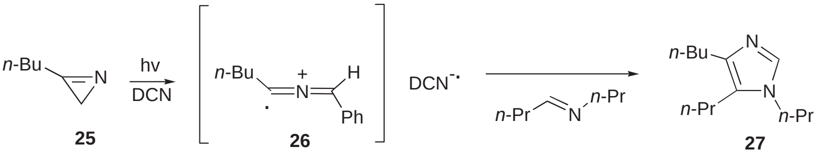
Scheme 4

The photochemical addition of 2*H*-azirines to the carbonyl group of aldehydes, ketones and esters is completely regiospecific (77H143). Besides the formation of the isomeric oxazolines **18** from **3** and ethyl cyanoformate, there is also formed the imidazole **19** from addition to the C=N in the expected regioselective manner. Thioesters lead to thiazolines **20**, while isocyanates and ketenes produce heterocycles **21** (Scheme 4). The photocycloaddition of arylazirines with a variety of multiple bonds proceeds in high yield and provides a convenient route for the synthesis of five-membered heterocyclic rings. Some of the dipolarophiles include azodicarboxylates, acid chlorides, vinylphosphonium salts and *p*-quinones.



22 **23** **24**

Scheme 5



25 **26** **27**

Scheme 6

Nitrile ylides may also undergo electrocyclization reactions with neighboring π-systems, as exemplified by the conversion of **22** into **24** as shown in Scheme 5 (93JCS(P1)675).

Photoinduced electron transfer reactions of 2*H*-azirines have also been studied, resulting in the formation of a radical cation (a 2-azaallenyl radical cation) rather than a nitrile ylide (92AG207, 93CB543, 93JOC4462). These species still undergo cycloaddition reactions with compounds such as alkenes, alkynes, imines and nitriles to produce five-membered ring heterocycles (i.e., **27**), as shown in Scheme 6 (92AG207). DCN is 1,4-dicyanonaphthalene, the agent which promotes electron transfer. The advantage of this method is that the substituents on the intermediate radical cation do not have to be aryl, thus providing a method that is complementary to the traditional nitrile ylide technique. These reactions are considered to be two-step processes.

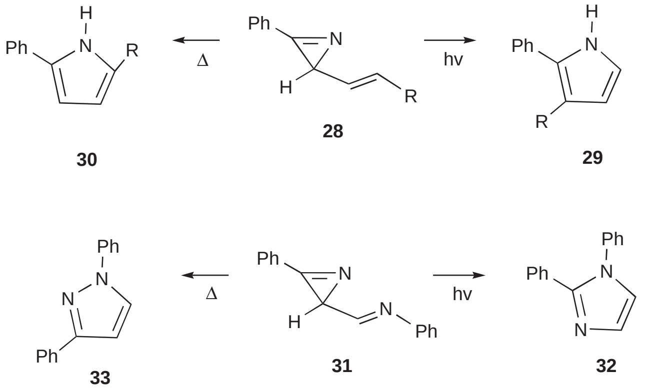
Irradiation of arylazirines with alkenes of low dipolarophilic activity produced no photoadduct but instead gave dimers (73JA1954). Originally, it was reported that photolysis of phenylazirine gave azabicyclo[2.1.0]pentane (68AG130). The dimer actually isolated was subsequently shown to be a diazabicyclo[3.1.0]hexane. In the absence of an added dipolarophile the nitrile ylide generated photochemically simply adds to the ground state 2*H*-azirine molecule. A crossed dimerization of 2*H*-azirines has also been realized (72CC409). Additional work showed that the dimerization of arylazirines to 1,3-diazabicyclo[3.1.0]hex-3-enes is a general reaction which is independent of the nature of the substituent groups attached to the C atom of the 2*H*-azirine ring. Care is required in the choice of solvent, photolysis time and substituents since the 1,3-diazabicyclohexenes are themselves photochemically labile (72JA7788).

2.2 Photochemical rearrangements

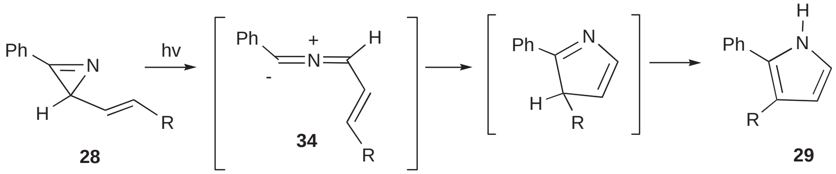
Whereas the cycloaddition of arylazirines with simple alkenes produces Δ^1-pyrrolines, a rearranged isomer (i.e., **29**) can be formed when the alkene and the 2*H*-azirine moieties are suitably arranged in the same molecule. This type of intramolecular photocycloaddition was first detected using 2-vinyl-substituted 2*H*-azirines (75JA4682).

Irradiation of 2*H*-azirine **28** in benzene afforded a 2,3-disubstituted pyrrole **29**, while thermolysis gave a 2,5-disubstituted pyrrole **30**. Photolysis of 2*H*-azirine **31** proceeded similarly and gave 1,2-diphenylimidazole (**32**) as the exclusive photoproduct. This stands in marked contrast to the thermal reaction of **31** which afforded 1,3-diphenylpyrazole (**33**) as the only product (Scheme 7).

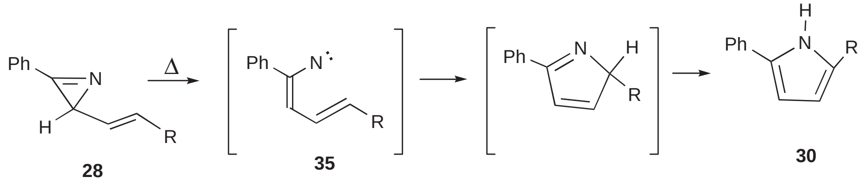
The evidence obtained clearly indicates that the above photorearrangements proceed by a mechanism involving a nitrile ylide intermediate **34** since dipolar cycloadducts could be isolated when the irradiations were carried out in the presence of trapping agents. Intramolecular cycloaddition of the nitrile ylide followed by a 1,3-sigmatropic hydrogen shift of the initially formed five-membered ring readily accounts for the formation of the final product **29** (Scheme 8).



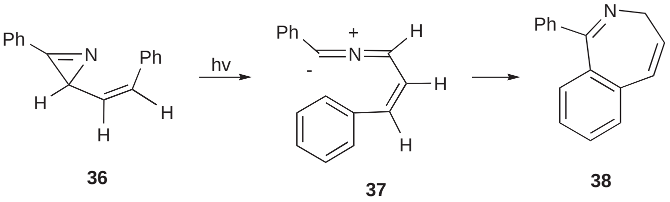
Scheme 7



Scheme 8



Scheme 9

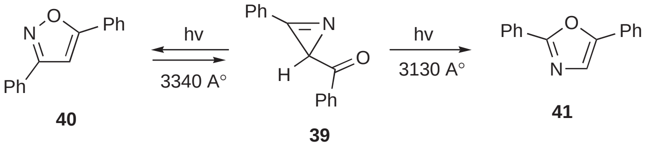


Scheme 10

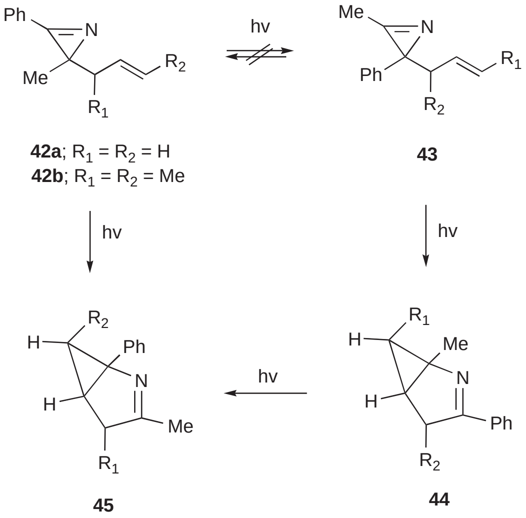
On the other hand, the thermal transformations observed with these systems can be rationalized in terms of an equilibration of the 2*H*-azirine **28** with a transient vinylnitrene **35** which subsequently rearranges to the 2,5-disubstituted pyrrole **30** (Scheme 9).

In contrast to the photochemical results encountered with **28**, the presence of a *cis*-styryl side chain in the 2-position of the 2*H*-azirine ring **36** leads to ring expansion and gives benzazepine **38** *via* nitrile intermediate **37**. The 2-[2-(α- and *β*-naphthyl)vinyl]3-phenyl-2*H*-azirine systems behaved similarly and proceeded with complete regiospecificity. The photolysis of the isomeric *trans*-styrylazirine followed an entirely different course and produced 2,3-diphenylpyrrole (**29**) as the major product. This observation requires that opening of the 2*H*-azirine ring followed by intramolecular cyclization proceeds faster than isomerization about the C=C bond. The formation of **38** indicates that the nitrile ylide obtained from **36** cyclizes more easily *via* a seven-membered transition state and leads to the preferential formation of benzazepine **38** (Scheme 10). Cyclization of the nitrile ylide derived from the *trans* isomer to a seven-membered ring is precluded on structural grounds, and formation of 2,3-diphenylpyrrole (**29**) occurs instead.

The photochemical rearrangement of 3,5-diphenylisoxazole (**40**) to 2,5-diphenyloxazole (**41**) was shown to proceed *via* 3-phenyl-2-benzoyl-2*H*-azirine (**39**) as a transient intermediate (67JA6911). The photobehavior of **39** was found to be dramatically controlled by the wavelength of the light used. With 3130 A light, **39** rearranges almost quantitatively to oxazole **41**, whereas 3340 A light causes rearrangement to isoxazole **40** (Scheme 11). The formation of the isoxazole was suggested to occur *via*



Scheme 11



Scheme 12

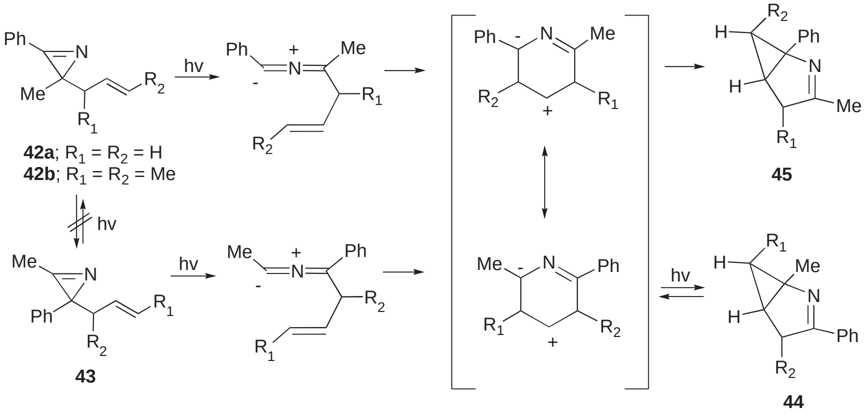
the n–π^{*3} state of the carbonyl chromophore. Oxazole formation was attributed to selective excitation of the n–π^* state of the 2*H*-azirine ring.

2.3 Intramolecular 1,1-cycloaddition reactions

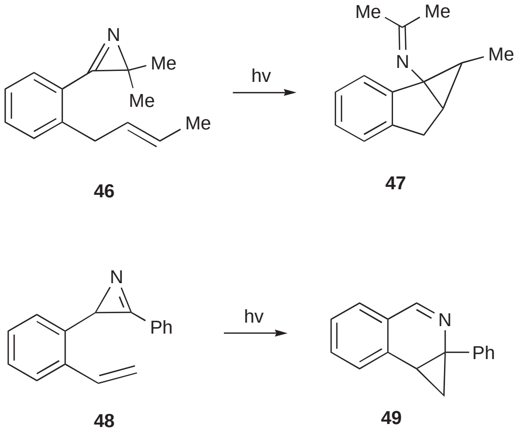
Nitrile ylides derived from the photolysis of 2*H*-azirines have also been found to undergo a novel intramolecular 1,1-cycloaddition reaction (75JA3862, 76JOC180). Irradiation of 2*H*-azirine **42** gave a 1:1 mixture of azabicyclohexenes **44** and **45**. On further irradiation, **44** was quantitatively isomerized to **45**. Photolysis of **42** in the presence of excess dimethyl acetylenedicarboxylate resulted in the 1,3-dipolar trapping of the normal nitrile ylide. Under these conditions, the formation of azabicyclohexenes **44** and **45** was entirely suppressed. The photoreaction of the closely related methyl-substituted 2*H*-azirine **42b** gave azabicyclohexene **45b** as the primary photoproduct. The formation of the thermodynamically less favored *endo* isomer (i.e., **45b**), corresponds to a complete inversion of stereochemistry about the π-system in the cycloaddition process (Scheme 12).

The photochemical behavior of the isomeric 3-methyl-2-phenyl-2-allyl-2*H*-azirine (**43**) system was also studied. Irradiation of **43** in cyclohexane gave a quantitative yield of azabicyclohexenes **44** and **45**. Control experiments showed that **42** and **43** were not interconverted by a Cope reaction under the photolytic conditions. Photocycloaddition of **43** with an added dipolarophile afforded a different 1,3-dipolar cycloadduct from that obtained from **42**. The thermodynamically less favored *endo* isomer **45b** was also formed as the exclusive product from the irradiation of 2*H*-azirine **43b** (Scheme 13).

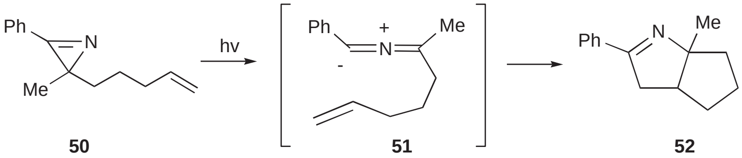
1,3-Dipolar cycloadditions proceed *via* a "two-plane" orientation complex in which the dipole and dipolarophile approach each other in parallel planes. Inspection of molecular models of the allyl-substituted nitrile ylides indicates that the normal "two-plane" orientation approach of the nitrile ylide and the allyl π-system is impossible as a result of the geometric restrictions imposed on the system. Consequently, the normal mode of 1,3-dipolar addition does not occur. In these systems, attack by the double bond is constrained to occur perpendicular to the plane of the nitrile ylide. The LUMO, which is perpendicular to the ylide plane, is low-lying and presents a large vacancy at C-l for attack by the more nucleophilic terminus of the neighboring double bond, without the possibility of simultaneous bonding at the C-3. This attack will generate a six-membered ring dipole which contains a secondary carbonium ion as well as an azallyl anion portion. Collapse of this new 1,3-dipole results in the formation of the observed azabicyclohexenes. Several additional examples demonstrate the generality of the intramolecular 1,1-cycloaddition reaction of unsaturated 2*H*-azirine derivatives. Thus, photolysis of 2*H*-azirine **46** gave rise to a mixture of *endo*- and *exo*-benzobicyclohexenes **47** in quantitative yield (76JA1048). No detectable quantities of the



Scheme 13



Scheme 14



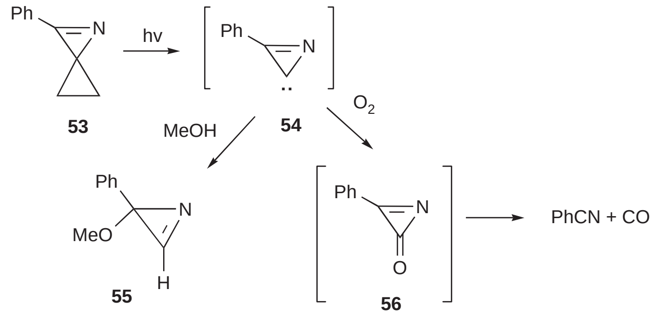
Scheme 15

isomeric 1,3-dipolar adduct were observed. Similarly, irradiation of 2*H*-azirine **48** resulted in an analogous 1,1-cycloaddition (Scheme 14).

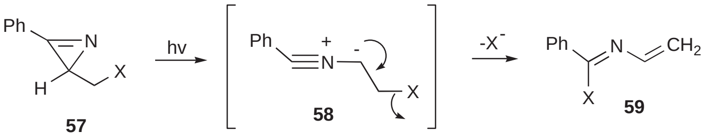
When the chain between the 2*H*-azirine ring and the alkene end is extended to three carbon atoms, the normal mode of 1,3-intramolecular dipolar cycloaddition occurs. For example, irradiation of 2*H*-azirine **50** gives Δ^1-pyrroline **52** in quantitative yield (77JA1871). In this case, the methylene chain is sufficiently long to allow the dipole and alkenic portions to approach each other in parallel planes (Scheme 15).

2.4 Miscellaneous photoreactions

Another interesting example involves the photolysis of 2-phenyl-L-azaspiropent-1-ene (**53**) (75JA5912). Irradiation of this spiroazirine in methanol results in a Griffin-fragmentation which produces ethylene and 2-phenylazirinylidene (**54**). This novel carbene undergoes subsequent reaction with methanol to produce 2-methoxy-2-phenyl-2*H*-azirine (**55**). When the irradiation of **53** is carried out in the presence of oxygen, benzonitrile and carbon monoxide are formed. In the absence of oxygen an extremely small quantity of benzonitrile is produced and is presumably derived by competitive cycloelimination from **53** (Scheme 16). The



Scheme 16



X = Cl, Br, OAc, $OCOCF_3$, OBz

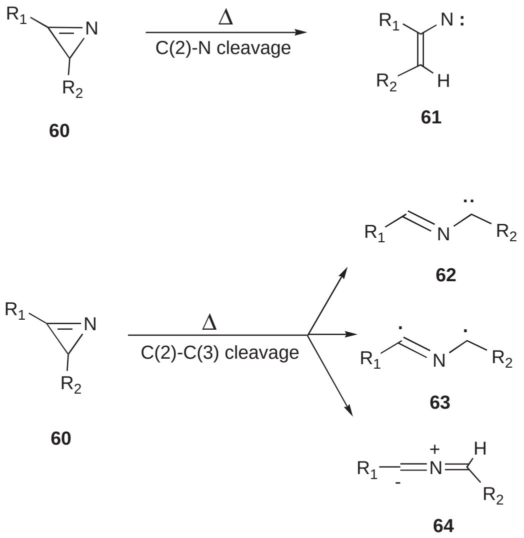
Scheme 17

formation of benzonitrile was attributed to the intermediacy of 2-phenylazirinone (**56**) as a transient species. Azirinones are known to be unstable and readily lose carbon monoxide to form nitriles (69T1637, 75JA5912).

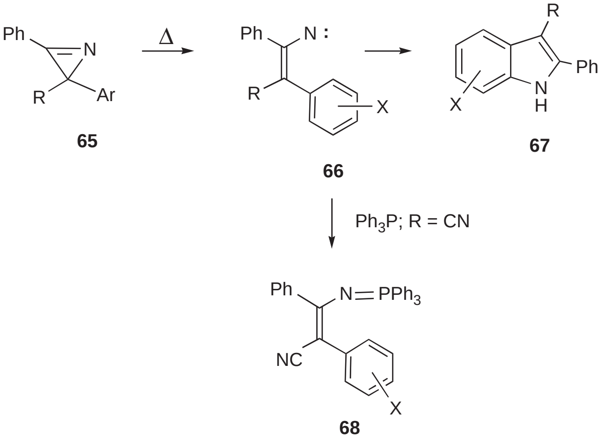
Irradiation of a series of hydroxymethyl-2*H*-azirine derivatives (**57**) which contain good leaving groups was found to give *N*-vinylimines **59** *via* a novel 1,4-substituent shift (Scheme 17) (78JA4481). The results indicate that the migrating substituent (X) must be a reasonably good leaving group in order for the rearrangement to occur. Involvement of a nitrile ylide intermediate **58** in these reactions was demonstrated by trapping experiments. The quantum efficiency and rate of reaction were shown to be directly related to the leaving group ability.

3. THERMAL CYCLIZATIONS OF 2*H*-AZIRINES

The major thermal reaction of 2*H*-azirines of type **60** generally involves C(2)–N bond cleavage to form vinyl nitrenes **61**. Cleavage of the C–C bond to produce iminocarbenes **62**, diradical species **63** or nitrile ylides **64** is also possible at higher temperatures (Scheme 18). Molecular orbital calculations suggest that C–C bond cleavage can actually occur more readily than C(2)–N bond cleavage (78JA6575). Excellent reviews of these

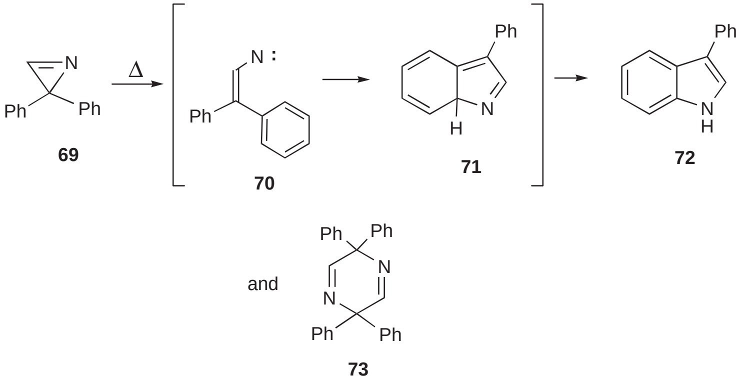


Scheme 18



Scheme 19

processes are available (82MI101-01, 83MI101-02, 84CHEC-1(7)47, 84MI101-03, 84MI101-04, 90H753, 91AG238). Evidence for the presence of transient vinyl nitrenes during thermolyses of 2*H*-azirines has been obtained from trapping experiments using both triphenylphosphine (71JCS3021, 72CC565, 72JCS(P1)1456, 84CHEC-1(7)47, 98H2551, 99JOC6239, 96CHEC-2(1)1, 72CC565) and tris(dimethylamino)phosphine (76JOC543). For example, thermolysis of 2*H*-azirine **65** in the presence of triphenylphosphine resulted in the formation of phosphine adduct **68**



Scheme 20

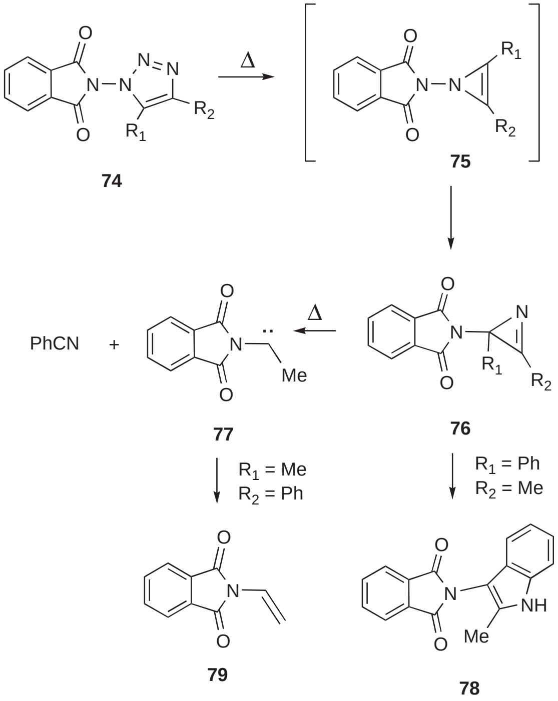
(Scheme 19) (72CC565). Taniguchi and coworkers have shown that the thermal reactivity of 2*H*-azirines varies with the substitution pattern on the azirine ring (69TL4073). Alkyl and aryl substituents at C(2) were found to increase the stability of the ring. Substitution at C(3) was also found to affect stability, with increasing reactivity in the order Ph>CH_3>H (77H1563).

The thermal chemistry of a number of aryl-substituted 2*H*-azirines often results in the formation of indole derivatives (68TL3499). Thus, heating a sample of 2*H*-azirine **69** gave 3-phenylindole (**72**) and dihydropyrazine **73**. The formation of **72** was suggested to proceed *via* a vinylnitrene intermediate which cyclizes and then undergoes a 1,5-sigmatropic shift (Scheme 20) (77H1563).

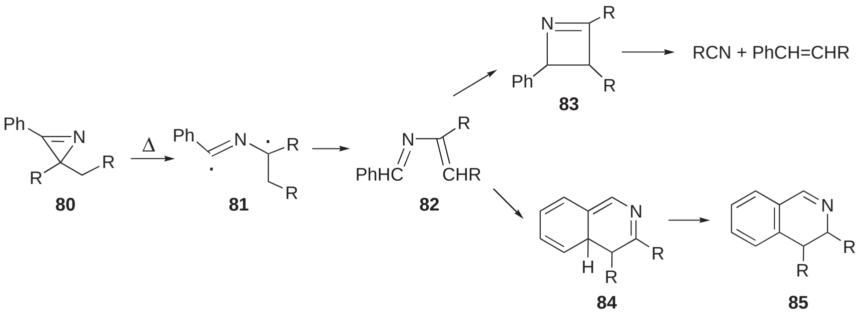
The 2*H*-azirines obtained from the vapor phase pyrolysis of 4,5-disubstituted 1-phthalimido-l,2,3-triazoles (**74**) have been found to undergo further thermal reactions (71CC1518). Those 2*H*-azirines which contain a methyl group in the 2-position of the ring are cleaved to nitriles and phthalimidocarbenes, whereas those 2*H*-azirines which possess a phenyl substituent in the 2-position rearrange to indoles (Scheme 21).

3.1 Internal hydrogen transfer processes

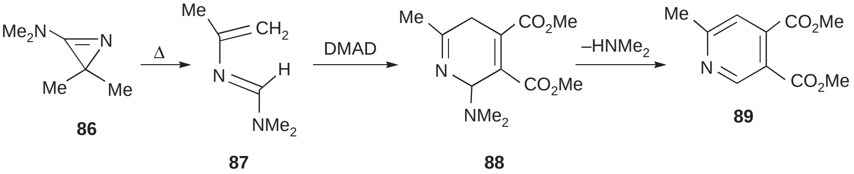
Products formed during photochemical isomerizations involve C–C bond rupture, while thermal isomerization products usually arise from initial C–N bond cleavage. Unambiguous evidence for a thermal C–C cleavage has been obtained, however, in the vapor phase pyrolysis of several 2*H*-azirines (76JOC831). The diradical species **81** generated from C–C cleavage is postulated to undergo a 1,4-hydrogen transfer to produce azadiene **82** which ultimately fragments to a nitrile and an alkene *via* an azacyclobutene intermediate **83**, or else undergoes an



Scheme 21



Scheme 22



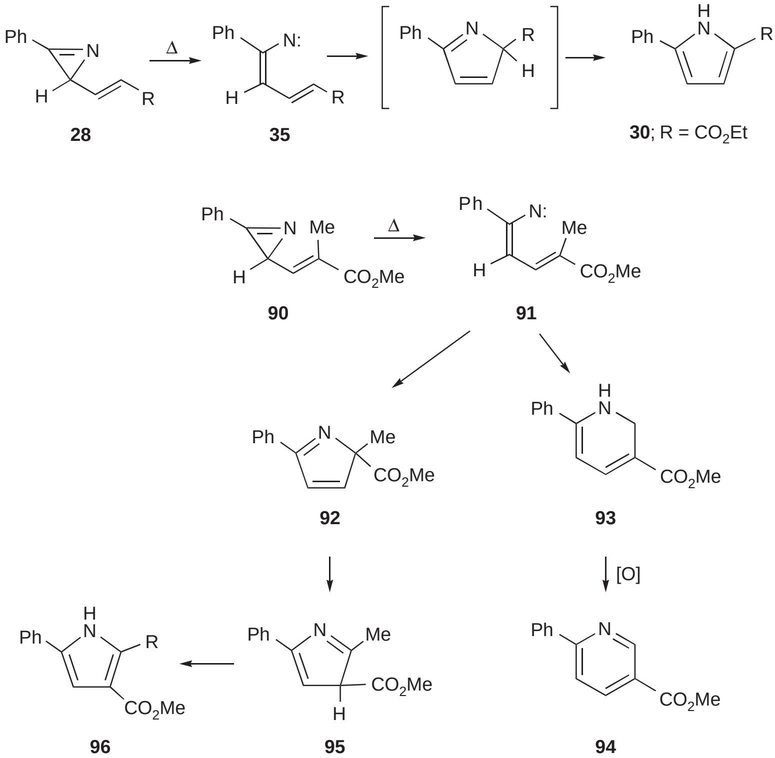
Scheme 23

electrocyclic ring closure followed by a 1,5-hydrogen shift to produce dihydroisoquinoline **85** (Scheme 22).

Vapor phase pyrolysis of 2-dimethylamino-2*H*-azirine (**86**) proceeds in a similar manner at 340 °C to give the substituted azadiene **87** in high yield (75JA4409). Azadiene **87** has been employed in the construction of heterocyclic rings such as pyridine **89** *via* a [4+2]-cycloaddition–elimination sequence (Scheme 23).

3.2 1,5-Electrocyclization of 3-vinyl-2*H*-azirines

The synthesis of a number of pyrrole derivatives has been effected by the thermal conversion of 3-vinyl-2*H*-azirines to butadienylnitrenes followed by 1,5-electrocyclization (75JA4682). For example, the thermal transformations observed on thermolysis of 2*H*-azirine **28** were rationalized in terms of an equilibration of the 2*H*-azirine with a butadienylnitrene, which subsequently rearranged to the final products. The rearrangement of **28** to pyrrole **30** was envisaged as occurring by an electrocyclic reaction followed by a 1,5-sigmatropic ethoxycarbonyl shift and subsequent tautomerization



Scheme 24

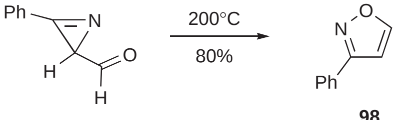
(76JOC543). Other examples of this rearrangement have been reported to occur with ester, acyl and cyano groups (72TL3479). The formation of pyridine **94** was postulated to arise by insertion of the butadienylnitrene into the neighboring allylic methyl group followed by oxidation of the transient dihydropyridine **93**. In the absence of factors such as strain, pyrrole formation (i.e., **96**) is generally favored over pyridine formation (Scheme 24) (90H753).

Thermolysis of 2*H*-azirines bearing an aldehyde or imine substituent at C(2) leads to the formation of isoxazoles and pyrazoles, respectively (e.g., Scheme 25) (74TL29, 75JA4682). The reverse reaction, thermolysis of an isoxazole to afford a 2*H*-azirine, has also been reported (69TL2049).

Thermolysis of 2*H*-azirines bearing aromatic substituents (i.e., **99**) generally produce indoles by electrocyclization of the intermediate vinyl **100** nitrene with the aromatic ring as illustrated in Scheme 26 (68TL3499, 71CC1518, 77H1563). However, when only one phenyl group is present on C(2), the intermediate vinyl nitrene can rearrange to a nitrile (68TL3499).

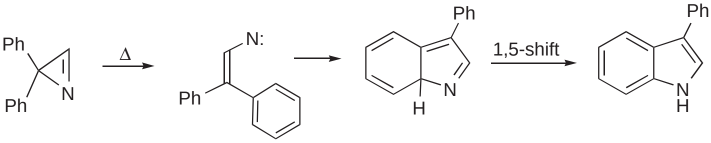
3.3 Thermal rearrangements of allyl and homo-allyl 2*H*-azirines

A number of allyl-substituted 2*H*-azirines were found to undergo smooth rearrangement on heating to give 2-azabicyclo[3.1.0]hexenes **105** (78JOC2029). The formation of **105** can be explained in terms of an equilibration of the 2*H*-azirine with a transient vinylnitrene which subsequently adds to the adjacent π-bond. The initially formed bicycloaziridine rearranges to the 3-azabicyclohexene ring system by means of a 1,3-sigmatropic shift. Evidence favoring this pathway is provided by the isolation of Δ^1-pyrroline **106** from the thermolysis of 2*H*-azirine (**42**; $R^1 = H$, $R^2 = Me$). The formation of **106** was rationalized as



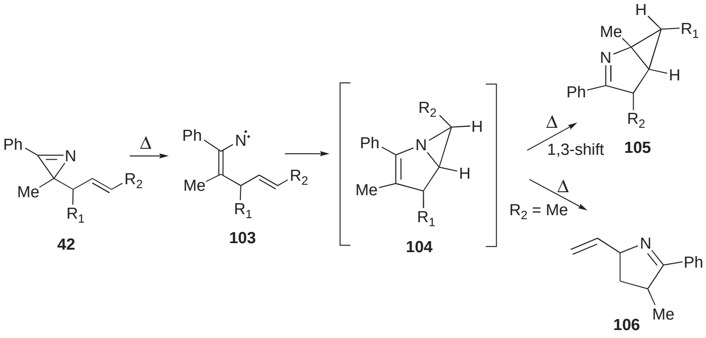
97 **98**

Scheme 25

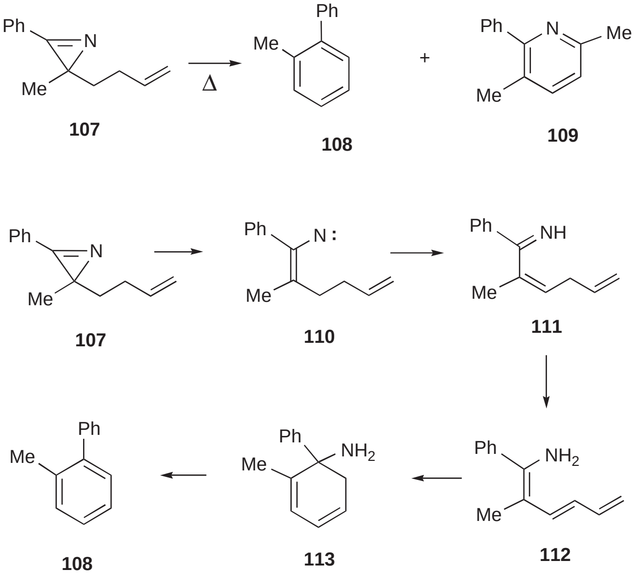


99 **100** **101** **102**

Scheme 26



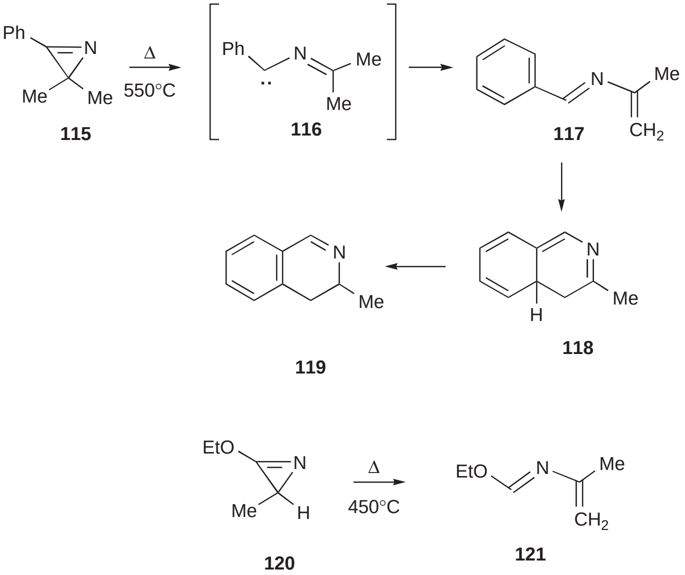
Scheme 27



Scheme 28

proceeding *via* a homo [1,5]-hydrogen migration from a 6-*endo*-methyl-substituted azabicyclic intermediate **104** (Scheme 27).

The thermal behavior of the closely related homoallyl-substituted 2*H*-azirine **107** has also been studied (77JA1871). Heating a solution of **107** in toluene gave 2-methylbiphenyl (**108**) and 2,5-dimethyl-6-phenylpyridine (**109**). The formation of these products is explained in terms of vinylnitrene **110** which undergoes a 1,4-hydrogen transfer from the neighboring methylene group to generate azatriene **111**. This reactive intermediate then undergoes a thermally allowed 1,5-sigmatropic shift to



Scheme 29

give triene **112**. Electrocyclic closure to cyclohexadiene **113** followed by loss of ammonia readily accounts for the formation of the substituted biphenyl derivatives. The formation of **109** involves an insertion of the vinylnitrene into the vinyl group followed by tautomerization and a subsequent oxidation (Scheme 28).

It should be noted that the thermal cleavage of the C–C bond of 2*H*-azirines is less common than C(2)–N bond cleavage and requires substantially higher temperatures (82MI101-01). These reactions are believed to proceed *via* iminocarbene intermediates which undergo a 1,4-hydrogen transfer to yield 2-aza-1,3-butadienes. The dienes which are formed often participate in subsequent intra- and intermolecular cyclization reactions (74JA308, 75JA4409, 76JOC831, 77H895, 83HCA262, 86RTC456). Scheme 29 shows an example where electrocyclization of the azabutadiene leads to a dihydroquinoline (76JOC831). The thermolysis of 3-amino-2*H*-azirines affords isolable 1-amino-2-azabutadienes (91AG238). A similar process involving 3-alkoxy-2*H*-azirines (86RTC456) is also given in the same scheme.

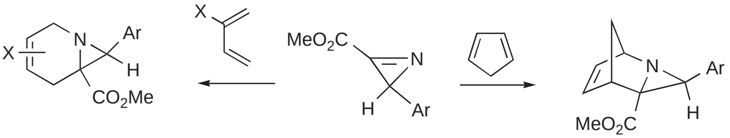
4. 2*H*-AZIRINES AS DIENOPHILES OR DIPOLAROPHILES IN CYCLOADDITION REACTIONS

The 2π-electrons of the carbon–nitrogen double bond of 2*H*-azirines can participate in thermal symmetry-allowed [4+2]-cycloadditions with a variety of substrates such as cyclopentadienones, isobenzofurans, triazines and tetrazines. Cycloadditions also occur with heterocumulenes such as ketenes, ketenimines, isocyanates and carbon disulfide. It is also possible for the 2π-electrons of 2*H*-azirines to participate in "ene" reactions (73HCA1351).

4.1 Diels–Alder and related processes

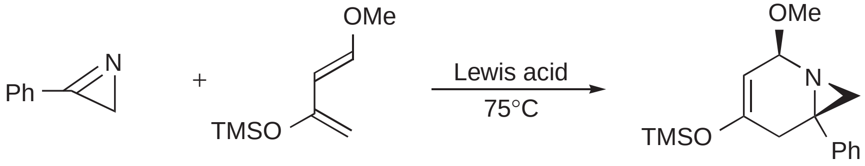
The strained, electron-rich carbon–nitrogen double bond present in the 2*H*-azirine ring is more reactive than the corresponding double bond in an imine and, while 2*H*-azirines participate in reverse electron-demand Diels–Alder reactions (96CHEC-2(1)1), there are only a few publications describing the normal electron-demand Diels–Alder reactions of 2*H*-azirines. Methyl 2-aryl-2*H*-azirine-3-carboxylates **123** are good dienophiles and they readily react with a variety of dienes to give bicyclic products such as **122** and **124** by cycloaddition across the C–N double bond (Scheme 30). The cycloadditions are *endo*-selective and the dienophile approach takes place from the less hindered face of the 2*H*-azirine (97S271, 98TL7579, 98JCS(P1)299). The Diels–Alder reactions of a chiral ester of 2*H*-azirine-3-carboxylic acid with cyclopentadiene was observed to be highly diastereoselective (99JCS(P1)1399).

Activation of 3-alkyl and 3-phenyl-2*H*-azirines by Lewis acids also promotes their participation in hetero Diels–Alder reactions with a variety of dienes. This methodology circumvents the previous requirement of needing an electron-withdrawing carboxyl moiety at the 3-position of the 2*H*-azirine ring (01TL9289). Thus, the reaction of 2*H*-azirine **125** with Danishefsky's diene gave the *endo*-cycloadduct **126**



122 **123** **124**

Scheme 30



125 **126**

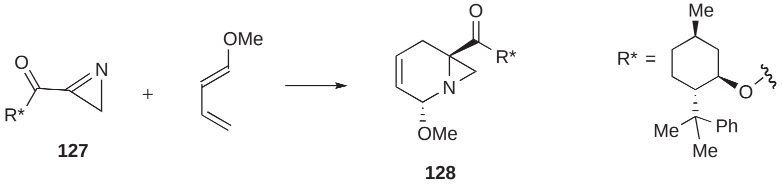
Scheme 31

when the reaction was carried out using 0.3 equiv. of a Lewis acid (i.e., $ZnCl_2$, $YbCl_3$, $CuCl_2$) at 75 °C (Scheme 31). Several other, less activated dienes, were also be used for this reaction.

Highly diastereoselective Lewis acid mediated aza-Diels–Alder reactions of chiral auxiliary derivatized 2*H*-azirines have been studied (02T5983, 03JOC9958, 03CC1150). The cycloaddition proceeded with high diastereoselectivity (97% de), with the absolute stereochemistry of the major product confirmed by X-ray crystallography. Without the presence of a Lewis acid, no diastereoselectivity was obtained at room temperature.

The dramatic effect observed on the reaction diastereoselectivity upon addition of a Lewis acid to 2*H*-azirine **127** was explained by a bidentate coordination of the Lewis acid to the 2*H*-azirine nitrogen and the carbonyl group. This chelation would lead to hindered rotation around the 2*H*-azirine carbonyl single bond and thus greater stereoselectivity. The increased reaction rate also indicates coordination of the Lewis acids to the 2*H*-azirine which leads to a lowering of the LUMO energy level and thus an increased reactivity toward the electron-rich diene (Scheme 32).

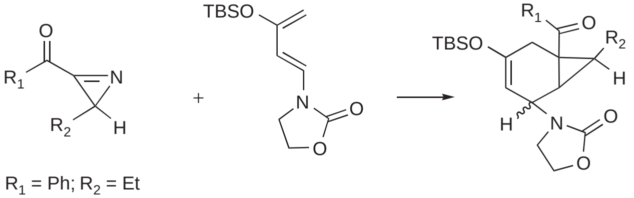
2*H*-Azirines are excellent partners in aza-Diels–Alder reactions that occur at room temperature when the C=N bond is activated with a conjugated oxo, alkoxycarbonyl or heteroaromatic group (05S555). For example, 3-(3-*tert*-butyldimethylsilyloxy)buta-1,3-dienyl)oxazolidin-2-one (**130**) reacted with several electrophilic 2*H*-azirines of type **129** to furnish the expected [4+2]-cycloadducts **131** in moderate to good yield (06T3095). 2*H*-Azirine **129b** underwent smooth [4+2]-cycloaddition with



127

128

Scheme 32



129a; R_1 = Ph; R_2 = Et
129b; R_1 = OMe; R_2 = 2,6-Cl_2Ph

130

131

Scheme 33

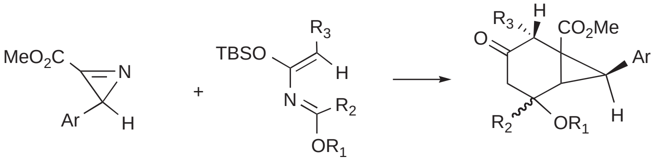
furan, diphenylisobenzofuran (01JCS(P1)2969) and several electron-rich 2-azadienes (Scheme 33) (03TL5079). All of the [4+2]-cycloaddition reactions were found to be *endo* and regioselective with the 2*H*-azirine being added from its less hindered face.

tert-Butyldimethylsiloxy-2-aza-1,3-butadienes (**133**) react with 2*H*-azirine **132** and produce the Diels–Alder cycloadducts **134** in moderate yield (04T6541, 03TL5079). A 1:1-mixture of diastereomers are formed which implies that an isomerization is taking place about C_3 to C_4 during the course of the reaction (Scheme 34). This cycloaddition represents the first example of a reaction between an activated 2-azadiene with an electron deficient 2*H*-azirine.

2*H*-Azirine **132** also undergoes reaction with various fulvenes in THF at 25 °C to afford the corresponding [2]pyridine **133** in 19% yield as the only isolable product. The yield of the [6+3]-cycloadduct **133** improved to 83% in the presence of 20 mol% $Y(OTf)_3$ in THF (04TL1663). [2] Pyrindine **133** proved to be unstable and was gradually converted to **134** after standing for a few days in the refrigerator (Scheme 35).

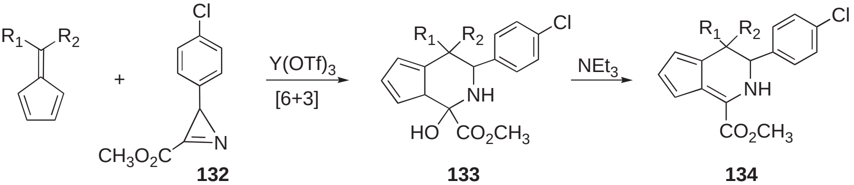
The formation of **133** was rationalized by a stepwise mechanism. The initial addition of the fulvene to the activated 2*H*-azirine generates the zwitterionic intermediate **135** which then cyclizes to [2]pyrindine **133** *via* intermediate **136** (Scheme 36).

Interestingly, the reaction of dimethyl fulvene (R = Me) with 2*H*-azirine **132** in an ultrasonic bath (neat) yielded the alkylation product **138**. The structure of **138** was unambiguously assigned by single crystal X-ray structure. A possible mechanism to account for the formation of **138** involves an initial [4+2]-cycloaddition followed by a subsequent



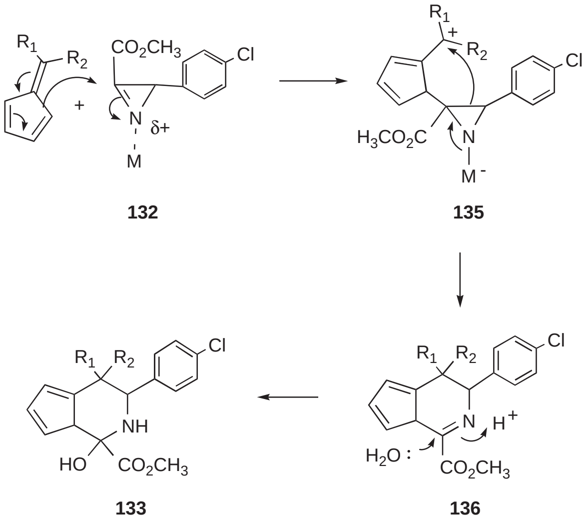
132; Ar = 2,6-dichlorophenyl **133** **134**

Scheme 34

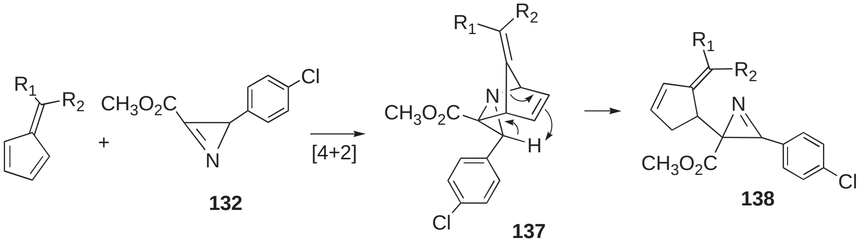


132 **133** **134**

Scheme 35



Scheme 36



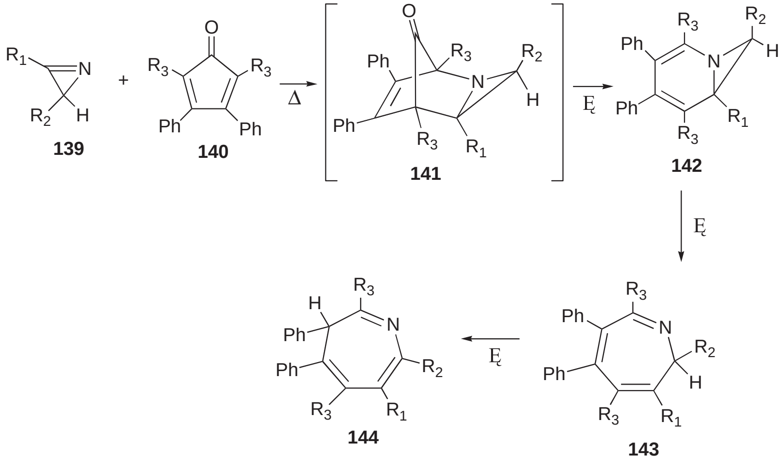
Scheme 37

rearrangement of the initially formed Diels–Alder cycloadduct **137** (Scheme 37).

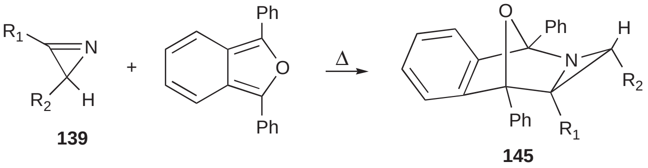
Still another example of a bimolecular cycloaddition of the 2*H*-azirine ring system involves the thermal reaction of **139** with cyclopentadienone **140** to give 3*H*-azepine **144** (72JOC802, 72JA8255). The first step of this reaction proceeds by a [4+2]-cycloaddition to give the *endo* adduct **141**. Cheletropic fragmentation of adduct **141** furnishes azanorcaradiene **142**. This material undergoes a disrotatory electrocyclic ring opening followed by a 1,5-suprafacial hydrogen shift to give the thermodynamically most stable 3*H*-azepine ring (Scheme 38).

1,3-Diphenylisobenzofuran has been reported to react with 2*H*-azirine **139** in refluxing toluene to give cycloadduct **145**, the primary product of a [4+2]-cycloaddition (Scheme 39) (72JOC2508, 74JOC2031, 05S555).

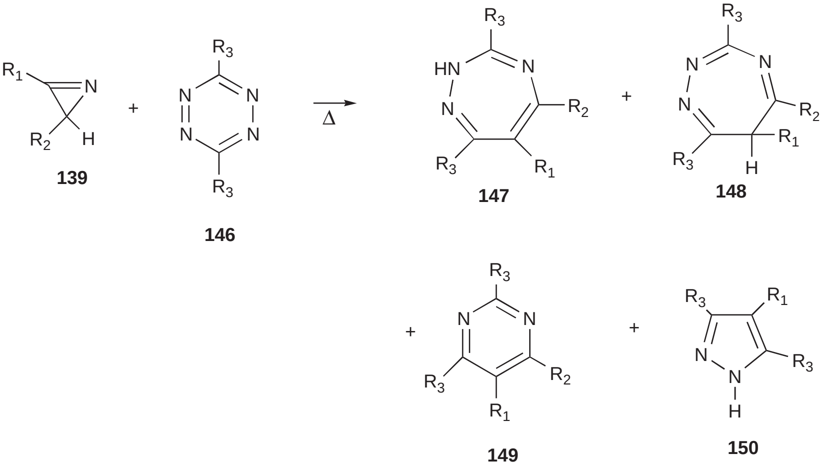
A particularly interesting system where nitrogen is lost cheletropically after formation of the initial [4+2]-cycloadduct involves the thermal



Scheme 38



Scheme 39



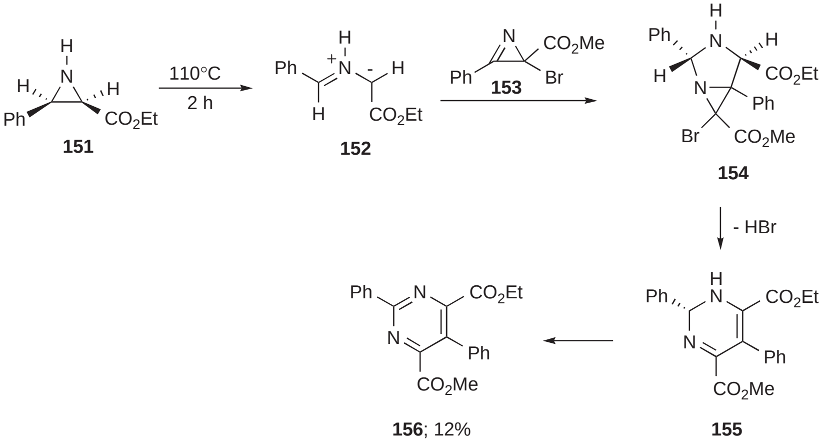
Scheme 40

reaction of 2*H*-azirines with tetrazines **146** (74TL2303, 74CC782, 74JOC3076, 75JHC183). A variety of heterocyclic products are produced depending on the structure of the 2*H*-azirine and tetrazine used and the reaction conditions (Scheme 40).

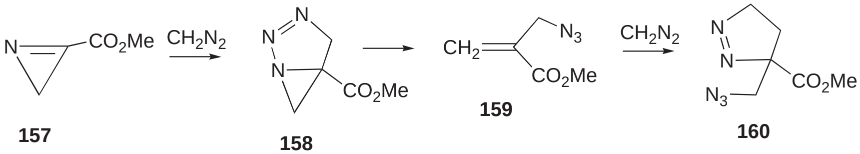
4.2 Bimolecular [1,3]-dipolar cycloadditions

The 2*H*-azirine ring can also be used as a dipolarophile. The formation of pyrimidine **156** from the reaction of aziridine **151** with 2*H*-azirine **153** in toluene was rationalized by a 1,3-dipolar cycloaddition across the 2*H*-azirine π-bond. Thus, thermal ring opening of aziridine **151** gave the expected azomethine ylide dipole **152** which reacted by way of a [3+2]-cycloaddition with 2*H*-azirine **153** to furnish cycloadduct **154**. This transient intermediate underwent a subsequent ring opening reaction with elimination of HBr leading to dihydropyrimidine **155** and this was followed by aromatization to give the observed product **156** (Scheme 41) (03TL6313).

The reaction of 2*H*-azirine-3-carboxylate **157** with diazomethane occurs to produce a 4,5-dihydro-3*H*-pyrazole derivative **160**. This reaction represents another example of the imino group acting as a



Scheme 41



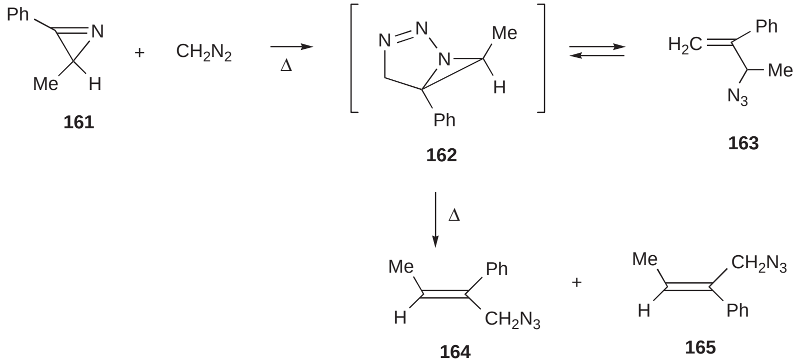
Scheme 42

2π-component in a 1,3-dipolar cycloaddition reaction (03TL6319, 68JOC2121). The process seemingly involves the reaction of 2*H*-azirine **157** with diazomethane to give cycloadduct **158** as a transient species which then undergoes a subsequent rearrangement to generate allyl azide **159**. This compound participates in a second 1,3-dipolar cycloaddition with diazomethane to give **160** (Scheme 42).

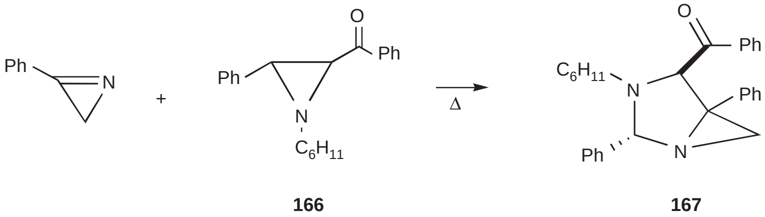
The interaction of diazomethane with 2*H*-azirines (**161**) was reported in 1964 (64JOC3049) and represents the first example of a 1,3-dipolar cycloaddition with this ring system. 1,3-Dipolar addition produces the triazoline adduct **162**. This material can exist in equilibrium with its valence tautomer **163**, and allylic azides **164** and **165** are subsequently produced from these triazolines by ring cleavage (Scheme 43).

Aziridines such as **166** undergo thermal ring opening in a conrotatory manner to generate azomethine ylides. These azomethine ylides are 4π-components and have also been found to participate in [4+2]-cycloadditions with 2*H*-azirines acting as the 2π-component to give **167** (Scheme 44) (73HCA1351).

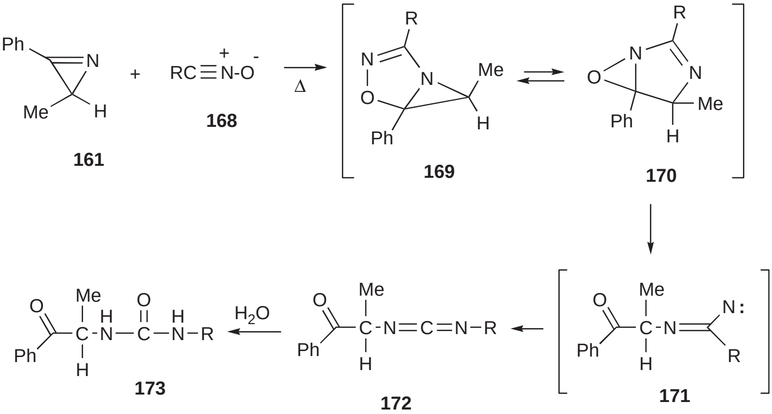
The 4π-electron system of nitrile oxides can also participate in 1,3-dipolar cycloaddition with 2*H*-azirines (71TL4831). For example,



Scheme 43



Scheme 44



Scheme 45

aromatic nitrile oxides react exothermically with 2*H*-azirines to furnish carbodiimides in high yield. A possible mechanism for the formation of the carbodiimide assumes the initial formation of a cycloadduct from a 1,3-dipolar addition between the nitrile oxide and the 2*H*-azirine. Ring cleavage of the bicyclic adduct or its valence tautomer is followed by a 1,2-migration of the R group of the nitrile oxide in a Beckmann-type rearrangement to give the carbodiimide **173** (Scheme 45).

The reactions of 2*H*-azirines with ketenes and ketenimines represent non-concerted additions and are formally different from the additions to 4π-systems of dienes and 1,3-dipolar compounds (73JOC3466, 71CB2789).

5. CONCLUDING REMARKS

A selective sampling of the photochemical cycloaddition and cyclization chemistry of 2*H*-azirines has been outlined in this chapter. Some photochemical sequences increase molecular complexity more than others, but each seems to provide complex heterocyclic structures in a very efficient manner. Indeed, many of these photoreactions rapidly construct hetero-polycyclic systems that are difficult to produce in other ways. In contrast to their photochemical behavior, the major thermal reaction of 2*H*-azirines generally involves C(2)–N bond cleavage to form vinyl nitrenes which further react by either insertion into an adjacent C–H bond or else undergo addition across a neighboring π-bond. The 2π-electrons of the carbon–nitrogen double bond of 2*H*-azirines can also participate in thermal symmetry-allowed [4+2]-cycloadditions with a variety of substrates. It is clear from the above discussion that the chemistry of 2*H*-azirines is both mechanistically complex and synthetically useful. No doubt additional work with this fascinating small ring nitrogen heterocycle will be forthcoming in the future.

ACKNOWLEDGMENT

AP wishes to acknowledge the research support of our program in heterocyclic chemistry by the National Science Foundation (CHE-0742663).

REFERENCES

64JOC3049	A. L. Logothetis, *J. Org. Chem.*, **29**, 3049–3052 (1964).
67JA6911	B. Singh and E. F. Ullman, *J. Am. Chem. Soc.*, **89**, 6911–6916 (1967).
68AG130	F. P. Woerner, H. Reimlinger, and D. R. Arnold, *Angew. Chem. Int. Ed. Engl.*, **30**, 130–131 (1968).
68JOC2121	V. Nair, *J. Org. Chem.*, **33**, 2121–2123 (1968).
68JOC2291	R. Huisgen, *J. Org. Chem.*, **33**, 2291–2297 (1968).
68TL3499	K. Isomura, S. Kobayashi, and H. Taniguchi, *Tetrahedron Lett.*, **9**, 3499–3502 (1968).
69T1637	A. Hassner, R. J. Isbister, R. B. Greenwald, J. T. Klug, and E. C. Taylor, *Tetrahedron*, **25**, 1637–1641 (1969).
69TL2049	T. Nishiwaki, *Tetrahedron Lett.*, **10**, 2049–2052 (1969).
69TL4073	K. Isomura, M. Okada, and H. Taniguchi, *Tetrahedron Lett.*, **10**, 4073–4076 (1969).
71CB2789	F. R. Woerner, H. Reimlinger, and R. Merenyi, *Chem. Ber.*, **104**, 2789–2792 (1971).
71CC1518	D. J. Anderson, T. L. Gilchrist, G. E. Gymer, and C. W. Rees, *J. Chem. Soc., Chem. Commun.*, 1518–1521 (1971).
71JCS3021	T. Nishiwaki and T. Saito, *J. Chem. Soc.*, 3021–3027 (1971).
71TL4831	V. Nair, *Tetrahedron Lett.*, **12**, 4831–4833 (1971).
72CC409	A. Padwa, J. Smolanoff, and S. I. Wetmore, Jr., *J. Chem. Soc., Chem. Commun.*, 409–410 (1972).
72CC565	T. Nishiwaki, *J. Chem. Soc., Chem. Commun.*, 565–566 (1972).
72JA7788	A. Padwa and E. Glazer, *J. Am. Chem. Soc.*, **94**, 7788–7797 (1972).
72JA8255	A. Hassner and D. J. Anderson, *J. Am. Chem. Soc.*, **94**, 8255–8256 (1972).
72JCS(P1)1456	T. Nishiwaki and F. Fujiyama, *J. Chem. Soc., Perkin Trans. 1*, 1456–1459 (1972).
72JOC802	V. Nair, *J. Org. Chem.*, **37**, 802–804 (1972).
72JOC2508	A. R. Doumaux, *J. Org. Chem.*, **37**, 508–510 (1972).
72TL3479	H. Diirr and R. Sergio, *Tetrahedron Lett.*, **13**, 3479–3482 (1972).
73HCA1351	N. S. Narasimhan, H. Heimgartner, H. J. Hansen, and H. Schmid, *Helv. Chim. Acta*, **56**, 1351–1370 (1973).
73JA1954	A. Padwa, M. Dharan, J. Smolanoff, and S. Wetmore, *J. Am. Chem. Soc.*, **95**, 1954–1961 (1973).
73JA7287	K. N. Houk, J. Sims, R. E. Duke, R. W. Strozier, and J. K. George, *J. Am. Chem. Soc.*, **95**, 7287–7301 (1973).
73JOC3466	M. J. Haddadin and A. Hassner, *J. Org. Chem.*, **38**, 3466–3471 (1973).

74CC782	R. E. Moerck and M. A. Battiste, *J. Chem. Soc., Chem. Commun.*, 782–783 (1974).
74JA308	L. A. Wendling and R. G. Bergman, *J. Am. Chem. Soc.*, **96**, 308–309 (1974).
74JOC2031	A. Hassner and D. J. Anderson, *J. Org. Chem.*, **39**, 2031–2036 (1974).
74JOC3076	D. J. Anderson, A. Hassner, and D. Y. Tang, *J. Org. Chem.*, **39**, 3076–3080 (1974).
74TL29	A. Padwa, L. Smolanoff, and A. Tremper, *Tetrahedron Lett.*, **15**, 29–32 (1974).
74TL2303	G. C. Johnson and R. H. Levin, *Tetrahedron Lett.*, **15**, 2303–2306 (1974).
75JA3862	A. Padwa and P. H. J. Carlsen, *J. Am. Chem. Soc.*, **97**, 3862–3864 (1975).
75JA4409	A. Demoulin, H. Gorissen, A.-M. Hesbain-Frisque, and L. Ghosez, *J. Am. Chem. Soc.*, **97**, 4409–4410 (1975).
75JA4682	A. Padwa, J. Smolanoff, and A. Tremper, *J. Am. Chem. Soc.*, **97**, 4682–4700 (1975).
75JA5912	A. Padwa and J. K. Rasmussen, *J. Am. Chem. Soc.*, **97**, 5912–5914 (1975).
75JHC183	V. Nair, *J. Heterocycl. Chem.*, **12**, 183–184 (1975).
76ACR371	A. Padwa, *Acc. Chem. Res.*, **9**, 371–378 (1976).
76JA1048	A. Padwa, A. Ku, A. Mazzu, and S. I. Wetmore, *J. Am. Chem. Soc.*, **98**, 1048–1050 (1976).
76JOC180	A. Padwa and P. H. J. Carlsen, *J. Org. Chem.*, **41**, 180–182 (1976).
76JOC543	A. Padwa, J. Smolanoff, and A. Tremper, *J. Org. Chem.*, **41**, 543–549 (1976).
76JOC831	L. A. Wendling and R. G. Bergman, *J. Org. Chem.*, **41**, 831–836 (1976).
77H143	P. Gilgen, H. Heimgartner, H. Schmid, and H. J. Hansen, *Heterocycles*, **6**, 143–152 (1977).
77H1563	H. Taniguchi, K. Isomura, and T. Tanaka, *Heterocycles*, **6**, 1563–1568 (1977).
77H895	L. Ghosez, A. Demoulin, M. Henriet, E. Sonveaux, M. Van Meerssche, G. Germain, and J.-P. Declercq, *Heterocycles*, **7**, 895–902 (1977).
77JA1871	A. Padwa and N. Kamigata, *J. Am. Chem. Soc.*, **99**, 1871–1880 (1977).
78JA4481	A. Padwa, P. H. J. Carlsen, and A. Tremper, *J. Am. Chem. Soc.*, **100**, 4481–4490 (1978).
78JA6575	B. Bigot, R. Ponec, A. Sevin, and A. Devaquet, *J. Am. Chem. Soc.*, **100**, 6575–6580 (1978).
78JOC2029	A. Padwa and P. H. J. Carlsen, *J. Org. Chem.*, **43**, 2029–2037 (1978).
82MI101-01	A. Padwa and P. H. J. Carlsen, in "*Reactive Intermediates*" (R. A. Abramovitch, ed.), Vol. 2, Plenum Press, New York.
83HCA262	K. Dietliker and H. Heimgartner, *Helv. Chim. Acta*, **66**, 262–295 (1983).
83MI101-02	V. Nair, in "*The Chemistry of Heterocyclic Compounds*" (A. Hassner, ed.), Vol. 42, part 1, pp. 215–242, Wiley, New York (1983).
84CHEC-1(7)47	A. Padwa and A. D. Woolhouse, in "*Comprehensive Heterocyclic Chemistry 1*" (A. R. Katritzky and C. W. Rees, eds.), Vol. 7, Pergamon, (1984).

84MI101-03 A. Hassner, in "*Azides and Nitrenes*" (E. F. V. Scriven, ed.), pp. 35–51, Academic Press, New York (1984).

84MI101-04 H.-J. Hansen and H. Heimgartner, in "*1,3-Dipolar Cycloaddition Chemistry*" (A. Padwa, ed.), Vol. 1, pp. 177–198, Wiley, New York (1984).

86RTC456 L. Ghosez, F. Sainte, M. Rivera, C. Bernard-Henriet, and V. Gouverneur, *Recl. Trav. Chim. Pays-Bas*, **105**, 456–461 (1986).

90H753 M. Saruwatari, K. Isomura, and H. Taniguchi, *Heterocycles*, **30**, 753–758 (1990).

91AG238 H. Heimgartner, *Angew. Chem. Int. Ed. Engl.*, **30**, 238–265 (1991).

92AG207 F. Mueller and J. Mattay, *Angew. Chem., Int. Ed. Engl.*, **31**, 207–208 (1992).

93CB543 F. Mueller and J. Mattay, *Chem. Ber.*, **126**, 543–549 (1993).

93JCS(P1)675 T. Benincori, E. Brenna, and F. Sannicolo, *J. Chem. Soc., Perkin Trans. 1*, 675–679 (1993).

93JOC4462 F. Muller, J. Mattay, and S. Steenken, *J. Org. Chem.*, **58**, 4462–4464 (1993).

95HCA935 C. B. Bucher, A. Linden, and H. Heimgartner, *Helv. Chim. Acta*, **78**, 935–945 (1995).

96CHEC-2(1)1 W. H. Pearson, B. W. Lian, and S. C. Bergmeier, in "*Comprehensive Heterocyclic Chemistry 2*" (A. R. Katritzky, C. W. Rees, and E. F. V. Scriven, eds.), Vol. 1A, Elsevier, Oxford, UK (1996).

97CEJ1757 V. Piquet, A. Baceiredo, H. Gornitzka, F. Dahan, and G. Bertrand, *Chem. Eur. J.*, **3**, 1757–1764 (1997).

97JA11605 E. Albrecht, J. Mattay, and S. Steenken, *J. Am. Chem. Soc.*, **119**, 11605–11610 (1997).

97S271 P. Bhullar, T. L. Gilchrist, and P. Maddocks, *Synthesis*, 271–272 (1997).

98H2551 N. Kanomata and T. Nakata, *Heterocycles*, **48**, 2551–2558 (1998).

98JCC912 S. Calvo-Losado, J. J. Quirante, D. Suarez, and T. L. Sordo, *J. Comput. Chem.*, **19**, 912–922 (1998).

98JCS(P1)299 M. J. Alves and T. L. Gilchrist, *J. Chem. Soc., Perkin Trans. 1*, 299–304 (1998).

98TL7579 M. J. Alves and T. L. Gilchrist, *Tetrahedron Lett.*, **39**, 7579–7582 (1998).

99JCS(P1)1399 M. J. Alves, J. F. Bickley, and T. L. Gilchrist, *J. Chem. Soc., Perkin Trans. 1*, 1399–1402 (1999).

99JOC6239 F. Palacios, E. Herran, and G. Rubiales, *J. Org. Chem.*, **64**, 6239–6246 (1999).

01EJOC2401 F. Palacios, A. M. Ochoa de Retana, E. M. de Marigorta, and J. M. de los Santos, *Eur. J. Org. Chem.*, 2401–2414 (2001).

01TL9289 C. A. Ray, E. Risberg, and P. Somfai, *Tetrahedron Lett.*, **42**, 9289–9291 (2001).

01JCS(P1)2969 M. J. Alves, N. G. Azoia, J. F. Bickley, A. Gil Fortes, T. L. Gilchrist, and R. Mendonca, *J. Chem. Soc., Perkin Trans. 1*, 2969–2976 (2001).

02EJOC1750 E. U. Würthwein, T. Hergenröther, and H. Quast, *Eur. J. Org. Chem.*, 1750–1755 (2002).

02OPP219 F. Palacios, A. M. Ochoa de Retana, E. M. de Marigorta, and J. M. de los Santo, *Org. Prep. Proc. Int.*, **34**, 219–269 (2002).

02T5983 B. Jousseaume, C. Laporte, T. Toupance, and J. M. Bernar, *Tetrahedron Lett.*, **44**, 5983–5985 (2002).

03CC1150	A. S. Timén, A. Fischer, and P. Somfai, *Chem. Commun.*, 1150–1151 (2003).
03JOC9958	A. S. Timén and P. Somfai, *J. Org. Chem.*, **68**, 9958–9963 (2003).
03TL5079	M. J. Alves, M. M. Duraes, and A. Gil Fortes, *Tetrahedron Lett.*, **44**, 5079–5082 (2003).
03TL6313	T. M. V. D. Pinho e Melo, A. L. Cardoso, C. S. B. Gomes, and A. M. d'A Rocha Gonsalves, *Tetrahedron Lett.*, **44**, 6313–6315 (2003).
03TL6319	Y. Yamauchi, T. Kawatee, H. Itahashi, T. Katagiri, and K. Uneyama, *Tetrahedron Lett.*, **44**, 6319–6322 (2003).
04T6541	M. J. Alves, M. M. Duraes, and A. G. Fortes, *Tetrahedron*, **60**, 6541–6553 (2004).
04TL1663	B. C. Hong, A. K. Gupta, M. F. Wu, and J. H. Liao, *Tetrahedron Lett.*, **45**, 1663–1666 (2004).
05JA2628	H. Inui and S. Murata, *J. Am. Chem. Soc.*, **127**, 2628–2636 (2005).
05S555	M. J. Alves, A. G. Fortes, and C. Martins, *Synthesis*, 555–558 (2005).
06T3095	M. J. Alves, A. G. Fortes, and F. T. Costa, *Tetrahedron*, **62**, 3095–3102 (2006).

CHAPTER 2

Heterocyclic BINAP Analogues

Nuzhat Arshad and **C. Oliver Kappe**

Contents

---

1. INTRODUCTION

Transition metal enantioselective catalysis is among the most challenging and widely investigated areas in modern synthetic chemistry. This statement is clearly supported by the award of the 2001 Nobel Prize in Chemistry to W. S. Knowles, R. Noyori, and K. B. Sharpless for their

---

Institute of Chemistry, Karl-Franzens University Graz, Heinrichstrasse 28, A-8010 Graz, Austria

Advances in Heterocyclic Chemistry, Volume 99
ISSN 0065-2725, DOI 10.1016/S0065-2725(10)09902-2

work on asymmetric hydrogenation and oxidation reactions, respectively (03ACR908). The success of any asymmetric reaction relies primarily on the proper combination of metal and ligand. Whereas the choice of transition metal is limited, a myriad of organic backbones may be employed as ligand structures. In fact, exploring and designing new effective chiral ligands continues to be an important area of synthetic organic chemistry. While designing a ligand several key factors are to be considered; for example: accessibility (whether the ligand can be prepared easily), stability (whether it would be stable under various conditions), reactivity and scope (whether and how it will form reactive catalytic species with transition metals, and for what type of substrate it will be useful), modularity (whether the structural motif is capable to be brought into a broad ligand series in order to fine-tune its electronic and steric properties), and how to facilitate its separation from the mixture. Indeed thus far, ligand design remains an empirical rather than a rational approach, where a useful ligand can only be discovered through extensive trial and error. Nevertheless, an inspiring prototype on further modification can often lead to improved catalytic efficiency (07ACR1278). In 1980, Noyori et al. initiated pioneering work on axially chiral 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (BINAP (**1a**), Figure 1) operating through Rh-catalyzed hydrogenation initially, and soon after made several breakthroughs including the development of BINAP–Ru complexes, which displayed an incredible range of efficiency and opened up many new classes of olefins and functionalized ketones

1a: R = Ph (BINAP)
1b: R = 4-MeC_6H_4 (Tol-BINAP)
1c: R = 4-*t*-BuC_6H_4 (*t*-Bu-BINAP)
1d: R = 4-MeO-C_6H_4 (MeO-BINAP)
1e: R = 3,5-$Me_2C_6H_3$ (DM-BINAP)
1f: R = 3,5-(*t*-Bu)$_2C_6H_3$ (DB-BINAP)
1g: R = 4-MeO-3,5-$Me_2C_6H_2$ (DMM-BINAP)
1h: R = cyclohexyl (Cy-BINAP)
1i: R = 2-furyl (TetFu-BINAP)
1j: R = 4-FC_6H_4 (*p*-F-BINAP)
1k: R = 4-ClC_6H_4 (*p*-Cl-BINAP)

2a: R = Me
2b: R = Ph
2c: R = SiMe
2d: R = CN
2e: R = NH_2
2f: R = $POPh_2$

Figure 1 Modifications on BINAP ligand.

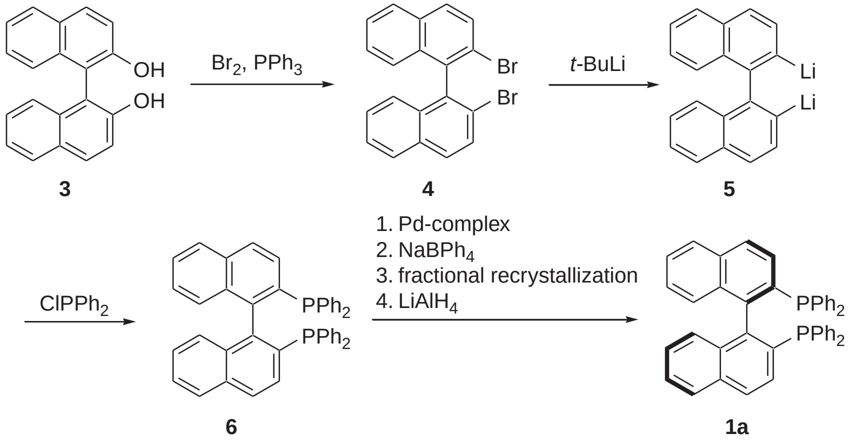
for enantioselective hydrogenations (05T5405). Since its discovery, the BINAP ligand family has been used in a variety of applications in synthesis as it induces very high ee's in several asymmetric transition-metal-catalyzed processes, including hydrogenations, hydrosilylations, hydrocyanations, Heck reactions, and enamine isomerizations (90ACR345, 03ASC15). The versatility and ready availability of the BINAP scaffold has allowed diverse approaches to modify BINAP (**1a**), for example by replacing the 2,2′-diphenylphosphino group with other disubstituted phosphino groups (ligands **1b–k**) in order to fine-tune its electronic and/or steric properties, or by attaching different functional groups on the binaphthyl backbone (ligands **2a–f**) to further extend its versatility (Figure 1). In addition, the binaphthyl backbone can be replaced with a variety of biheteroaryl or biheterocyclic backbones. Phosphine ligands with atropisomeric biheterocyclic (biheteroaryl) backbones were first reported by Sannicolo et al. in 1996. This new category of ligands has the advantage of facile tuning of electronic properties as the variation of heteroatoms incorporated in the ring will have a direct impact on the electronic properties of the phosphine ligators which ultimately may result in more flexible chemistry and selectivities. In addition, a much wider variety of potential frameworks offering more flexible synthetic routes are available for heterocyclic motifs as compared to the standard binaphthyl ligands (96JOC6244).

Several examples of heterocyclic BINAP analogues have been reported which sometimes offer an improved performance in a variety of transition-metal-catalyzed transformations when compared to standard BINAP ligands. In this review, we survey the efforts of developing atropisomeric biheteroaryl backbone-containing bisphosphines, their designing concept, synthetic approaches and some of their important applications.

2. DEVELOPMENT OF SYNTHETIC ROUTES FROM BINAP TO HETEROCYCLIC BINAP ANALOGUES

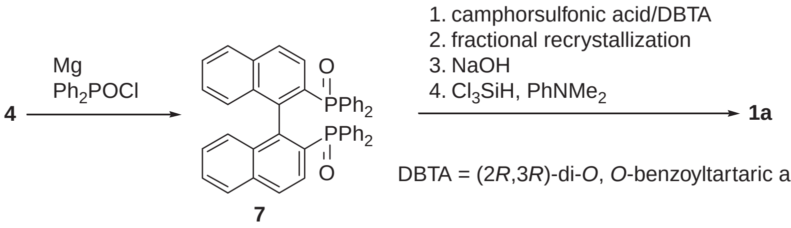
The synthesis of BINAP has continued to evolve in search of more economical, easier and efficient procedures. Initially, Noyori and Takaya synthesized BINAP starting from *rac*-BINOL (**3**) by converting BINOL to the racemic dibromide **4** under forcing conditions. The corresponding dilithiated species (**5**) was then reacted with chlorodiphenylphosphine to obtain BINAP (**6**). Enantiomerically pure BINAP (**1a**) was obtained *via* fractional crystallization of the Pd-complex (Scheme 1, 80JA7932).

Recently, this method was replaced by a more economical route, in which instead of racemic BINAP, racemic BINAPO (**7**) (diphenylphosphinoxide) was prepared which can be resolved using camphorsulfonic acid or 2,3-*O*,*O*-dibenzoyl tartaric acid (Scheme 2, 86JOC629).



Pd-complex = di-μ-Cl-bis[(S)-dimethyl(α-methylbenzyl)aminato-C^{2}N]Pd$_2$

Scheme 1 Synthesis of BINAP (**1a**) (1980, Noyori and Takaya).

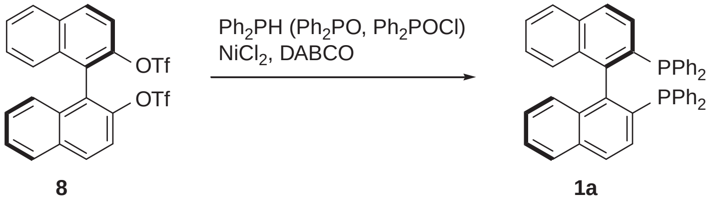


DBTA = (2*R*,3*R*)-di-*O*, *O*-benzoyltartaric acid

Scheme 2 Synthesis of BINAP (**1a**) (1986, Noyori and Takasago).

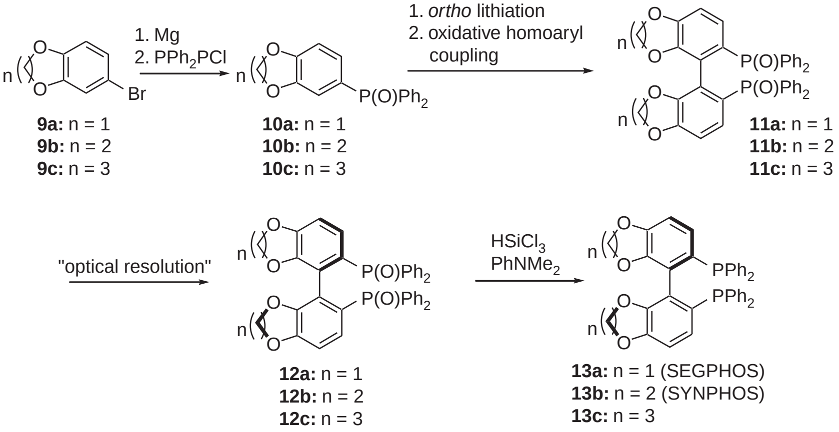
This method is still used today as the standard method for optical resolution of chiral bisphosphines. Further advancements in the preparation of enantiomerically pure BINAP (**1a**) were made in recent years. In some instances, the ditriflate of optically active binaphthol (**8**) was used in the coupling with diphenylphosphine (94JOC7180, 94USP252306, 95USP5399771), diphenylphosphinoxide (97EPP0771812, 98EPP0839819) or chlorodiphenylphosphine (97CC2359, 97USP5902904) using Ni-catalyzed cross-coupling transformations (Scheme 3).

Presently, for the synthesis of heterocyclic BINAP analogues generally the same methodology is adapted with only minor variation in conditions. For convenience, the general methodology is highlighted in Scheme 4 for the preparation of heterocyclic BINAP analogues **13a–c**. In cases where different approaches are employed, the synthetic aspects are discussed in the following sections.



DABCO = 1,4-diazabicyclo[2.2.2]octane

Scheme 3 Synthesis of BINAP (**1a**) from optically active BINOL ditriflate (1994–1997).



Scheme 4 General synthetic scheme for heterocyclic BINAP analogues.

3. LIGANDS WITH PHOSPHINE GROUPS ATTACHED TO THE HETEROCYCLIC RING

3.1 Five-membered biheteroaromatic diphosphines ligands

Ligands, structurally characterized by an atropisomeric backbone consisting of two interconnected five-membered heteroaromatic units were initially developed by Sannicolo et al. in 1996 (Figure 2). The authors recognized the oxidation potential as a good tool to evaluate the electronic availability of the phosphorous atom in this series of biheteroaromatic diphosphines (00JOC8340). The increasing order of oxidative potential determined by voltametry is: N-Me-2-BINP (**20**) ($E^\circ = 0.52$ V), TetraMe-BITIOP (**17**) ($E^\circ = 0.57$ V), N-MOM-2-BINP (**21**) ($E^\circ = 0.60$ V), TetraMe-BITIANP (**15**) ($E^\circ = 0.76$ V), BITIANP (**14**) ($E^\circ = 0.83$ V), BISCAP (**18**) ($E^\circ = 0.90$ V), BICUMP (**16**) ($E^\circ = 1.03$ V), BIMIP (**19**) ($E^\circ = 1.15$ V). A higher value of the oxidation potential reflects a lower electron density at phosphorous.

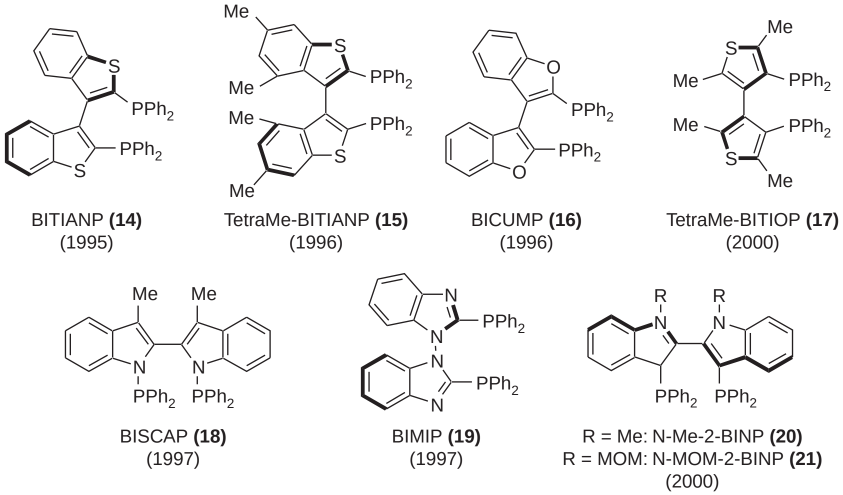
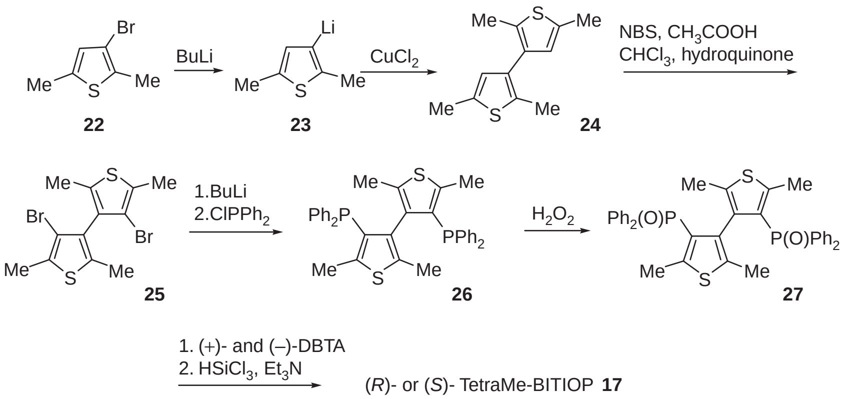

BITIANP **(14)** (1995)
TetraMe-BITIANP **(15)** (1996)
BICUMP **(16)** (1996)
TetraMe-BITIOP **(17)** (2000)
BISCAP **(18)** (1997)
BIMIP **(19)** (1997)
R = Me: N-Me-2-BINP **(20)**
R = MOM: N-MOM-2-BINP **(21)**
(2000)

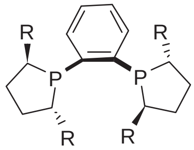
Figure 2 Five-membered biheteroaromatic diphosphines.

Since a high electron density at phosphorus is known to be a favorable parameter in Ru-catalyzed hydrogenation reactions of ketonic carbonyl groups in ketoesters, the authors have performed comparative experiments for the hydrogenation of *β*-ketoesters using all their biheteroaryl diphosphines as ligands of Ru(II). The results demonstrate not only the complete agreement with the above mentioned relation, but also show undeniably the enhanced catalytic activity (reaction rate) for electron-rich diphosphines, for example N-Me-2-BINP (**20**) which is nearly three times more as reactive than BINAP (**1a**) (00JOC8340).

TetraMe-BITIANP (**15**) and the parent unsubstituted system BITIANP (**14**) were the first heterocyclic diphosphine ligands successfully employed in the Ru(II)-catalyzed asymmetric hydrogenation of *α*- or *β*-ketoesters and of olefinic substrates, which produced the same or slightly higher enantioselectivities than Ru(II)-BINAP-catalyzed reactions (96JOC6244). For example, the Ru-complex of (+)-BITIANP provided much higher yields and enantioselectivities in asymmetric hydrogenations (93% yield, >98% ee), a key step during the synthesis of (+)-dihydrokawain, a natural product, while BINAP (**1a**) failed in achieving good yields (12–25% yield, 93% ee) (96TL6503). Moreover, (*R*)-BITIANP (**14**) provided complete regioselectivity and high enantioselectivity in asymmetric Heck reactions (99CC1811, 00CC583). However, BICUMP (**16**), the oxygenated analogue of BITANP (**14**) proved configurationally unstable at room temperature. BIMIP (**19**) with hindered rotation around a nitrogen–nitrogen bond was synthesized



Scheme 5 Synthesis of optically pure TMBTP.



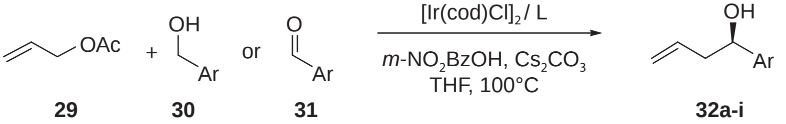
R = Me (Me-DuPHOS)
R = Et (Et-DuPHOS)
R = *i*-Pr (*i*-Pr-DuPHOS)

28

Figure 3 DuPHOS ligands series.

via a three-step sequence starting from 3,3-dimethyl-1,1′-benzimidazole. In a related manner BISCAP (**18**) with a phosphino group bonded to an aromatic nitrogen atom was synthesized *via* a five-step sequence (97JOM445). TetraMe-BITIOP (**17**, TMBTP) having a diphenylphosphino group at the *β* position – which is the electron-deficient position of an inherently electron-rich heterocyclic ring (thiophene) – is one of the most efficient diphosphine chiral chelating ligands for use in enantioselective homogeneous hydrogenation. It can be synthesized through a simple six-step procedure in enantiomerically pure state with 30% overall yield starting from inexpensive bromothiophene (**22**) (Scheme 5).

Ru(II)- and Rh(I)-catalyzed asymmetric hydrogenations of *α*- or *β*-ketoesters and olefinic substrates using the TMBTP ligand (**17**) demonstrated that this ligand has very high enantiofacial recognition and is comparable to the well-known BINAP (**1a**) and DuPHOS (**28**, Figure 3) ligand systems (00JOC2043). Its Rh-complex has been used in the asymmetric hydrogenation of unprotected enamines with good enantioselectivity (04JA9918). However, it is only marginal successful in

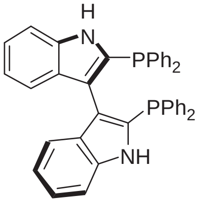


30a, 31a: Ar = Ph
30b, 31b: Ar = *p*-NO2Ph
30c, 31c: Ar = *p*-MeOPh
30d, 31d: Ar = *p*-BrPh
30e, 31e: Ar = *o*-(MeO)Ph
30f, 31f: Ar = *p*-(CO2Me)Ph
30g, 31g: Ar = 3,5-Cl_2Ph
30h, 31h: Ar = piperonyl
30i, 31i: Ar = 2-(N-Me-indolyl)

(R)-BINAP
(55–80% yield) (90–93% ee)

(–)-TMBTP
(75–86% yield) (94–98% ee)

Scheme 6 Enantioselective Ir-catalyzed carbonyl allylation.



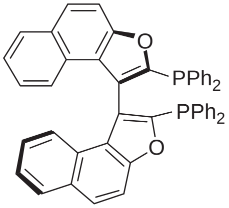
33

Figure 4 2,2′-Bis-diphenylphosphino[3,3′]-biindolyl ligand.

Heck reactions (99CC1811), but highly efficient for silane-terminated Heck reactions (00CC583).

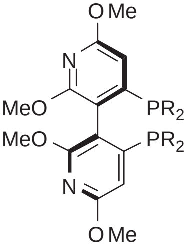
Recently, TMBTP (**17**) has also been used as a ligand in an Ir-complex employed in enantioselective carbonyl allylations (*via* coupling of allylacetates (**29**) and aldehyde (**31a–i**)) furnishing good-to-excellent yields with exceptional levels of selectivity. In this transformation, TMBTP (**17**) shows better yield and selectivities as compared to BINAP (**1a**) (Scheme 6, 08JA6340).

Enantiopure (+)- and (−)-N-Me-2-BINP (**20**) and (+)- and (−)-N-MOM-2-BINP (**21**) were synthesized *via* a five-step reaction sequence in satisfactory yields and were initially tested in the Ru(II)-catalyzed asymmetric hydrogenation of α- and β-ketoesters. These reactions were outstandingly efficient in term of catalytic activity (reaction rate) compared to BINAP (**1a**) under the same conditions and provided high levels of enantiomeric product excess (00JOC8340). Selke et al. reported 2,2′-bis-diphenylphosphino[3,3′]-biindolyl (**33**) (Figure 4), but its application as a ligand has not been reported (96TA285).



BINAPFu **34**

Figure 5 3,3′-Binaphtho[2,1-*b*]furan-based diphosphine ligand BINAPFu.



35a: R = C_6H_5, P-PHOS
35b: R = 4-MeC_6H_4, Tol-P-PHOS
35c: R = 3,5-$Me_2C_6H_3$, Xyl-P-PHOS
35d: R = cyclohexyl, Cy-P-PHOS

Figure 6 P-PHOS ligands series.

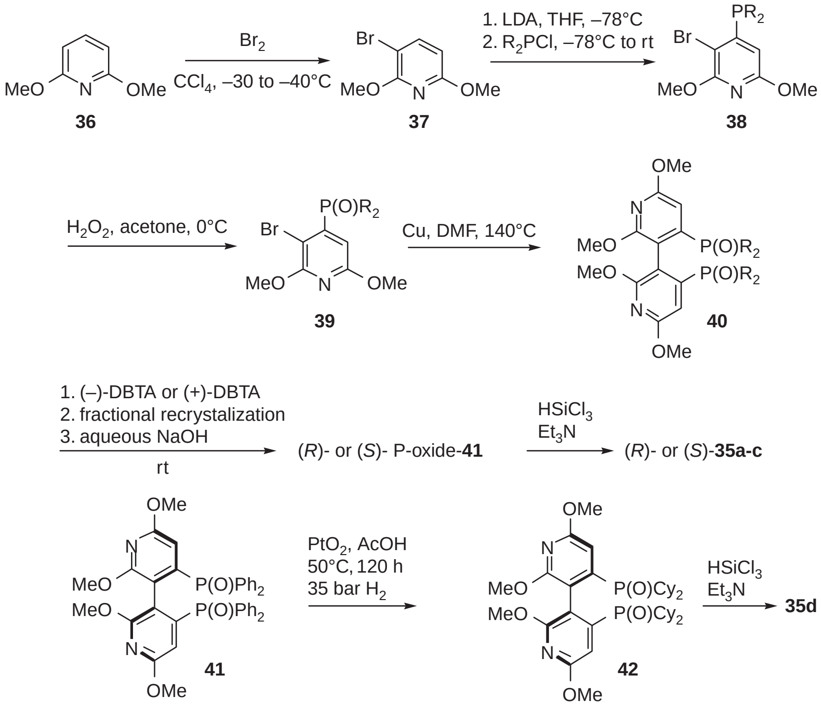
3.1.1 BINAPFu

Keay et al. designed 3,3′-binaphtho[2,1-*b*]furan-based diphosphine, BINAPFu (**34**) (Figure 5), based on the success of the less basic tri-2-furylphosphine (TFP) as ligand in Stille cross-coupling reactions. In this context, the previously synthesized benzofuran-derived ligands by Sannicolo (see Figure 2) were found unstable at room temperature. The authors therefore aimed to synthesize a configurationally stable 3,3′-bifuryl ligand, having phosphino groups at the C-2 position. The enantiopure BINAPFu ligand (**34**) was synthesized in five steps starting from 2-naphthoxyacetic acid. This ligand outperformed BINAP (**1a**) in an asymmetric Heck reaction between 2,3-dihydrofuran and phenyl triflate (01JOC7478, 04CJC145, 00OL2817).

3.2 Six-membered biheteroaromatic diphosphines ligands

3.2.1 Dipyridylphosphine ligands: P-PHOS

Chan et al. reported this class of highly effective atropisomeric, heteroaromatic ligands consisting of two interconnected 2,6-dimethoxy-pyridyl units. The MeO substituents in an *ortho* position to the nitrogen in the pyridyl rings are introduced very logically to block the access of the pyridyl ring to the metal center which may exert adverse effects, as it



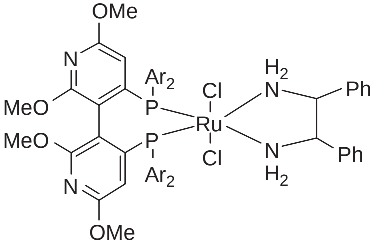
Scheme 7 Synthesis of optically pure P-PHOS ligands.

is known for homogenous hydrogenations reactions with Rh- and Ru-pyridylphosphine complexes (93CRV2067, 95S36, 95CC1721, 90JCD55, 97OM3469, 98TA3241, 98TA4183). In order to prepare a diverse range of diphosphine ligands with a variety of different electronic properties, they attached different P-substituents on the dipyridyl backbone represented in four examples of novel P-PHOS ligands (**35a–d**) (Figure 6, (99USP5886182, 00JA11513, 01SL1050, 02TL1539, 05ASC507).

The enantiopure ligands (**35a–c**) can be synthesized by the same method in six steps starting from commercially available 2,6-dimethoxypyridine (**36**) (Scheme 7). Enantiopure **35d** can be conveniently prepared from enantiopure **41** *via* hydrogenation as shown in Scheme 7.

By utilization of various catalyst systems based on the P-PHOS family of ligands, a broad scope of unsaturated substrates can be hydrogenated with high ee's. For example its Rh- and Ru-complexes outperform BINAP in the hydrogenation of prochiral olefins, *β*-ketoesters, aromatic ketones and quinolines (006ACR711). In addition, a system arrived from ligands of the P-PHOS series in combination with CuF_2/$PhSiH_3$ surprisingly performed very effectively in the asymmetric hydrosilylation of simple ketones as well as unsymmetrical ketones. In the asymmetric hydrosilylation of unsymmetrical diaryl ketones, the highest ee reported in the literature is only 20%, but the above mentioned catalytic system achieved excellent ee's up to 98%. The Pd- and Rh-complexes of the P-PHOS series have also been successfully used in C–C bond forming reactions. The details of these reactions are as follows:

1. 2-(6′-Methoxy-2′-naphthyl)propenoic acid, when hydrogenated to the corresponding saturated analogue (naproxen) by utilizing Ru (P-PHOS **35a**)$(acac)_2$-complex the best result was achieved with up to 96.2% ee while with the corresponding Ru(BINAP **1a**) system, it was 94.8% ee in a side-by-side comparison (99USP5886182, 00JA11513).
2. A number of (*Z*)-*β*-aryl-substituted *α*-(acylamino)acrylates were hydrogenated with Ru(P-PHOS) very successfully (05ASC507, 03TA987). The parent ligand P-PHOS (**35a**) proved more efficacious than its analogues under Ru-catalyzed, low pressure hydrogenation conditions with 90–97% ee, while Rh-(R-Xyl-P-PHOS **35c**) provided quantitative hydrogenation with high enantioselectivities (92–94% ee). Rh-(R-Cy-P-PHOS **35d**) provided the same level of selectivity but also showed substantially higher catalytic activity as compared to Rh-(R-Xyl-P-PHOS **35c**).
3. A series of (*E*)- and (*Z*)-*β*-alkyl-substituted *β*-(acylamino)acrylates were hydrogenated *via* the Ru- and Rh-complexes of the P-PHOS ligand series. For the *E*-isomers, Ru-based complexes of all P-PHOS ligands displayed remarkably better efficiency than the corresponding Rh-complexes in enantioselective hydrogenations (03JOC2490). In the cases of Ru-complexes, the sterically hindered ligands provided higher ee's and reaction rates. For example, the Ru-(Xyl-P-PHOS **35c**) catalyst provided extremely high enantiopurities (97.9–99.7%). On the other hand, *Z*-isomers Ru-(Xyl-P-PHOS **35c**) showed markedly inferior selectivities than *E*-isomers. Here the Rh-based complexes proved more favorable than the Ru-complexes. An interesting feature is that both Rh- and Ru-complexes of the same ligand enantiomer exert opposite asymmetric control and provide the opposite enantiomer of the hydrogenated product under the same reaction conditions.
4. Several different Ru-complexes with the P-PHOS family of ligands (**35a–d**) have been employed in the hydrogenation of *β*-ketoesters and high enantioselectivities (up to 99%) have been obtained (00JA11513, 01SL1050, 02TL1539). In some cases, a higher ee as compared to Ru-BINAP was obtained (00JA11513, 01SL1050, 02TL1539, 88TL1555, 87JA5856).
5. The preformed complex *trans*-$[RuCl_2\{(R)\text{-Xyl-PHOS}\}\{(R,R)\text{-DPEN}\}]$ (**43**) (Figure 7) proved to be an extremely versatile catalyst precursor



43

Figure 7 *trans*-[RuCl$_2${(*R*)-Xyl-PHOS}{(*R*,*R*)-DPEN}].

for the asymmetric hydrogenation of a wide spectrum of prochiral ketones (02JOC7908, 03CEJ2963).

6. The catalytic system generated from $[Ir(COD)Cl]_2$ and the P-PHOS ligand (**35a**) in combination with I_2 served as a highly efficient system providing 90–92% ee's (96T15031) for the hydrogenation of quinolines to obtain tetrahydroquinolines which are synthetic intermediates for many biologically active compounds (05CC1390). Furthermore, the catalytic system is air-stable and recyclable, with essentially no loss of ee's even after many recycles.
7. The asymmetric hydrosilylation of simple ketones as well as unsymmetrical ketones was also achieved in extraordinary efficiency by a system derived from ligands of the P-PHOS series in combination with $CuF_2/PhSiH_3$ and provided up to 97% product ee's. The remarkable high activities, very mild reaction conditions and compatibility with of traces of moisture make this system practically viable (05PNA3570).
8. The Pd- and Rh-complexes of the P-PHOS series have also been successfully used in C–C bond forming reactions (03JMO171, 03TL6505).

3.2.2 Bisquinolone-based diphosphine ligands: BIQUIP

Kappe and coworkers recently introduced 4,4′-bisquinolone-based mono- and diphosphine ligands (**44**) as a novel family of biheteroaromatic biphosphines. The designed framework offers several potential advantages compared to their binaphthyl counterparts (BINAP **1a**) as the electronic properties of the cyclic enamide system in the quinolone moiety exert a unique impact on the electronic properties of the phosphine ligators. In addition, the presence and proximity of soft (phosphine) and hard (carbonyl) donor groups in the ligand molecule provide the potential of hemilabile coordinating abilities in this type of hybrid ligand. The 2(1*H*)-quinolone system itself offers several readily

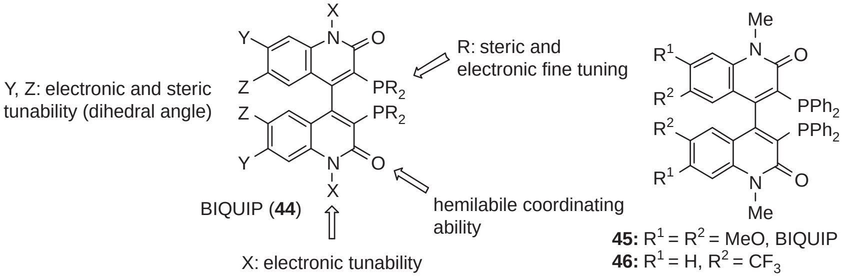


Figure 8 Bisquinolone-based diphosphine ligands.

available diversification sites, and therefore the basicity at phosphorus can be readily adjusted by incorporating substituents with different predefined electronic properties onto the bisquinolone core. In addition, this also allows some influence on the dihedral angle by variation of the Z-substituents (Figure 8).

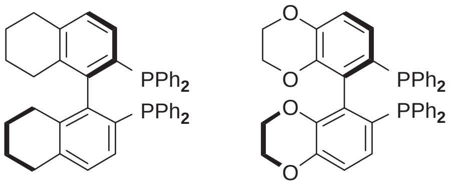
The electron-rich BIQUIP analogue with four methoxy substituents on the phenyl ring (**45**) was successfully synthesized and isolated in a two-step bromination/phosphination protocol starting from the basic 4,4′-bisquinolone core. Its electron-deficient analogue with two trifluoromethoxy substituents on the phenyl ring (**46**) proved oxidatively sensitive during isolation (08JOC4755). Its ligand activity was studied in a Heck reaction between phenyl triflate and 2,3-dihydrofuran. However, the real scope of reactivity and selectivity has yet to be explored.

4. LIGANDS WITH PHOSPHINE GROUPS ATTACHED TO THE NON-HETEROCYCLIC RING

4.1 BisbenzodioxanPHOS (SYNPHOS)

Chan et al. reported bisbenzodioxane-based ligands (SYNPHOS, **13b**) as oxygenated analogues of H_8-BINAP (**47**) (Figure 9, 02TL2789). This ligand has proven to be superior to its binaphthyl counterpart in a series of asymmetric catalytic reactions (91TL7283, 94JCS(P1)2309, 96TL2813, 96JOC5510). The synthesis of the same ligand family was also subsequently reported by Genet et al. who also provided a scalable synthesis (03OPD399, 03EJO1931, 03TL823).

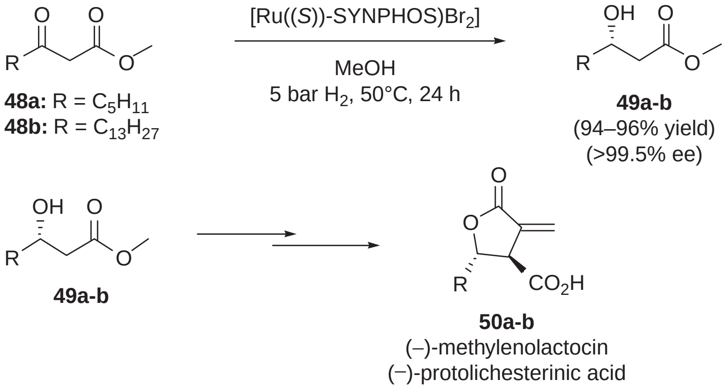
The SYNPHOS ligand (**13b**) has been used in the Ru-catalyzed asymmetric hydrogenation of 2-(6′-methoxy-2′-naphthyl)propenoic acid. The reduced product naproxen, an important drug molecule, was obtained in high ee's (92.2%) (02TL2789). Moreover, it is also employed in the asymmetric hydrogenation of β-keto esters with high ee's (99.5%) (02TL2789), α-ketoesters (03OPD399, 03EJO1931, 03TL823), functionalized ketones (03OPD399, 03EJO1931, 03TL823), aldehyde decarbonylation



H_8-BINAP (**47**)

BisbenzodioxanPHOS
SYNPHOS (**13b**, Scheme 4)

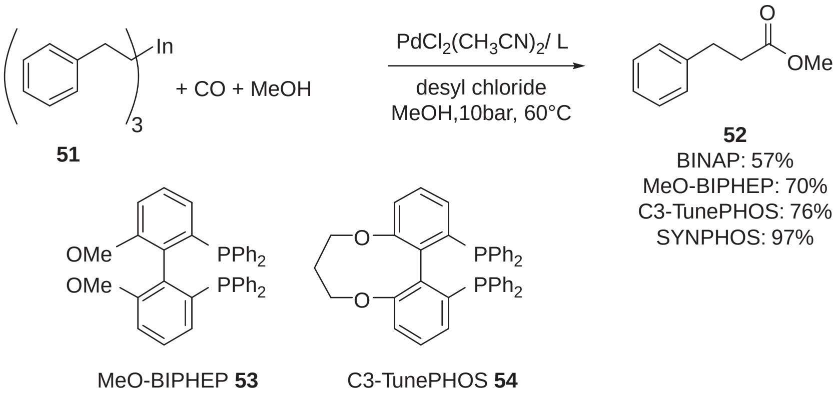
Figure 9 BisbenzodioxanPHOS (SYNPHOS).



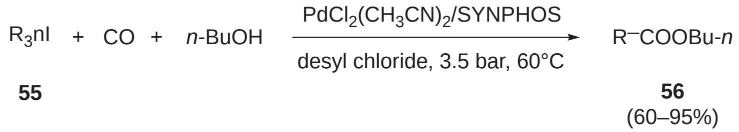
Scheme 8 Asymmetric hydrogenation in the synthesis of butyrolactones.

and cascade enantioselective Pauson–Khand-type reactions (PKR) (05ASC1750). Products for these transformations were obtained with high ee's and the results with the SYNPHOS ligand (**13b**) were always higher as compared to BINAP (**1a**) in side-by-side comparisons studies. More than 23 applications of this ligand have been reported since its discovery in 2003. It was widely studied in synthesizing biologically active natural products, for example 3-hydroxy-2-methylpropanoic acid esters (useful building blocks for both naturally occurring and synthetic biologically active molecules) (07ASC1592, 08ASC2525), Dolabelide A (a macrolide exhibiting cytotoxic activity against HeLa-S_3-cells (05SL429), and in the synthesis of butyrolactone natural products (**50**) (07ASC943), as shown in (Scheme 8).

More recently the ligand has been used in the Pd-catalyzed oxidative carbonylation of different alkyl indiums (**51**) (08JA195) where it provided the best results in comparison with other screened ligands. As shown in Scheme 9, by utilizing SYNPHOS (**13b**) as the ligand remarkably high product yields can be obtained. Interestingly, while decreasing the CO pressure from 10 to 3.5 bar the yield is almost the same (96%). The performance of the Pd-SYNPHOS catalyst was then examined over a



Scheme 9 Pd-catalyzed oxidative carbonylation of allyl indiums.



$$\underset{\mathbf{55}}{R_3nI} + CO + n\text{-}BuOH \xrightarrow[\text{desyl chloride, 3.5 bar, 60°C}]{PdCl_2(CH_3CN)_2/SYNPHOS} \underset{\substack{\mathbf{56}\\(60–95\%)}}{R{-}COOBu\text{-}n}$$

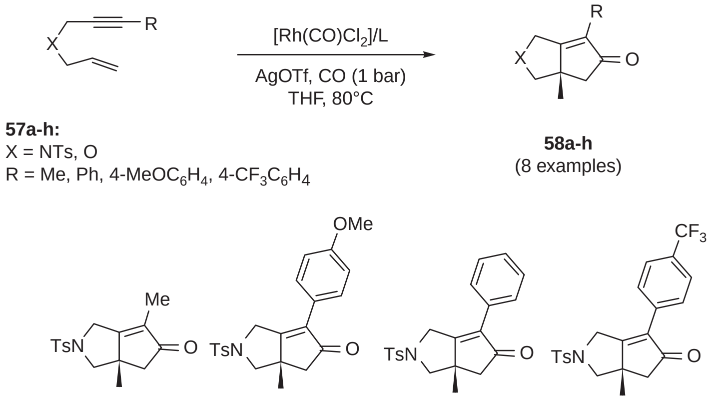
Scheme 10 Pd-catalyzed oxidative carbonylation of trialkyl indiums.

range of trialkyl indium reagents containing β-hydrogens; the yields are good to high (Scheme 10, 08JA9429).

The Rh-complexes of SYNPHOS (**13b**) and DIFLUORPHOS (**81**) (see Figure 14) have provided improved activities and enantioselectivities in asymmetric PKR, as compared to BINAP-type ligands (Scheme 11). The improved yields are attributed to the low dihedral angles of this ligand family (07ASC1999).

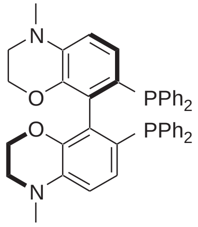
4.2 Bis(2*H*-1,4-benzooxazine) (SOLPHOS)

The Solvias company has disclosed benzoxazine-based ligands (SOLPHOS, **59**) in this category of biheterocyclic diphosphine ligands. The design of this ligand family was made because of the attractive performance of MeO-BIPHEP (**53**) (see Scheme 9) and SEGPHOS (**13a**) (see Scheme 4). The presence of an additional N-based substituent *ortho* to the MeO and *para* to the phosphine in MeO-BIPHEP makes the ligand more electron rich and provides the possibility to further tune the ligand (Figure 10, 07ACR1240, 03EPP1611114). SOLPHOS demonstrated very good catalytic activity in Ru-catalyzed hydrogenations of various β-ketoesters (95–99% ee, substrate/catalyst ratio (S/C) up to 100000), of acetyl acetone (>99% ee) and of an exocyclic α,β-unsaturated acid (98.6% ee, S/C 250) (08CAJ1384).



	58a	58b	58c	58d
(S)-BINAP	70% (83% ee)	92% (71% ee)	99% (65% ee)	99% (63% ee)
(S)-SYNPHOS	57% (93% ee)	74% (89% ee)	98% (65% ee)	93% (68% ee)
(S)-DIFLUORPHOS	62% (89% ee)	90% (75% ee)	90% (70% ee)	90% (71% ee)

Scheme 11 Rh(I)-catalyzed enantioselective PKR.



SOLPHOS (**59**)

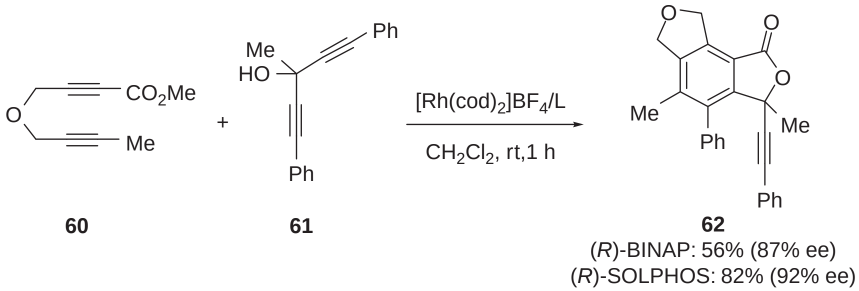
Figure 10 SOLPHOS ligand.

The Rh(I)-complex of SOLPHOS (**59**) has been used in a novel synthesis of 3,3-disubstituted phthalides where its complex outperformed BINAP (**1a**) by achieving high enantioselectivities up to 92% ee (Scheme 12, 07OL1307).

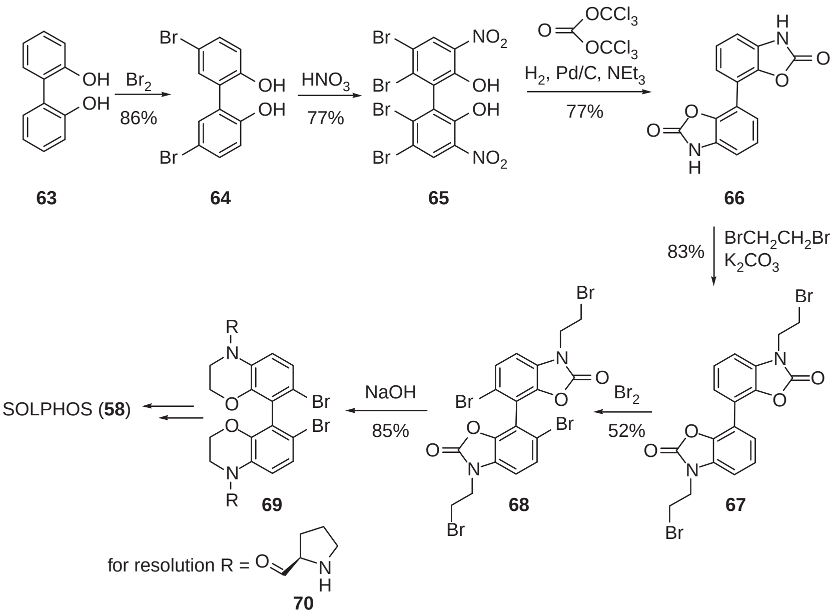
Furthermore, its Ir-complexes have performed successfully in the reductive coupling of alkynes with *N*-sulfonyl imines (08CAJ1384). The general synthetic route to SOLPHOS derivatives of type **59** is depicted in Scheme 13.

4.3 Bis(dibenzofuran)diphosphine (BIFAP)

In 1999, the Hiemstra group reported the dibenzofuran-based diphosphine ligand BIFAP (**71**) and its water-soluble derivative BIFAPS (**72**) (Figure 11). Both ligands are used in Ru-catalyzed hydrogenations of

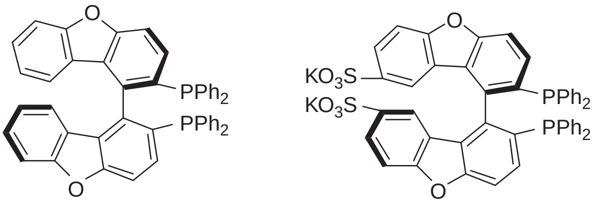


Scheme 12 Rh(I)-catalyzed enantioselective PKR.



Scheme 13 Synthetic route to SOLPHOS analogues.

olefins and β-ketoesters in organic, aqueous and two-phase solvent systems. In an organic phase, both ligands provided almost the same high ee's as BINAP (**1a**) but in water the enantioselectivity is slightly lower. However, in the presence of a small amount of acid, the rate of asymmetric induction is enhanced in organic as well as in aqueous phases (99CEJ2472). The five-step route to BIFAP (**71**) starting from *rac*-BIFOL follows the same method as the original synthesis of BINAP (**1a**) reported by Noyori and coworkers (89OS20, 86JOC629), which starts with the double bromination of *rac*-BIFOL at very high temperature



BIFAP (**71**) BIFAPS (**72**)

Figure 11 Diphosphine ligand BIFAP and its water-soluble derivative BIFAPS.

(355 °C) followed by double lithiation *via* *n*-butyllithium. The lithiated product is then treated with $ClPPh_2$ to obtain *rac*-BIFAP. However, for enantiopure BIFAP, at this stage, it was quantitatively oxidized into diphosphinoxide BIFAPO which was resolved by treatment with *O*,*O*-dibenzoyltartaric acid [(+)-or (−)-DBTA] in a very easy and efficient procedure. The enantiopure (*S*)-(−) and (*R*)-(−)-BIFAP (**71**) was obtained by reduction in the presence of the base scavenger prevent partial racemization (99CEJ2472).

4.4 SEGPHOS

Saito et al. disclosed the bi-1,3-benzodioxole-based ligands of the SEGPHOS-type (**13a**, see also Scheme 4) (Figure 12) exhibiting a very narrow dihedral angle of the biaryl backbone. The authors discovered a close relationship between the dihedral angle of the biaryl backbones (θ) and the observed enantioselectivities in the asymmetric hydrogenation (Figure 12). These observations led to a working hypothesis that a narrower dihedral angle should cause a stronger interaction between the ligand and the substrate, thus enhancing enantioselectivities. Working on this hypothesis, Saito et al. envisioned that a ligand with a dihedral angle narrower than MeO-BIPHEP (**53**) would provide the ultimate enantioselectivity. This rationale led to the design of the SEGPHOS ligand (**13a**) which was supported by the calculated dihedral angle of 64.99° and this ligand achieved the highest level of chiral recognition in the asymmetric hydrogenation of hydroxyaceton (01ASC264).

Various modifications of SEGPHOS (**74–78**) have been pursued by attaching different substituents on phosphorus (Figure 13). A number of complexes of SEGPHOS (**13a**) and its variants **74–78** have been developed and subsequently used in a variety of enantioselective transformations. For example, its Ir-, Pd-, Rh(0)/(I)- and Ru-complexes excellently perform in the hydrogenation of prochiral olefins, β-ketoesters, aromatic ketones, enamides, cyclic enones and quinolines. DM-SEGPHOS (**74b**) and DTBM-SEGPHOS (**74d**) are frequently being

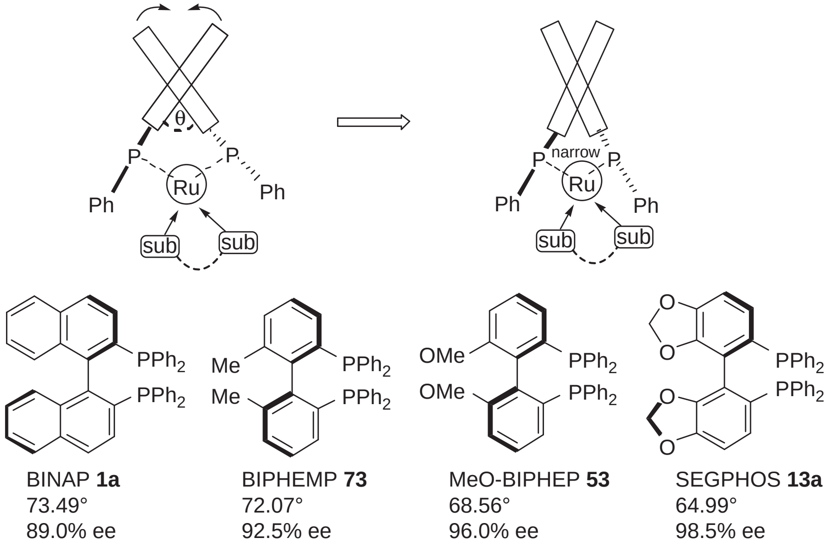


Figure 12 Relationship between dihedral angle and enantioselectivities.

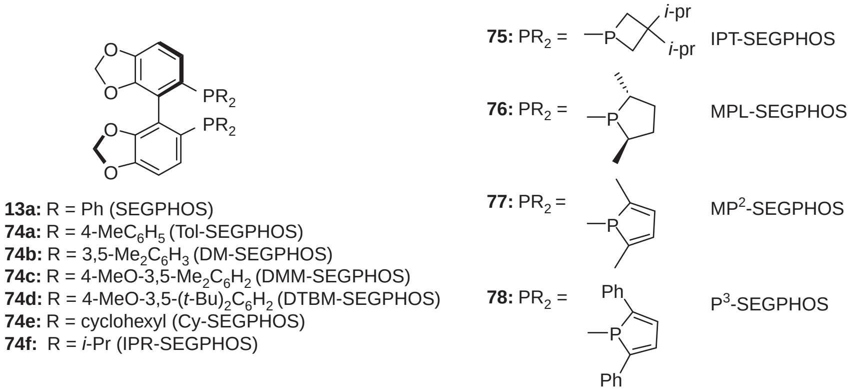
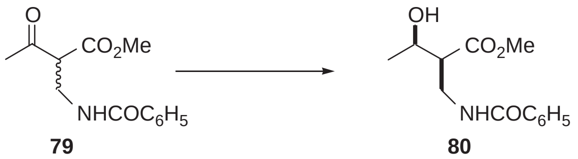

13a: R = Ph (SEGPHOS)
74a: R = 4-MeC_6H_5 (Tol-SEGPHOS)
74b: R = 3,5-$Me_2C_6H_3$ (DM-SEGPHOS)
74c: R = 4-MeO-3,5-$Me_2C_6H_2$ (DMM-SEGPHOS)
74d: R = 4-MeO-3,5-(*t*-Bu)$_2C_6H_2$ (DTBM-SEGPHOS)
74e: R = cyclohexyl (Cy-SEGPHOS)
74f: R = *i*-Pr (IPR-SEGPHOS)

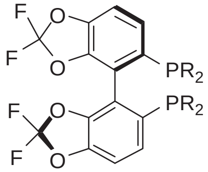
Figure 13 Modifications of SEGPHOS ligands.

used in Ru-catalyzed asymmetric hydrogenations (01ASC264), whereas Cy-SEGPHOS (**74e**) and IPR-SEGPHOS (**74f**) are good ligands for Ru-catalyzed reactions (04TA2169). Furthermore, its complexes are being used in hydrosilylations, C–C bond forming reactions like cycloadditions, Mannich-type and Michael reactions very frequently. Despite providing very high enantioselectivity, both BINAP and SEGPHOS-type ligands are not providing satisfactory diastereoselectivity. In contrast, DTBM-SEGPHOS (**74d**) provided essentially only one stereoisomer out of the four possible isomers. For example, in the hydrogenation of



DTBM-SEGPHOS	98.6% de (99.4% ee)
Tol-BINAP	86.0% de (99.0% ee)
SEGPHOS	79.6% de

Scheme 14 Diastereoselective hydrogenation of α-substituted β-ketoesters.



81

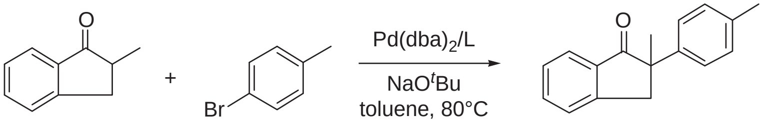
Figure 14 DIFLUORPHOS.

α-substituted β-ketoesters such as 2-benzamidomethyl-3-oxobutanoate (**79**), the Ru(II)-complex of (−)-DTBM-SEGPHOS provided (2*S*,3*R*)-methyl 2-benzamidomethyl-3-hydroxybutanoate (**80**) almost quantitatively in 98.6% de and 99.4% ee, while Tol-BINAP achieved 86.0% de and 99.0% ee and SEGPHOS provided only 79.6% de (Scheme 14, 01ASC264).

4.5 DIFLUORPHOS

Genet et al. generated a ligand with a backbone structurally close to the electron-rich ligands SYNPHOS (**13b**) and SEGPHOS (**13a**), but with potentially different electronic properties, having electron-deficient fluoro substituents on the backbone, named as DIFLUORPHOS (**81**) (Figure 14). This ligand has almost the same narrow dihedral angle as SEGPHOS (**13a**) (67.6° and 67.2°, respectively) but has poor σ donor and the best π acceptance ability as calculated by P^{31}–Se^{77} coupling constants (04AGE320).

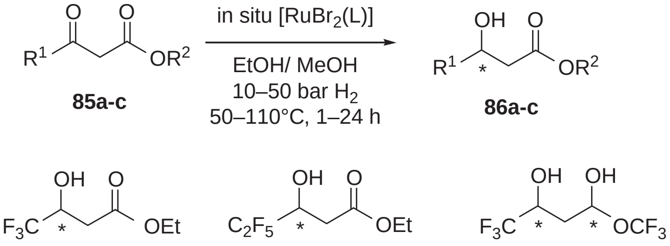
More recently, Liao et al. showed a comparison between Pd-complexes of different biaryl-linked bisphosphines possessing varied dihedral angles, Scheme 15, in an enantioselective arylation of methylindanone (**82**). The result not only demonstrates the effect of the dihedral angle on enantioselectivities but also illustrates the influence of the electronic properties on the achieved enantioselectivity. The DIFLUORPHOS ligand (**81**) having a narrower dihedral angle and poor



82 **83** **84**

ligand	dihedral angle	ee
(*R*)-BINAP	87°	9
(*R*)-MeO-BIPHEP	87°	11
(*R*)-SEGPHOS	67°	72
(*R*)-DIFLUORPHOS	67°	78

Scheme 15 Effect of dihedral angle on enantioselective α-arylation.



85a-c **86a-c**

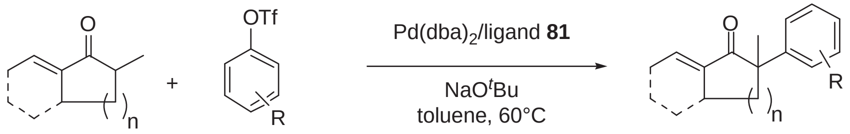
	86a	**86b**	**86c**
(S)-BINAP	23% ee	44% ee	91% ee
(S)-MeO-BIPHEP	40% ee	57% ee	87% ee
(S)-SYNPHOS	49% ee	63% ee	85% ee
(R)-SEGPHOS	59% ee	76% ee	88% ee
(S)-DIFLUORPHOS	70% ee	81% ee	98% ee

Scheme 16 Asymmetric hydrogenation of fluorinated substrates.

σ donor ability provided the highest enantioselectivity (08JA195). The DIFLUORPHOS ligand (**81**) showed high ee's in the asymmetric hydrogenation of β-ketoesters.

Fluorinated β-functionalized ketones are tricky substrates for asymmetric hydrogenation and a low ee value is typically obtained by using biphenyl atropisomeric diphosphanes ligands (00JOM128, 01T2563, 88EPP295109). Interestingly, in the asymmetric hydrogenation of fluorinated β-functionalized ketones (**85a–c**), DIFLUORPHOS (**81**) provided a very high ee value, which is the best reported ee value for this transformation (Scheme 16).

Its Pd- and Ni-complexes have also been used successfully in C–C coupling reactions (08JA195). For example, the asymmetric α-arylation of ketones catalyzed by the DIFLUORPHOS–Pd complex occurred in high ee and high yield (Scheme 17). In many cases involving electron rich and neutral aryl triflates, the ee's are typically higher than those

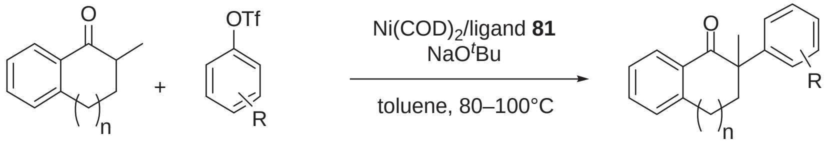


87a: n = 0
87b: n = 1

88a: R = ^{t}Bu
88b: R = MeO

89a-l
70–85% (70–95% ee)

Scheme 17 Pd-catalyzed enantioselective α-arylation with aryl triflates.

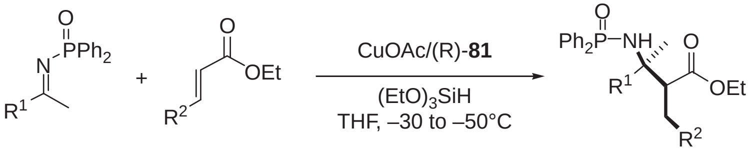


90a: n = 0
90b: n= 1

91a: R = CN
91b: R = CF_3

92a-e
40–84% (95–98% ee)

Scheme 18 Ni-catalyzed enantioselective α-arylation with aryl triflates.



93a: R^1 = naphthyl
93b: R^1 = *p*-ClPh
93c: R^1 = cyclohexenyl

94a: R^2 = H
94b: R^2 = CO_2Et

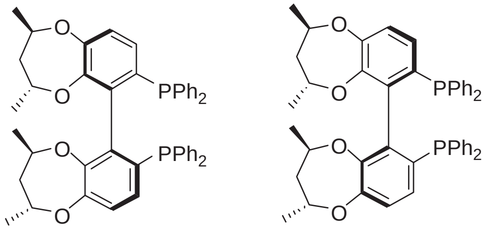
95a-g
47–95% (30/1-3/1 dr), 82–93% ee

Scheme 19 Catalytic asymmetric reductive Mannich reaction of ketimines.

obtained with BINAP as ligand in a side-by-side comparison. On the other hand, the reaction with electron-poor aryltriflates occurred with much lower enantioselectivities. Interestingly, this limitation was overcome by using a Ni catalyst containing the same DIFLUORPHOS ligand (**81**) (Scheme 18).

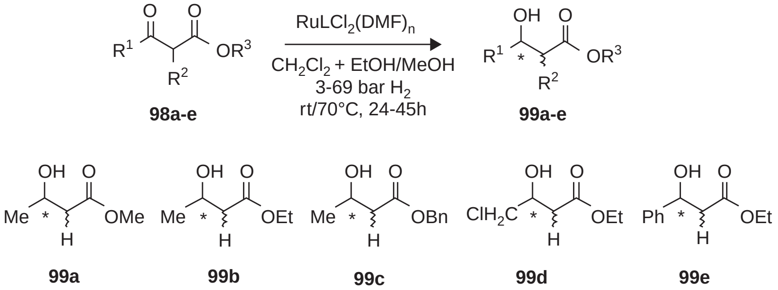
In addition, Ir-complexes of DIFLUORPHOS (**81**) have been used in the asymmetric hydrogenation of quinolines (07SL2743). Very recently, its Cu(I)-complex (as CuOAc-DIFLOURPHOS) was identified as the catalyst of choice for the asymmetric reductive Mannich reaction of ketimines (**93a–c**) with a broad substrate scope providing high enantio- and diastereoselectivities (Scheme 19, 08JA16146).

96



97

Figure 15 Propylenedioxy-type ligands.



	99a	99b	99c	99d	99e
(*S*) -**96**	(S) 99.4% ee	(S) 99.2% ee	(S) 99.7% ee	(S) 95.1% ee	(S) 97.7% ee
(*R*) -**97**	(R) 99.3% ee	(R) 99.4% ee	(R) 99.4% ee	(R) 96.7% ee	(R) 82.4% ee
(*S*) -**1a**	(S) 97.7% ee	(S) 98.0% ee	(S) 96.1% ee	(S) 94.2% ee	(S) 89.3% ee

Scheme 20 Asymmetric hydrogenation of *β*-ketoesters.

4.6 Propylenedioxy type ligands

Chan et al. reported two diastereomeric ligands **96** and **97** both possessing added chiral centers on the backbone and high steric hindrances (Figure 15). Both ligands provided high enantiomeric excesses in asymmetric hydrogenations of *β*-ketoesters (**98a–e**) catalyzed by their Ru-complexes as shown in Scheme 20 (02OL4599).

ACKNOWLEDGMENT

NA thanks the Higher Education Commission of Pakistan for a Ph.D. scholarship.

REFERENCES

80JA7932 A. Miyashita, A. Yasuda, H. Takaya, K. Toriumi, T. Ito, T. Souchi, and R. Noyori, *J. Am. Chem. Soc.*, **102**, 7932 (1980).

86JOC629 H. Takaya, K. Mashima, K. Koyano, H. Yagi, H. Kumobayashi, T. Taketomi, S. Akutagawa, and R. Noyori, *J. Org. Chem.*, **51**, 629 (1986).

87JA5856 R. Noyori, T. Ohkuma, M. Kitamura, H. Takaya, N. Sayo, H. Kumobayashi, and S. Akutagawa, *J. Am. Chem. Soc.*, **109**, 5856 (1987).

88EPP295109	N. Sayo, S. Akutagawa, T. Saito, R. Noyori, H. Kumobayashi, and H. Takaya, (Takasago International Corporation), *Eur. Pat.* 295109 (1988).
88TL1555	M. Kitamura, T. Ohkuma, H. Takaya, and R. Noyori, *Tetrahedron Lett.*, **29**, 1555 (1988).
89OS20	H. Takaya, S. Akutagawa, and R. Noyori, *Org. Synth.*, **67**, 20 (1989).
90ACR345	R. Noyori and H. Takaya, *Acc. Chem. Res.*, **23**, 345 (1990).
90JCD55	K. Kurtev, D. Bibola, R. A. Jones, D. J. Cole-Hamilton, and G. Wilkinson, *J. Chem. Soc., Dalton Trans.*, 55 (1990).
91TL7283	X. Zhang, K. Mashima, K. Koyano, N. Sayo, H. Kumobayashi, S. Akutagawa, and H. Takaya, *Tetrahedron Lett.*, **32**, 7283 (1991).
93CRV2067	G. R. Newkome, *Chem. Rev.*, **93**, 2067 (1993).
94JCS(P1)2309	X. Zhang, K. Mashima, K. Koyano, N. Sayo, H. Kumobayashi, S. Akutagawa, and H. Takaya, *J. Chem. Soc., Perkin Trans. 1*, 2309 (1994).
94JOC7180	D. Cai, J. F. Payack, D. R. Bender, D. L. Hughes, T. R. Verhoeven, and P. J. Reider, *J. Org. Chem.*, **59**, 7180 (1994).
94USP252306	D. Cai (Merck), *US Pat.* 252306 (1994).
95CC1721	H. Yang, M. Alvarez, N. Lugan, and R. J. Mathieu, *J. Chem. Soc., Chem. Commun.*, 1721 (1995).
95S36	H. Brunner and P. Bublak, *Synthesis*, 36 (1995).
95USP5399771	D. Cai (Merck), *US Pat.* 5399771 (1995).
96JOC5510	T. Uemura, X. Zhang, K. Matsumura, N. Sayo, H. Kumobayashi, T. Ohta, K. Nozaki, and H. Takaya, *J. Org. Chem.*, **61**, 5510 (1996).
96JOC6244	T. Benincori, E. Brenna, F. Sannincolo, L. Trimarco, P. Antognazza, E. Cesarotti, F. Demartin, and T. Pilati, *J. Org. Chem.*, **61**, 6244 (1996).
96T15031	A. R. Katritzky, S. Rachwal, and B. Rachwal, *Tetrahedron*, **52**, 15031 (1996).
96TA285	U. Berens, J. M. Brown, J. Long, and R. Selke, *Tetrahedron: Asymmetry*, **7**, 285 (1996).
96TL2813	J. Xiao, S. C. A. Nefkens, P. G. Jessop, T. Ikariya, and R. Noyori, *Tetrahedron Lett.*, **37**, 2813 (1996).
96TL6503	C. Spino, N. Mayes, and H. Desfossés, *Tetrahedron Lett.*, **37**, 6503 (1996).
97CC2359	S. A. Laneman, *Chem. Commun.*, 2359 (1997).
97EPP0771812	N. Sayo, X. Zhang, T. Ohmoto, A. Yoshida, and T. Yokozawa, *Eur. Pat.* 0771812 (1997) [*Chem. Abstr.*, **127**, 50792 (1997)].
97JOM445	T. Benincori, E. Brenna, F. Sannincolo, L. Trimarco, P. Antognazza, E. Cesarotti, F. Demartin, and T. Pilati, *J. Organomet. Chem.*, 445 (1997).
97OM3469	A. S. C. Chan, C. C. Chen, and R. Cao, *Organometallics*, **16**, 3469 (1997).
97USP5902904	S. A. Laneman (Monsanto), *US Pat.* 5902904 (1997).
98EPP0839819	X. Zhang and N. Sayo, *Eur. Pat.* 0839819 (1998) [*Chem. Abstr.*, **129**, 16234 (1998)].
98TA3241	W. Hu, C. C. Pai, C. C. Chen, G. Xue, and A. S. C. Chan, *Tetrahedron: Asymmetry*, **9**, 3241 (1998).
98TA4183	W. Hu, C. C. Chen, G. Xue, and A. S. C. Chan, *Tetrahedron: Asymmetry*, **9**, 4183 (1998).

99CC1811 L. F. Tietze, K. Thede, and F. Sannicolo, *Chem. Commun.*, 1811 (1999).

99CEJ2472 A. E. S. Gelpke, H. Kooijman, A. L. Spek, and H. Hiemstra, *Chem., Eur. J.*, **5**, 2472 (1999).

99USP5886182 A. S. C. Chan and C.-C. Pai, *US Pat.* 5886182 (1999).

00CC583 L. F. Tietze, K. Thede, R. Schimpf, and F. Sannicolo, *Chem. Commun.*, 583 (2000).

00JA11513 C.-C. Pai, C.-W. Lin, C.-C. Lin, C.-C. Chen, A. S. C. Chan, and W. T. Wong, *J. Am. Chem. Soc.*, **122**, 11513 (2000).

00JOC2043 T. Benincori, E. Cesarotti, O. Piccolo, and F. Sannincolo, *J. Org. Chem.*, **65**, 2043 (2000).

00JOC8340 T. Benincori, O. Piccolo, S. Rizzo, and F. Sannincolo, *J. Org. Chem.*, **65**, 8340 (2000).

00JOM128 D. Blanc, V. Ratovelomanana-Vidal, J.-P. Gillet, and J.-P. Genêt, *J. Organomet. Chem.*, **128**, 603 (2000).

00OL2817 N. G. Andersen, M. Parvez, and B. A. Keay, *Org. Lett.*, **2**, 2817 (2000).

01ASC264 T. Saito, T. Yokozawa, T. Ishizaki, T. Moroi, N. Sayo, T. Miura, and H. Kumobayashi, *Adv. Synth. Catal.*, **343**, 264 (2001).

01JOC7478 N. G. Andersen, P. D. Ramsden, D. Che, M. Parvez, and B. A. Keay, *J. Org. Chem.*, **66**, 7478 (2001).

01SL1050 J. Wu, H. Chen, Z.-Y. Zhou, C.-H. Yeung, and A. S. C. Chan, *Synlett*, 1050 (2001).

01T2563 J. Madec, X. Pfister, P. Phansavath, V. Ratovelomanana-Vidal, and J.-P. Genêt, *Tetrahedron*, **57**, 2563 (2001).

02JOC7908 J. Wu, H. Chen, W. Kwok, R. Guo, Z. Zhou, C. Yeung, and A. S. C. Chan, *J. Org. Chem.*, **67**, 7908 (2002).

02OL4599 L. Qiu, J. Qi, C.-C. Pai, S. Chan, Z. Zhou, M. C. K. Choi, and A. S. C. Chan, *Org. Lett.*, **4**, 4599 (2002).

02TL1539 J. Wu, H. Chen, W.-H. Kwok, K.-H. Lam, Z.-Y. Zhou, C.-H. Yeung, and A. S. C. Chan, *Tetrahedron Lett.*, **43**, 1539 (2002).

02TL2789 C.-C. Pai, Y.-M. Li, Z.-Y. Zhou, and A. S. C. Chan, *Tetrahedron Lett.*, **43**, 2789 (2002).

03ACR908 J.-P. Genêt, *Acc. Chem. Res.*, **36**, 908 (2003).

03ASC15 R. Noyori, *Adv. Synth. Catal.*, **345**, 15 (2003).

03CEJ2963 J. Wu, J.-X. Ji, R. Guo, C.-H. Yeung, and A. S. C. Chan, *Chem., Eur. J.*, **9**, 2963 (2003).

03EJO1931 S. Duprat de Paule, S. Jeulin, V. Ratovelomanana-Vidal, J.-P. Genêt, N. Champion, and P. Dellis, *Eur. J. Org. Chem.*, 1931 (2003).

03EPP1611114 B. Pugin, P. Martin, M. Müller, F. Naud, F. Spindler, M. Thommen, G. Melone, and M. Kesselgruber, *Eur. Pat.* 1611114 (2003) [assigned to Solvias AG].

03JMO171 L. Wang, W. Kwok, J. Wu, R. Guo, T. T.-L. Au-Yeung, Z. Zhou, A. S. C. Chan, and K.-S. Chan, *J. Mol. Catal. A*, **196**, 171 (2003).

03JOC2490 J. Wu, X. Chen, R. Guo, C.-H. Yeung, and A. S. C. Chan, *J. Org. Chem.*, **68**, 2490 (2003).

03OPD399 S. Duprat de Paule, S. Jeulin, V. Ratovelomanana-Vidal, J.-P. Genêt, N. Champion, G. Deschaux, and P. Dellis, *Org. Process Res. Dev.*, **7**, 399 (2003).

03TA987 J. Wu, C.-C. Pai, W. H. Kwok, R. W. Guo, T. T. L. Au-Yeung, C. H. Yeung, and A. S. C. Chan, *Tetrahedron: Asymmetry*, **14**, 987 (2003).

03TL823 S. Duprat de Paule, S. Jeulin, V. Ratovelomanana-Vidal, J.-P. Genêt, N. Champion, and P. Dellis, *Tetrahedron Lett.*, **44**, 823 (2003).

03TL6505 Q. Shi, L. Xu, X. Li, X. Jia, R. Wang, T. T.-L. Au-Yeung, A. S. C. Chan, T. Hayashi, R. Cao, and M. Hong, *Tetrahedron Lett.*, **44**, 6505 (2003).

04AGE320 S. Jeulin, S. Duprat de Paule, V. Ratovelomanana-Vidal, J.-P. Genêt, N. Champion, and P. Dellis, *Angew. Chem., Int. Ed. Engl.*, **43**, 320 (2004).

04CJC145 N. G. Andersen, M. Parvez, R. McDonald, and B. A. Keay, *Can. J. Chem.*, **82**, 145 (2004).

04JA9918 Y. Hsiao, N. R. Rivera, T. Rosner, S. W. Krska, E. Njolito, F. Wang, Y. Sun, J. D. Armstrong, E. J. J. Grabowski, R. D. Tillyer, F. Spindler, and C. Malan, *J. Am. Chem. Soc.*, **126**, 9918 (2004).

04TA2169 H. Shimizu, T. Ishizaki, T. Fujiwara, and T. Saito, *Tetrahedron: Asymmetry*, **15**, 2169 (2004).

05ASC507 J. Wu, T. T.-L. Au-Yeung, W.-H. Kwok, J.-X. Ji, Z.-Y. Zhou, C.-H. Yeung, and A. S. C. Chan, *Adv. Synth. Catal.*, **347**, 507 (2005).

05ASC1750 Y. F. Kwong, W. H. Lee, L. Qiu, H. W. Lam, Y.-M. Li, L. H. Kwong, and A. S. C. Chan, *Adv. Synth. Catal.*, **347**, 1750 (2005).

05CC1390 L. Xu, K.-H. Lam, J.-X. Ji, J. Wu, Q.-H. Fan, W.-H. Lo, and A. S. C. Chan, *Chem. Commun.*, 1390 (2005).

05PNA3570 J. Wu, J.-X. Ji, and A. S. C. Chan, *Proc. Natl. Acad. Sci. U.S.A.*, **102**, 3570 (2005).

05SL429 R. Le Roux, N. Desroy, P. Phansavath, and J.-P. Genêt, *Synlett*, **3**, 429 (2005).

05T5405 H. Shimizu, I. Nagasaki, and T. Saito, *Tetrahedron*, **61**, 5405 (2005).

006ACR711 J. Wu and A. S. C. Chan, *Acc. Chem. Res.*, **39**, 711 (2006).

07ACR1240 H.-U. Blaser, B. Pugin, F. Spindler, and M. Thommen, *Acc. Chem. Res.*, **40**, 1240 (2007).

07ACR1278 W. Zhang, Y. Chi, and X. Zhang, *Acc. Chem. Res.*, **40**, 1278 (2007).

07ASC943 D. Blanc, J. Madec, F. Popowyck, T. Ayad, P. Phansavath, V. Ratovelomanana-Vidal, and J.-P. Genêt, *Adv. Synth. Catal.*, **349**, 943 (2007).

07ASC1592 S. Jeulin, T. Ayad, V. Ratovelomanana-Vidal, and J.-P. Genêt, *Adv. Synth. Catal.*, **349**, 1592 (2007).

07ASC1999 D. E. Kim, C. Choi, I. S. Kim, S. Jeulin, V. Ratovelomanana-Vidal, J. P. Genêt, and N. Jeong, *Adv. Synth. Catal.*, **349**, 1999 (2007).

07OL1307 K. Tanaka, T. Osaka, K. Noguchi, and M. Hirano, *Org. Lett.*, **9**, 1307 (2007).

07SL2743 C. Deport, M. Buchotte, K. Abecassis, H. Tadaoka, T. Ayad, T. Ohshima, J.-P. Genêt, K. Mashima, and V. Ratovelomanana-Vidal, *Synlett*, 2743 (2007).

08ASC2525 C. Pautigny, S. Jeulin, T. Ayad, Z. Zhang, J.-P. Genêt, and V. Ratovelomanana-Vidal, *Adv. Synth. Catal.*, **350**, 2525 (2008).

08CAJ1384 M. Kesselgruber, M. Lotz, P. Martin, G. Melone, M. Müller, B. Pugin, F. Naud, F. Spindler, M. Thommen, P. Zbinden, and H.-U. Blaser, *Chem., Asian J.*, **3**, 1384 (2008).

08JA195 X. Liao, Z. Weng, and J. F. Hartwig, *J. Am. Chem. Soc.*, **130**, 195 (2008).

08JA6340	I. S. Kim, M.-Y. Ngai, and M. J. Krische, *J. Am. Chem. Soc.*, **130**, 6340 (2008).
08JA9429	Y. Zhao, L. Jin, P. Li, and A. Lei, *J. Am. Chem. Soc.*, **130**, 9429 (2008).
08JA16146	Y. Du, L.-W. Xu, Y. Shimizu, K. Oisaki, M. Kanai, and M. Shibasaki, *J. Am. Chem. Soc.*, **130**, 16146 (2008).
08JOC4755	N. Arshad, J. Hashim, and C. O. Kappe, *J. Org. Chem.*, **73**, 4755 (2008).

CHAPTER 3

Monocyclic Hetarenes with π-Electron Aromatic Sextet

Alexandru T. Balaban

Contents

Texas A&M University at Galveston, 5007 Ave. U. Galveston, TX 77551, USA

Advances in Heterocyclic Chemistry, Volume 99
ISSN 0065-2725, DOI 10.1016/S0065-2725(10)09903-4

1. INTRODUCTION

The normal way to build a house is to acquire a piece of land on planet Earth, and then according to a master plan, to dig and make a foundation, to anchor in this foundation the solid structure allowing to place the walls and floors and at the end to cover the house with a roof. In contrast, theory and virtual reality allow us to proceed in reverse order, starting with a roof somewhere in cosmos and looking for ways to accommodate under it interesting structures that become stable when we add a planet with its gravitational field.

The chemical counterpart of the roof will be a set of valence-shell electrons, and we shall look at atomic and molecular architectures that can be hosted under such a roof when bringing in stable nuclei and corresponding core electrons. In order to see what happens with such an idea in a Chemical Aufbau approach, let us start with an octet of electrons under which we place a nucleus with atomic number $Z = 10$ and a K-shell with two core electrons. The result is a neon atom, an exceptionally stable architecture with *spherical* (*three-dimensional*) *symmetry*. The same result would happen for $Z = 18$ (argon) with one more "floor", and so on or the following noble gas atoms. Actually, we start with the closed electronic shells allowed by the Pauli Exclusion Principle and the "$n + \ell$ Rule", and we supply the nuclei corresponding to such shells. The proof for the stability of this architecture is provided by the high ionization potential and the low electron affinity.

Now let us look at diatomic molecules that possess the highest binding energies, allowing them to stay bonded at the highest temperatures and to form at such temperatures from any precursors that possess the corresponding atoms. For this purpose, let us start with the closed electronic shells of homo- and heterodiatomic molecules. Using the familiar Mulliken–Coulson correlation diagrams displaying the united atom and the separated atoms, we obtain 10 electrons in the combined valence shells of the diatomic molecule, in addition to core electrons. The resulting molecules are: the homodiatomic neutral dinitrogen N_2, dianionic C_2^{2-} and dicationic dioxygen O_2^{2+}; heterodiatomic neutral CO and BF, monocationic NO^+ and monoanionic CN^-. There are practically no data for CF^+, NF^{2+} and BN^{2-}, but all the previously mentioned ones are well-documented triple-bonded stable molecules with sp-hybridization and *linear* (*unidimensional*) *symmetry*. Other interesting neutral double-bonded molecules are the well-documented homodiatomic isoelectronic dioxygen O_2 and heterodiatomic nitrogen monofluoride (fluoroimidogen) NF (02JA366, 67TFS801).

We shall see in the following sections how a *planar two-dimensional symmetry* with molecules having sp^2-hybridization is achieved under the "roof" of the classical aromatic π-electron sextet (04CRV2777, 05CRV3436).

2. THE AROMATIC π-ELECTRON SEXTET

Proceeding similarly, namely by starting with a molecular π-electron sextet, one needs to fill in a number m of nuclei with their core and σ-electrons. In agreement with the Frost–Musulin diagram of molecular orbitals in annulenes with variable m values, no closed shell with a π-electron aromatic sextet is possible for $m = 3$. We are at liberty to vary m ($m \geq 4$) and the nature (atomic number) of the nuclei. "Exotic" aromaticity such as σ-aromaticity of cyclopropane and triphosphirane, or three-dimensional aromaticity of carboranes will not be considered in this chapter. Neither will we examine the interesting borocarbons with hypercoordinated planar carbon having fluxional structure and Hückel-type aromaticity due to π- and σ-electrons (02RCR869, 05AGE1078).

Before exploring all imaginable possibilities, we need to recall the three types of sp^2-hybridized atoms that may form aromatic rings in accordance with Pauli's exclusion principle: the non-hybridized atomic orbital may contain 2, 1 or 0 π-electrons, and the corresponding atoms will be denoted by X, Y and Z, respectively (Z corresponds to zero π-electrons) (87MI3). Whenever two odd-numbered chains of Y-type atoms appear in a ring, separated by X- and/or Z-type atoms, the aromatic system is "mesoionic" (although for larger rings a valence isomerization to bicyclic and in some cases tricyclic non-aromatic systems may occur). Chains containing two or more adjacent Z- or X-type atoms lower the stability of a hetarene. By contrast, Y-type atoms or alternating X- and Z-type atoms form chains of higher stability. Adjacent non-carbon heteroatoms belonging to X- and Y-types do not decrease the stability as proved by pyrazole with adjacent X- and Y-type nitrogen atoms, whose stability is comparable to that of imidazole with non-adjacent nitrogen atoms.

The prototype of aromatic compounds is the hydrocarbon benzene $(CH)_6$. It has equally long carbon–carbon bonds (140 pm), as the result of the tug-of-war between the tendency of the σ-electrons which win by preferring bond equalization, and of the six π-electrons ($n = 1$ in Erich Hückel's $4n+2$ π-electron rule) which prefer alternating bond lengths. Other characteristics of benzene are its planar structure and thermal stability, its propensity toward electrophilic substitution of hydrogen atoms, and its remarkable diamagnetic susceptibility. The ring current gives rise to characteristic low-field chemical shifts of the external in-plane hydrogens, and to high-field chemical shifts for any hydrogen atoms of substituents that are situated above or below that plane. Other chemical manifestations of benzene's aromaticity are reflected in (i) the much higher acidity of phenol than alcohols, and the preference of the phenolic tautomeric form over cyclohexadienone, in contrast to the enol-carbonyl tautomerism; (ii) the much lower basicity of aniline as compared to non-aromatic primary amines; (iii) the stabilizing influence allowing the isolation of aromatic diazonium salts; (iv) the conjugation effects accounting for the stability of triphenylmethyl or diphenylamino radicals or cations, of diphenylhalonium, triphenyloxonium, tetraphenylammonium or tetraphenylphosphonium salts as compared to non-aromatic congeners. All these manifestations of aromaticity and conjugation are common also to heteroanalogues of benzene.

Confining ourselves to First-Row atoms (Second Period in Mendeleev's Periodic System), we present in Figure 1 the X-, Y- and Z-type atoms that can form aromatic rings (it may also be observed that pairs of [Yb]-type atoms form diatomic molecules that have been mentioned in Section 1 and are isoelectronic with N_2). The groups are numbered from 3 to 6, that is from boron (IUPAC Group number 13) to oxygen (IUPAC Group number 16), and with [a] for one substituent R attached to the ring atom, or [b] for a ring atom having a lone electron pair. For each of these three types, one can associate an "atomic aromaticity constant" k expressing the electronegativity contribution, which for "[a]-type atoms" also depends on the substituent R modeled by its Hammett σ-value. Conventionally, for benzene, which corresponds to six [Y4a] atoms with $R = H$, we have chosen $k = 0$, and the same value is obtained on summing all atomic contributions into the "molecular aromaticity constant" $K = 0$. For tropylium with six [Y4a] atoms and one [Z4a] atom, $R = H$, $k = K = +100$; for cyclopentadienide with four [Y4a] atoms and one [X4a] atom, $R = H$, $k = K = -100$. As a result, on summing atomic contributions, practically all known heterocycles have molecular aromaticity constants in the range from $K = -200$ to $K = +200$ (76T315). One should mention that the idea of X-, Y- and Z-type atoms in aromatic systems was found independently in Bucharest (59MI257) and in Norwich, but Katritzky's manuscript remained

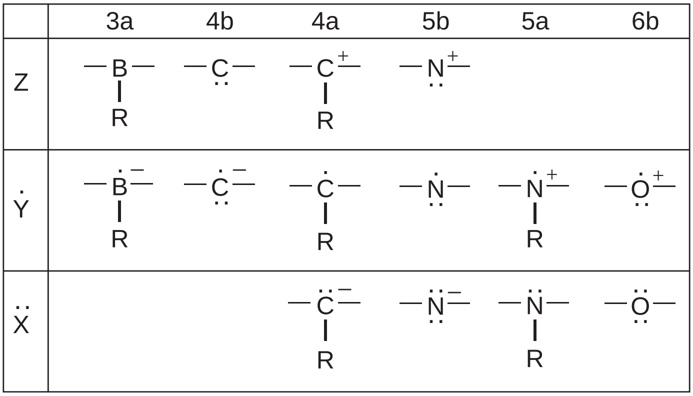


Figure 1 The three types of First-Row (Second Period) atoms in aromatic rings.

unpublished. It should also be mentioned that many other elements follow the pattern of Figure 1.

An interesting graph-theoretical problem, known as the "necklace problem" is to find how many non-isomorphic necklaces may be obtained from *m* beads of three colors. The solution may be found by applying Polya's theorem (76MI1). Its chemical application is to find all possible arrangements for isomeric $X_xY_yZ_z$ rings, with ring size $m = x+y+z$, and for π-electron sextet molecules with $2x+y = 6$. This set of two Diophantine equations have solutions that are derived from the four and only four partitions of the number 6 in ones and twos (according to Pauli's exclusion principle): 1+1+1+1+1+1, 1+1+1+1+2, 1+1+2+2 and 2+2+2. The number of Z-type atoms may increase indefinitely together with *m*, but we may restrict most meaningless solutions by forbidding two or more Z-type atoms to be adjacent, based on the decreasing stability of systems with extended electron-deficient centers (even systems with two or more X-type atoms have lower stability, but there are not many such solutions). The solutions are presented in Table 1 (with no adjacency restrictions in the upper panel, but with no Z–Z adjacency in the lower panel). The latter solutions require a more elaborate mathematical approach. It will be seen that X-type atoms are important for ring size $m \leq 6$, whereas Z-type atoms are important for $m \geq 6$.

Table 1 Numbers of isomeric $X_xY_yZ_z$ rings followed by ring size *m* (in brackets): upper panel without adjacency restrictions as in Figures 2 and 4; lower panel with no Z–Z adjacency allowed as in Figure 3; numbers of isomers presented in Figures 2, 3 and 4 are denoted by boldface characters

\ y x \	2	4	6	2	4	6	0	2	4	6	0	2	4	6
0			1 (6)			1 (7)				4 (8)				**7** (9)
1		**1** (5)			**3** (6)				9 (7)				**19** (8)	
2	2 (4)			**4** (5)				11 (6)				**18** (7)		
3							**2** (5)				**3** (6)			
	z = 0			z =1			z = 2				z = 3			

\ y x \	0	2	4	6	0	2	4	6
0				**3** (8)				**3** (9)
1			**6** (7)				**6** (8)	
2		**7** (6)				**4** (7)		
3	**1** (5)				**1** (6)			
	z = 2				z = 3			

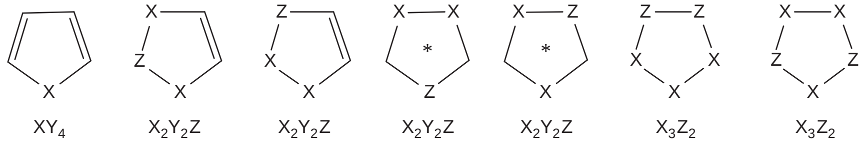


Figure 2 Five-membered aromatic heterocycles; Y-type atoms are not shown explicitly.

In Table 1 we have limited the value of *m* to 9. As an example for five-membered aromatic heterocycles, Figure 2 shows the unique XY_4, the four X_2Y_2Z, and the pair of X_3Z_2 heterocycles, in agreement with numbers shown in the upper panel of Table 1. As usual for organic chemical texts where only heteroatoms different from carbon are shown explicitly, in the present text Y-type atoms (which may be carbon, but also other elements) are not shown explicitly.

When considering heterocycles with more than one Z-type heteroatom, the number of possible isomers increases tremendously, as shown in the last eight columns of the upper panel of Table 1, in comparison with the numbers of the lower panel. Most of such systems are mesoionic, and have little chance of leading to stable aromatics. Examination of Figures 3 and 4 will confirm this statement.

Now comes the "combinatorial explosion" for finding all allowed aromatic systems with a π-electron sextet. Just for discussing Y_6 hetarenes with one ring composed of five carbon atoms and one atom different from carbon, a whole chapter was written that discussed thousands of molecules (09MI2).

We shall endeavor in the following sections to provide a few leading bibliographical references about the millions of existent aromatic heterocycles with π-electron aromatic sextet, and hints about the billions of possible but not yet made congeners. If in the story of the π-electron aromatic sextet Kekulé, Bamberger, Robinson (and perhaps Crocker (05CRV3436)) contributed with *What?*, and Hückel with *Why?*, then many other chemists dared to ask *What if?* For this purpose, Figures 1–4 may be of some use in the future. A surge of interest in aromaticity and heterocycles could be observed in the first years of the new millennium, reflected in special issues of *Chemical Reviews* (01CRV1115, 04CRV2125, 05CRV3433). In order to avoid repetitions, we shall confine the discussion to topics that are not covered in these special issues.

One should note that we do not put barriers between organic and inorganic cyclic structures. We have on one hand *aromatic organic homocycles* such as benzene, cyclopentadienide anions, cyclooctatetraenide dianions and tropylium cations, and on the other hand *aromatic inorganic homocycles*, and then we gradually fuse them into *aromatic heterocycles*. The only restriction we observe is for discussing only

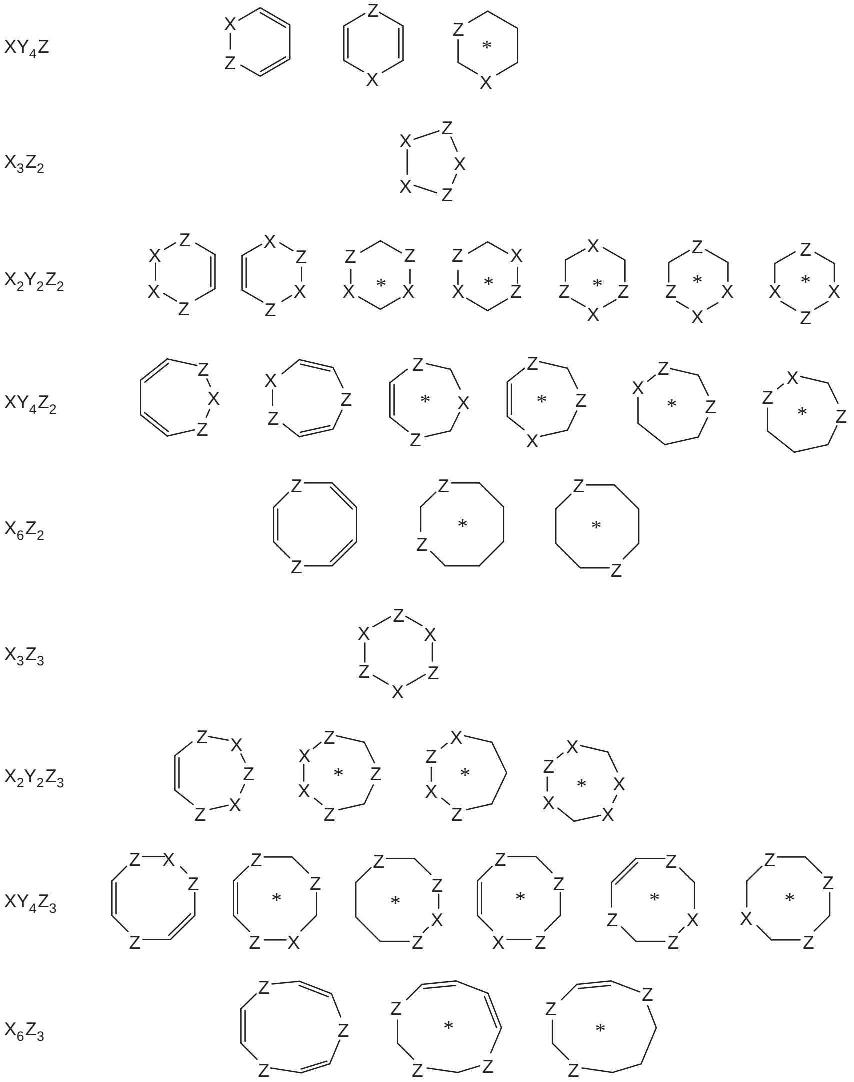


Figure 3 Structures of seven sets of π-electron sextet six-, seven-, eight- and nine-membered rings with no Z–Z adjacencies; mesoionic structures are indicated by an asterisk.

monocyclic molecules with an aromatic π-electron sextet. As noted by Haiduc and Sowerby (87MI1), organic chemists tend to regard even pentazole as an organic ring, and indeed *N*-arylpentazoles have been discovered by organic chemists (Ugi, Huisgen and Clusius, as will be discussed in a later section), with the aid of the tremendous stabilizing

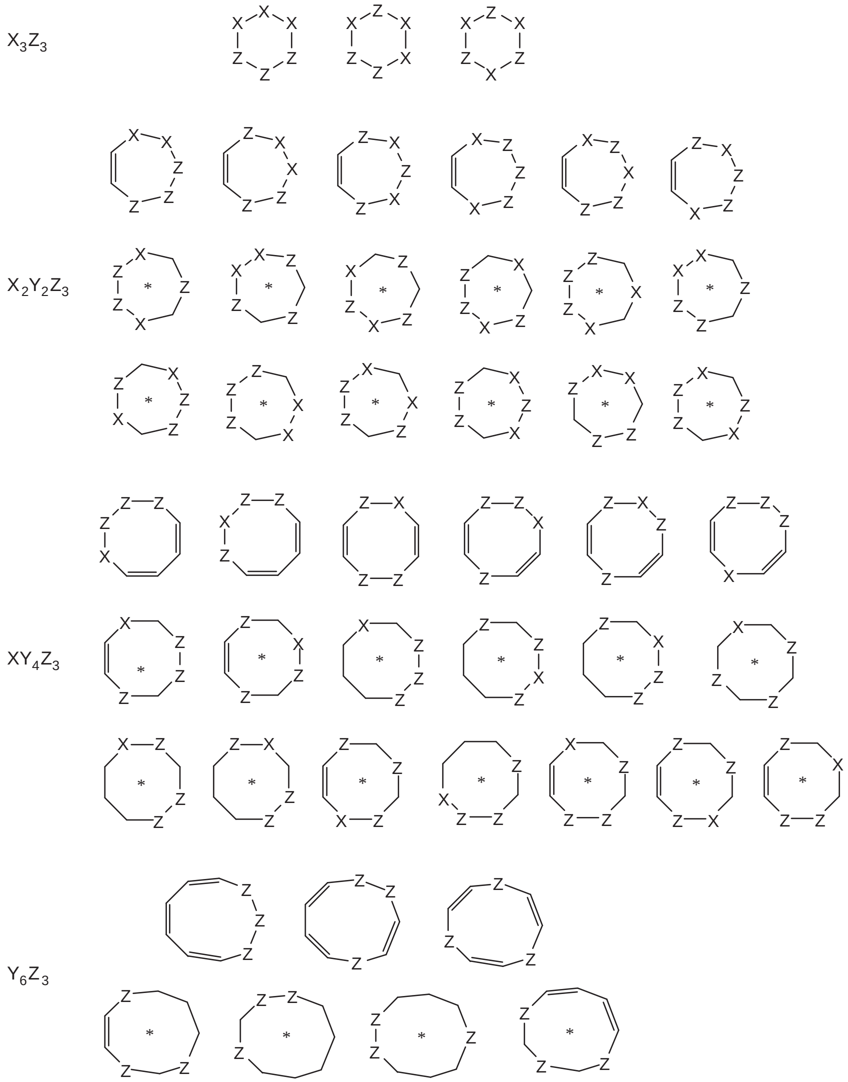


Figure 4 Structures of three sets of π-electron sextet isomeric seven-, eight- and nine-membered rings with three Z-type atoms; no restriction on X–X or Z–Z adjacencies; mesoionic structures are indicated by an asterisk.

effects of aryl groups. One should be reminded of a remark by W. Treibs: *phenyl groups are crutches* (he meant it in a derogatory way, aiming at the hard-to-make parent unsubstituted compounds). It comes as no surprise that triarylmethyl and diarylaminyl free radicals, or diarylhalonium, triaryloxonium, tetraarylammonium and aryldiazonium salts are much more stable than the corresponding alkyl or unsubstituted derivatives.

On using the most familiar approach to heteroaromaticity, two theoretical ways have been discussed in textbooks for obtaining nitrogen-containing heteroanalogues of benzene: (i) replacement of a CH group [Y4a] in benzene by a nitrogen [Y5b], when the *π-electron-deficient* pyridine results; owing to the higher electronegativity of nitrogen than that of carbon, this replacement leads to a chemical behavior reminiscent of that of nitrobenzene, namely low reactivity in electrophilic substitutions of pyridine with *β*-regioselectivity, and the possibility of nucleophilic *α*-substitution; and (ii) replacement of a CH=CH group in benzene by an NR group [X5a], when the *π-electron-excessive* pyrrole results, owing to the availability of six *π*-electrons over five-ring atoms; this leads to the well-known vanishing basicity of pyrrole in comparison with secondary amines, and to its similar reactivity to that of phenol.

With many treatises about heterocyclic compounds, and with the impressive series *Comprehensive Heterocyclic Chemistry* in three series (84CHEC1, 96CHEC2-1, 08CHEC3-1), it makes little sense to deal in detail with individual compounds. Rather, this review will discuss trends observed when m increases stepwise from $m = 4$ to $m = 9$. Actually, it will be seen that there are no heterocyclic sextet-aromatic systems with eight- or nine-membered rings, but we have included such structures because it may be worthwhile to explore whether their strain-free bicyclic isomers may evidence isomerization to planar monocyclic mesoionic systems.

It should be remembered that the Hückel rule involving $4n+2$ π-electrons (with $n = 0, 1, 2, \ldots$) is necessary but insufficient, because other factors may interfere with the extent of delocalization. The most obvious ones are the existence of a closed shell of filled bonding electrons, the absence of occupied anti-bonding levels and the absence of non-bonding levels. As a consequence, no classically aromatic three-membered ring with a π-electron sextet is possible. As will be discussed in the section devoted to four-membered rings, steric strain is an important factor.

Owing to Michael J. S. Dewar's brilliant experimental and theoretical contributions in the field of tropolone derivatives, it was believed that tropone and the pair of isomeric *α*- and *γ*-pyrones had considerable aromaticity, with the zwitterionic resonance formula of the carbonyl playing the role of a Z-type atom. Soon, however, it was shown that the extent of aromaticity was very low, and it increased only after combining with electrophiles, for example on protonation or alkylation (such as the formation of methiodides) (69JA5286, 72T5299, 03OBC3410).

The syntheses of the two possible cyclooctatriene-diones (1,2 and 1,4) were discussed in 1977 and 1975, respectively; the former dimerizes at room temperature and the latter is a non-planar stable non-aromatic compound; the planar diprotonated 1,4-cyclooctatriene-dione is calculated to be slightly aromatic (00JMT181).

The confirmation of Hückel's rule with the discovery of tropylium by Doering and Knox (54JA3203) triggered by Dewar's research on tropolones, led to an explosive research and the publication of several reviews (80PAC1409, 96PAC209) and books on non-benzenoid aromatics, discussed at several international meetings (59MI1, 66MI1, 69MI1, 71MI1, 71MI2, 84MI2, 86MI1, 94MI1).

One should recall that Merling had isolated crystalline tropylium bromide in 1891 but, in the absence of a theoretical reason for finding a water-soluble C_7H_7Br salt, he could not realize the importance of his experiment (54JA3203). Interestingly, a similar situation was encountered later with the diacylation of alkenes (studied for almost a century) leading to pyrylium salts; these could be identified only in the late 1950s by Balaban and Nenitzescu in Romania, and Praill in England; see the "Balaban–Nenitzescu–Praill reaction" in the book edited by Hassner and Stumer (02MI1).

In the following, the emphasis will not be on all-carbon rings, as it is well known that the aromatic character of π-electron sextet aromatics increases stepwise from the cyclobutadiene dianion to cyclopentadiene anion, reaching a maximum with benzene, and then decreases stepwise with the tropylium cation and finally with the cyclooctatetraene dianion. Thus, in the following we will discuss heterocyclic compounds with ring sizes increasing from 4 to 7. We are especially interested in the limits close to which the aromaticity of the electron sextet ceases to be operative due to various factors such as strain, high stability of decomposition products, for example N_2 molecules like pentazoles, mono- or di-cations or -anions, small and large rings will be discussed in more detail than "run-of-the-mill" hetarenes. As a general organizational principle, we shall deal with heteroatoms in the order of their decreasing electronegativity.

An interesting comparison between several aromaticity indices (harmonic oscillator model, nucleus-independent chemical shift, *para*-delocalization index, aromatic fluctuation index, multicenter indices, atoms-in-molecules theoretical indices and graph-theoretical indices) concluded that the most reliable ones are based on electron delocalization (08JCC1543).

3. SEXTET π-ELECTRON HETEROAROMATICS WITH FOUR-MEMBERED RINGS

After a careful theoretical analysis by *ab initio* MO methods, Schleyer and coworkers concluded that 1,2-dioxetenes and 1,2-diazetines are non-aromatic 6π-systems with completely localized C=C double bonds and normal C–X and X–X single bonds (X = O or NH). The unsubstituted 1,2-dioxetene and 1,2-diazetine undergo conrotatory ring opening to glyoxal and α-diimine, respectively, in highly exothermic reactions with lower activation energies than the corresponding conversion of cyclobutene to 1,3-butadiene. The corresponding mesoionic isomers, 1,3-dioxetenes and 1,3-diazetines, are also non-aromatic 6π-systems; the unsubstituted 1,3-dioxetene undergoes without activation energy a ring-opening reaction to (formyloxy)methylene, but the ring opening of the unsubstituted 1,3-diazetine has a considerable activation energy, so that though highly reactive and non-aromatic, 1,3-diazetines may be experimentally accessible (87JA6290).

There are extensive data about the sulfur congener, 1,2-dithiete, a substituted derivative of which was first isolated by Krespan et al. from the reaction of hexafluoro-2-butyne with sulfur vapor (60JA1515, 61JA3434). Bis-(trifluoromethyl)-1,2-dithietene is a thermally stable yellow liquid with normal boiling point (NBP) 95–96 °C. It is reactive toward dimerization to tetrakis-(trifluoromethyl)-1,5-tetrathiaoctadiene, and it reacts with alkenes or alkynes by cycloaddition to yield six-membered ring compounds. Krespan argued on the basis of electronic, infrared and NMR data that this heterocycle is aromatic. The ring opening of 1,2-dithiete to dithioglyoxal gave rise to a long-lasting discussion in the literature among theoretical chemists (91CPL175, 00JCP8430, 96IJQ859, 90JA7529, 04CPL192, 05JMT(732)71,99JCP7705, 96CPL407).

In the review by Shimizu and Kamigata on cyclic compounds having S–S bonds (00JOM106) and in other reviews (95SR371, 00AHC(77)221) numerous literature references on 1,2-dithietes are provided.

It was mentioned that dithietes are more stable than dithioglyoxal derivatives. The diithiete substituted with carbomethoxy groups (E) dimerizes to a tetrathia-cyclooctadiene and to a 16-membered cyclic tetramer, but no trimer was observed (Figure 5).

With transition metal ions (M), five-membered dithiolene complexes derived from the ring-opened dithioglyoxal isomers are obtained from the bis-trifluoromethyl-dithiete (63IC641, 63JA1584, 63JA1587, 64IC814, 68PIC49, 71CCA3254, 71IC1410, 75IC2011, 06JA11026). This compound also forms a cyclic dimer, and undergoes cycloadditions with alkenes and acetylenes (Figure 6).

Janssen and coworkers (93JPC6384, 90JA4155) presented theoretical data for a variety of four-membered rings, showing that rings containing carbon in addition to heteroatoms are less likely to be stable than rings containing

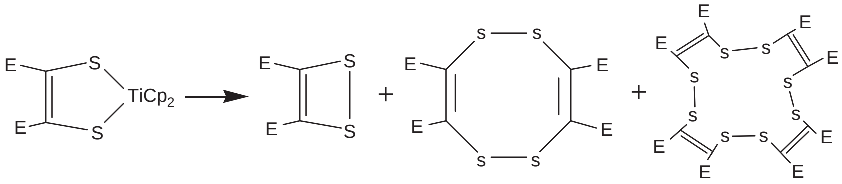


Figure 5 Synthesis of 3,4-dicarbomethoxy-1,2-dithiete.

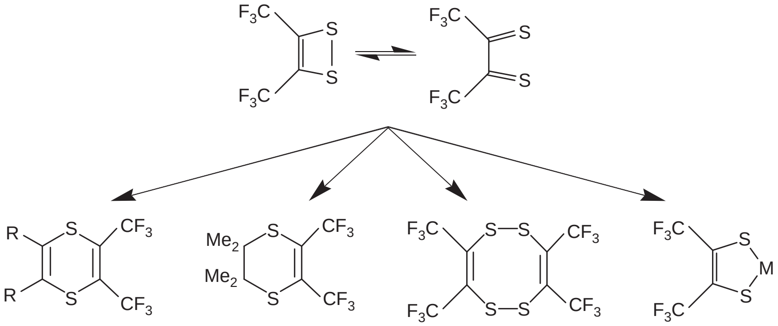


Figure 6 Reactions of 1,3-bis(trifluoromethyl)-1,2-dithiete.

only heteroatoms, see also (06JOM4359). Investigating 6π-aromaticity in four-membered rings, Janssen and coworkers found that the lithium salt with the cyclotetrazene dianion Li_2N_4 was calculated to be stable and aromatic (93JPC6384, 90JA4155). Sulfur-containing rings are calculated to be remarkably stable, due to the relative ease with which sulfur can accommodate π-electrons. Exciting developments have taken place in such all-non-metal aromatic four-membered rings involving pnictogen (Pn) dianions, or chalcogen (Ch) dications: Pn_4^{2-} (namely, P_4^{2-}, As_4^{2-}, Sb_4^{2-}, Bi_4^{2-}) and Ch_4^{2+} (namely, O_4^{2+}, S_4^{2+}, Se_4^{2+}, O_4^{2+}). One must mention Jug (84JOC4475), Gimarc (90PAC423), Corbett and coworkers (77IC2482, 84IC770) as well as Boldyrev and coworkers (05PCA236, 05CRV3716) for pnicotgenic species, and Gillespie with coworkers (71ACR413) as well as other authors for chalcogenic species. In all cases the aromatic rings are planar and almost square, usually with the counter-ions stacked between these rings. All these rings are isoelectronic with the cyclobutadiene dianion, but owing to the electronegativity of the atoms the HOMOs are bonding.

One should mention that the formation of 3,4-dideuteriocyclobutene on treating *cis*-dichlorocyclobutene with sodium naphthalide followed by addition of MeOD (all the time at −40 °C) proves the formation and reactivity of cyclobutene dianion (72CC365, 02JA1119). Theoretical studies reveal that the dilithium salt increases the stability of the tetrakis(trimethylsilyl)cyclobutene dianion, (01JA5356, 05JMT(728)61), in agreement with experiment (00JA5652). A similar result was found by computation for tetramethyl- and tetra-*t*-butyl-derivatives (00PCA1246). One must note that the "cyclobutadiene dianion" mentioned in the literature should actually be called "cyclobutene dianion".

3.1 1,2-Dithietes *versus* the mesoionic 1,3-dithietes

Returning to dithietes, one has to consider not only the previously mentioned Kekuléan 1,2-dithiete derivatives but also the *mesoionic*

1,3-dithietes. Their valence isomers with a bicyclo[1.1.0]butane structure have considerable steric strain and higher energy than the delocalized mesoionic monocyclic form, as shown by theoretical calculations (93JPC6384). However, till now no experimental data on such systems are available.

4. SEXTET π-ELECTRON HETEROAROMATICS WITH FIVE-MEMBERED RINGS

Starting with "inorganic aromatics", five-membered aromatic systems with π-electron sextet involving non-metal elements have been obtained experimentally and checked by X-ray crystallography and by quantum-computational methods as pentaatomic species Pn_5^{5-} pentaanions (with Pn = N, P, As, Sb and Bi) and M_5^{6-} hexaanions (with M = Ge, Sn and Pb) (04IC6490).

Inorganic aromatics involving also metals have been discovered, involving systems having a π-electron doublet or sextet. Boldyrev, Wang and coworkers (05CRV3716, 01SCI859) observed aromaticity in the Al_4^{2-} dianion, confirmed by all criteria: resonance energy, planarity with equal bond lengths, ring current, NICS values, electronic (ELF plots), hardness and polarizability values.

On comparing calculations for pentapnictogen anion aromatics [*cyclo*-$Pn_5]^-$, Tsipis (05CCR2740) reported the following stability order: $P_5^- < As_5^- < Sb_5^-$.

For $m = 5$ ring atoms, some of the most stable hetarenes are known. Indeed, in the nitrogen-containing heterocycle *N*-phenylpyrazole, it is the phenyl and not the pyrazole ring that undergoes destructive oxidation. A simple explanation lies in the fact that whereas the [X5a] heteroatoms (as in pyrrole) increase the π-electron availability in aromatic rings, the [Y5b] heteroatoms (as in pyridine) decrease it, but enhance the "ring-current aromaticity". When both types of nitrogen atoms replacing carbon in benzene are carried out simultaneously, these effects cancel out but the enhancement of aromaticity remains.

A few historical data are interesting to recall in order to show the role of serendipity in this field. Among the π-electron-excessive five-membered heteroaromatics with one heteroatom $(CR)_4X$, *thiophene* has physico-chemical properties so similar to those of benzene that until 1882/3 it stayed hidden as an impurity in the benzene obtained from coal tar. Then Victor Meyer discovered it serendipitously at what is nowadays the Eidgenössische Technische Hochschule in Zürich, during a lecture demonstration by the assistant Traugott Sandmeyer in front of undergraduates. It was believed at that time that the deep blue color produced by heating benzene with isatin and concentrated sulfuric acid (the indophenine reaction) was due to benzene. On the eve of the lecture, seeing that the stock supply of commercial benzene had been exhausted, Sandmeyer quickly prepared a small sample of pure benzene by decarboxylating benzoic acid, and it failed to produce the expected color to the amazement of the professor and the amusement of the students. Meyer soon discovered that the sulfur-containing impurity had almost the same boiling point and chemical reactivity with benzene, but reacted slightly faster in sulfonation, so that sulfuric acid could eliminate it from benzene. He introduced the name "thiophene", which means "sulfur-benzene".

Although 2-furoic acid (pyromucic acid) was known to Scheele in 1780, *furan* was obtained only in 1870 by Limpricht. Furfural began to be produced commercially in the 1930s by the Quaker Oats Company and its subsidiary, the Miner Laboratory. It had been observed that oat husks (waste from breakfast cereals) afforded furfural on treatment with acids in about 10% yield, along with non-volatile cattle food. Among the many uses of furfural, one should mention (i) the manufacture of plastics based on the phenol–furfural–formaldehyde reaction, (ii) its use as selective solvent for aromatics in the petrochemical industry and oil refinement, and (iii) the separation of saturated from unsaturated fats (triglycerides) in the refinement of vegetable oils. Furfural can be recovered by steam distillation and recycled.

Runge discovered *pyrrole* in coal tar in 1834, but pure pyrrole was obtained in pure form by Anderson in 1857/8 in the condensate from the destructive distillation of bones. Like the two preceding congeners, thiophene and furan, the regioselective reactivity in electrophilic substitutions favors α-positions due to three possible resonance structures of the quasi-Wheland intermediate, whereas a β-attack would yield an intermediate with only two resonance structures. The aromaticity increases in the order furan < pyrrole < thiophene, that is in the order of decreasing heteroatom electronegativity reaching practically the same electronegativity for carbon and sulfur. Thus, pyrrole reacts in electrophilic substitutions similarly to phenol. The much lower basicity of pyrrole in comparison with secondary amines, and the tendency of furan and pyrrole to polymerize in the presence of acids, are due to the involvement of the lone electron pair in the aromatic sextet. The reduced aromaticity of furan is also manifest in its reactivity toward dienophiles such as acetylenedicarboxylic esters, when 7-oxa-bicyclo [2.2.1]heptadiene compounds are formed, which yield benzene derivatives with triarylphosphines.

A remarkable feature of the dipole moment of five-membered heteroaromatics is that its direction changes on going from furan or thiophene (whose dipole moments are oriented toward the heteroatom), to pyrrole, whose dipole moment is oriented away from the heteroatom.

4.1 Azoles

Progressive replacement of [Y4a] carbon atoms of azoles $(CR)_4(NR')$ by [Y5b] nitrogen atoms affords diazoles, triazoles, tetrazoles and pentazole. The pK_a values from Table 3 show that imidazole is the strongest base among the five-membered aromatic heterocycles with π-electron sextet discussed in the present article, and that tetrazole is the strongest stable acid, comparable in strength with acetic acid. The preparation of $N_5^+ AsCl_6^-$ has stimulated the search for the pentazolate anion, derived from the unsubstituted pentazole. Theoretically, the NH-unsubstituted pentazole should be a strong acid, comparable with nitric acid. Its formation was published by Butler and coworkers (08JOC1354). They showed that ceric ammonium nitrate dearylates *N*-*p*-anisylazoles ranging from pyrazole, triazoles, tetrazole and pentazole. In the latter case, the unsubstituted unstable HN_5 or its anion is generated at −40 °C (08JOC1354, 08CHEC3-739).

Considerable effort has been invested in attempts to explore the total replacement of CH groups by nitrogen in cyclopentadienide anions or benzene. The ability of aryl groups to stabilize free radicals, cations or anions is due to extension (conjugation) of π-orbitals. More than a century ago, it was observed that alkylbenzenes afford benzoic acid on oxidation and that the stability of arylazoles toward oxidants and acids increased with the number of N atoms, so that the oxidants attack the benzene ring in phenylpyrazole, and that benzotriazole survives refluxing with aqua regia.

Phenylpentazole was proved to be an intermediate in the reaction between benzenediazonium cations and azide anions yielding phenylazide and dinitrogen independently by Clusius (Zurich) (54HCA798) and by Huisgen and Ugi (Munich) using isotopic labeling and kinetic methods, as seen in Figure 7 (94MI2). They published together a consolidated report (56AGE466). In cleverly conceived experiments they

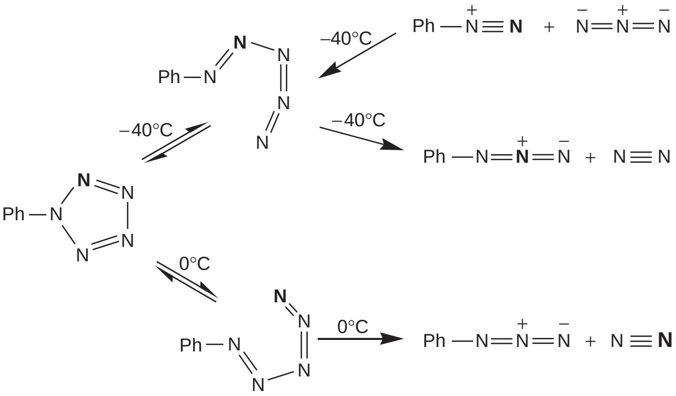


Figure 7 Formation and decomposition of ^{15}N-labeled phenylpentazole.

made use of ^{15}N isotopic labeling and followed the release of dinitrogen by kinetic measurements at low-to-medium temperatures. When aryldiazonium cations combine rapidly with azide anions, the primary product appears to be a *syn*-pentazene which reacts further by two pathways: (i) release of nitrogen at $-40\,^{\circ}C$ accompanied by azide formation, and (ii) conversion into a more stable *anti*-pentazene that cyclizes to afford a pentazole, which is aromatic and decomposes more slowly into the same two products, needing more elevated temperatures. The symmetry of the pentazole ring leads to a different labeling pattern for the ^{15}N isotopic composition of the products of these two pathways.

Then Ugi and coworkers, reasoning that the π-electron deficit of pentazole could be compensated by electron-donating substituents, were able to obtain crystalline 4-alkoxyphenyl- and 4-dialkylaminophenylpentazoles that did not decompose at room temperature. They showed also that the decomposition rate of phenylpentazole at $0\,^{\circ}C$ slows down according to the increasing solvent polarity (57CB2914, 58CB531, 58CB2324).

With electron-donor substituents on the aryl group, the stability of *N*-arylpentazoles increases (except for *ortho*-substituents). With increasing Hammett σ values for the *para*-substituent in the *N*-aryl group, crystalline *N*-arylpentazoles decompose at increasing temperatures between $-10\,^{\circ}C$ for phenyl and $+55\,^{\circ}C$ for dimethylamino (64AHC373, 85AGE513). The latter pentazole could even be studied by X-ray diffraction (83CC910).

The molecular structure of 4-dimethylaminopentazole was determined by X-ray diffraction and proved to display practically coplanar rings with bond lengths agreeing with the aromatic character of the pentazole ring with a π-electron sextet (83CC910).

The mechanism of degradation of the arylpentazoles was investigated kinetically by means of NMR spectroscopy in CD_3OD–CD_2Cl_2 at $-5\,^{\circ}C$ and proved to be analogous to that of 1,5-disubstituted tetrazoles by the fact that the rate-determining steps involve ring opening to azido-azoderivatives and azido-azomethines, respectively (96JP2-801).

On examining the NMR data from Table 2, a strong deshielding is expected and observed for protons and ^{13}C-atoms situated between two heteroatoms (oxazole, thiazole, 1,2,4-triazole and tetrazole). Not indicated in Table 2 is the fact that on cooling to $-34\,^{\circ}C$, the CH signal of 1,2,4-tetrazole is split into two peaks, namely at $\delta = 7.92$ for 3H and 8.85 for 5H. The rapid tautomerization is responsible for averaging at room temperature the NMR signals for non-equivalent CH groups of azaheterocycles such as 1,2- and 1,3-azoles and their congeners.

Various quantitative experimental data (partially presented in Table 3) as well as theoretical measures of aromaticity have been published for five-membered aromatic heterocycles (02JOC1333, 79TL437, 81CS230).

Table 2 NMR data for five-membered aromatic heterocycles with π-electron sextet

Five-membered heterocycle	Proton NMR chemical shift						Carbon-13 NMR chemical shift				
	1	2	3	4	5	Solvent	2	3	4	5	Solvent
Furan	–	7.46	6.36	6.36	7.46	dmso	143.6	110.4	110.4	143.6	dmso
Thiophene	–	7.18	6.99	6.99	7.18	CS_2	125.6	127.3	127.2	125.6	MeOH
Pyrrole	–	6.68	6.22	6.22	6.68	$CDCl_3$	118.2	109.2	109.2	118.2	CD_2Cl_2
Oxazole	–	7.95	–	7.09	7.69	CCl_4	150.6	–	125.4	138.1	$CDCl_3$
Isoxazole	–	–	8.19	6.32	8.44	CCl_4	–	149.1	103.7	157.9	$CDCl_3$
Thiazole	–	8.77	–	7.86	7.27	CCl_4	153.6	–	143.4	119.6	CCl_4
Isothiazole	–	–	8.54	7.26	8.72	CCl_4	–	157	123.4	147.8	$CDCl_3$
Imidazole	–	7.73	–	7.14	7.14	$CDCl_3$	135.4	–	121.9	121.9	$CDCl_3$
Pyrazole	12.64	–	7.61	6.31	7.61	CCl_4	–	134.6	105.8	134.6	CD_2Cl_2
1,2,5-Oxadiazole	–	–	8.19	8.19	–	$CDCl_3$	–	139.4	139.4	–	$CDCl_3$
1,2,3-Triazole	13.5	–	–	7.91	7.91	dmso	–	–	130.3	130.3	dmso
1,2,4-Triazole	15.1	–	8.17	–	8.17	hmpt	–	147.4	–	147.4	MeOH
Tetrazole	–	–	–	–	9.50	D_2O	–	–	–	143.9	dmf

Table 3 Numerical data for five-membered aromatic heterocycles with π-electron sextet[a]

Five-membered heterocycle	I.P. (eV)	Dipole (D)	Electron density					Base pK_a	Acid in H_2O	pK_a in DMSO
			1	2	3	4	5			
Furan	8.89	0.71	1.710	1.078	1.067	1.067	1.078	–	–	–
Thiophene	8.87	0.52	–	–	–	–	–	–	–	–
Pyrrole	8.23	1.58	1.647	1.087	1.090	1.090	1.087	–3.8	–	23.0
Oxazole	9.83	1.50	1.730	1.021	1.115	1.058	1.076	0.80	–	–
Isoxazole	10.17	2.75	1.753	1.166	0.998	1.079	1.003	–2.97	–	–
Thiazole	9.50	1.61	1.970	0.870	1.190	0.960	1.010	2.52	–	–
Isothiazole	9.42	2.40	–	–	–	–	–	–0.51	–	–
Imidazole	8.78	*3.70*	1.502	0.884	1.502	1.056	1056	7.00	14.52	18.6
Pyrazole	9.15	1.92	1.649	1.278	0.972	1.105	0.957	2.52	14.21	19.8
1,2,5-Oxadiazole	11.79	3.39	–	–	–	–	–	–5.00	–	–
1,2,3-Thiadizole	–	–	1.917	1.126	1.070	0.965	0.921	–	–	–
1,2,4-Thiadiazole	–	–	–	–	–	–	0.780	–	–	–
1,2,3-Triazole	10.06	1.82	–	–	–	–	–	1.17	9.3	13.9
1,2,4-Triazole	10.00	*2.72*	–	–	0.744	–	0.744	2.19	10.26	14.8
		3.27	–							
Tetrazole	11.3	*2.19*	–	–	–	–	–	–3.00	4.76	8.2
		5.15								

[a] I.P. stands for ionization potential; italic characters denote dipole moments measured in gas phase (imidazole, 1,2,4-triazole and tetrazole) and for the two last compounds (value below the first one) also in 1,4-dioxane solution; electron densities are from (03MI)

Using thermochemical data (enthalpies of formation) based on fragment analysis, Liebman and coworkers were able to compare aromaticities of various heterocycles and cyclopolyenones (91TL3949, 92TL2303, 98ACS967).

In 2001, Sharpless and coworkers (01AGE2004) introduced the "click chemistry" philosophy: terminal alkynes react with organic azides in a high-yield copper(I)-catalyzed reaction forming 1,4-disubstituted 1,2,3-triazoles. Such reactions can be traced back to Huisgen's 1,3-dipolar cycloadditions (63AGE633, 84MI1, 94MI2), and can be made regiospecific and stereospecific under proper conditions. A parallel can be established between nature's ubiquitous amidic linking and the triazole linking. Numerous applications of the click chemistry were described, especially as a ligation method for glycoconjugates (07CAJ700), polymers, macrocycles, etc. resulting in an avalanche of recent reviews (Figure 8) (03DDT1128, 05AGE5188, 06EJO51, 07AM2197, 07CSR1249, 07CSR1369, 08PR2216, 09OL1587).

An interesting and somewhat paradoxical ring closure – ring-opening reaction occurs on oxidizing a deeply colored formazan, when a colorless or yellow aromatic tetrazolium salt is formed reversibly. The paradox is that with so many nitrogen atoms one would expect such cations to be destabilized, yet the reaction proceeds cleanly. The vivid color of formazans allows varied applications for detecting the presence of reducing enzymes in live cells, such as the ability of seeds to germinate (due to the presence of dehydrogenases in live seeds). Other applications are for distinguishing reducing sugars from non-reducing ones, and for detecting tumor cells (Figure 9) (96CHEC2(4)897). By analogy, it would be interesting to find which arylazides may react with aryldiazonium cations yielding diarylpentazolium salts.

Nitrogen-rich hetarenes have been evaluated favorably as energy-rich materials useful as explosives, rocket propellants and in pyrotechnics (08CHEC3-739). Most nitro derivatives or perchlorates have drawbacks for such uses, except perhaps for octanitrocubane. However, the aromatic

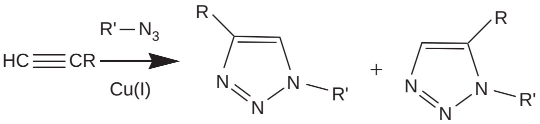


Figure 8 Click chemistry for the formation of 1,2,3-triazoles.

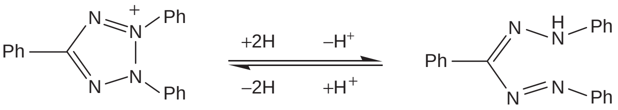


Figure 9 Redox reactions between tetrazolium salts and deeply colored formazans.

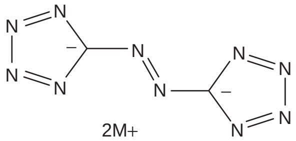


Figure 10 Azo-tetrazolates.

stabilization for tetrazoles and tetrazines allows a high nitrogen content in such molecules, especially when they are substituted with amino, hydrazino or azido groups as in bis-tetrazole, bis-tetrazoleamine, 3,6-dihydrazino-1,2,4,5-tetrazine or 3,6-bis(tetrazolyl)-1,2,4,5-tetrazine (08AGE3330).

An extremely high amount of energy is released when dinitrogen molecules are formed by fragmentation, in the absence of other fragments that absorb energy (such as water or carbon dioxide molecules that dissociate endothermally at temperatures higher than about 1500 K). Other examples are salts of azotetrazolates with M = ammonium, guanidinium or triaminoguanidinium cations. Alkali metal salts of tetrazolates have been known for more than a century to result from 5-aminotetrazole by oxidation with permanganate (98LA(303)57, 98JEM119) (Figure 10).

4.2 Mesoionic and pnictogen-containing π-electron sextet aromatic compounds with five-membered rings

The best known mesoionic compounds have five-membered rings, and initially it was advocated by Baker, Ollis, Ramsden and other authors that only five-membered heterocycles which cannot be satisfactorily represented by any one covalent or ionic structure possessing a sextet of π-electrons in association with the five atoms comprising the ring may be called “mesoionic”. Here, following Katritzky, mesoionic means a mesomeric betaine. The first such compounds to be discovered were sydnones, followed by münchnones and then by diazolones. In all these compounds the Z-type atom is part of a carbonyl group, and two Y-type atom chains separate two odd-numbered chains of X- and Z-atom chains. Only the main resonance structures are displayed in formulas (Figure 11).

Phospholes are less stable than azoles because phosphorus prefers a pyramidal geometry rather than a planar one. However, *P*-mesityl derivatives are forced into planarity. 1,3-Di- and 1,2,4-triphospholes with a *P*-mesityl group are nearly or fully planar, and so are also 1,2,4-azadiphospholes, 1,2,4-thiadiphospholes and 1,2,4-diazaphospholes. Most interestingly, unlike the explosive pentazoles, pentaphospholes are thermally stable but dimerize by a [4+2]-cycloaddition. Pentaphosphole P_5H is planar, in contrast to phospholes (96JPC13447).

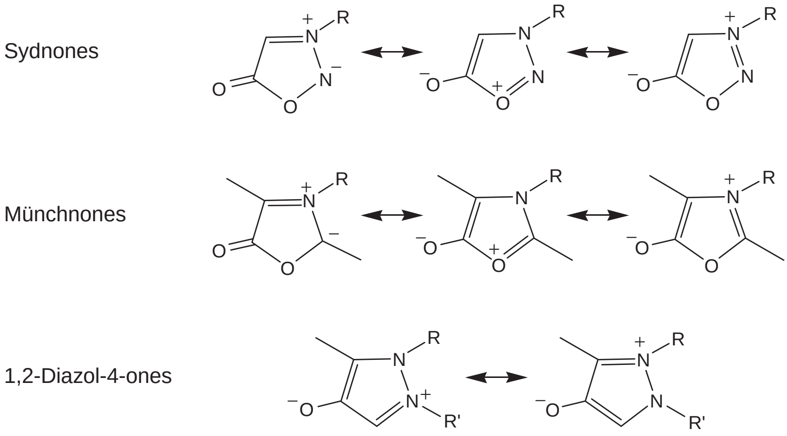


Figure 11 Mesoionic systems.

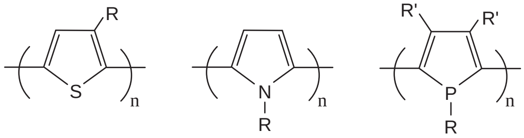


Figure 12 Poly(thiophenes), poly(pyrroles) and poly(phospholes).

Comprehensive reviews of aromatic phosphorus heterocycles including heterophospholes were recently published (01CRV1229, 09MI1).

In the field of organic electrical conductors ("organic metals"), a spectacular success was the introduction of doped polyaromatics such as poly(thiophene) for applications in electronic devices which are changing the way people communicate with each other even at present. This is due in part to chemistry *via* organic (or polymer-based) light-emitting diodes (OLEDs/PLEDs), photovoltaic cells, field-effect transistors, photoresists, non-linear optical (NLO) devices, etc. However, even with thiophene rings having various substitutents R, there is only a limited range of variation for the electronic properties (HOMO–LUMO gap) of the OLED. However, poly(pyrroles) with an N-substituent R offer a larger range of properties because the availability of the unshared nitrogen's electron pair is directly and strongly influenced by the N-attached group R (Figure 12).

Recently, it was found that poly(phospholes) provide an even better perspective for such devices (06CRV4681). Indeed, the calculated aromaticity of the unsubstituted phosphole is quite low in comparison with that of pyrrole in terms of aromatic stabilization energy (ASE) and nucleus-independent chemical shift (NICS): pyrrole, ASE = 25.5 (kcal/mol), NICS = −15.1 (ppm); phosphole, ASE 7.0 (kcal/mol), NICS = −5.3 (ppm) (06CRV4681).

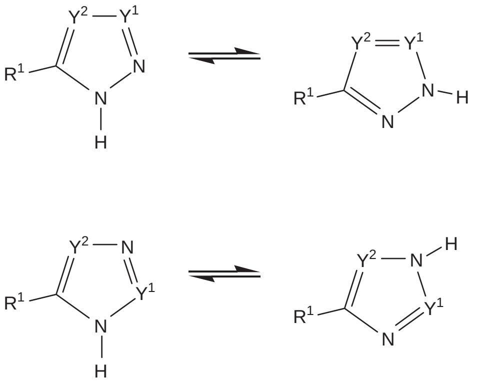


Figure 13 The tautomerism of azoles.

The chemical behavior of phosphole confirms this conclusion: at −100 °C it was characterized by NMR spectra, but at room temperature it isomerizes rapidly to 2*H*-phosphole which dimerizes to a tricyclic compound *via* a 1,5-sigmatropic H-shift and a [4+2]-cycloaddition (04ACR9549). Synthetic efforts of Mathey resulted in a lithium-based pathway for obtaining oligophospholes, allowing the investigation of electronic properties of such promising compounds.

Early observations on the tautomerism of substituted imidazole and pyrazole derivatives were proved to be general, and to apply also to triazoles, tetrazoles and to related heterocyclic systems such as benzo derivatives. In the formulas of Figure 13 the Y^1 and Y^2 atoms may be replaced by other heteroatoms (e.g., N, P) or by CR^2/CR^3 groups.

5. SEXTET π-ELECTRON HETEROAROMATICS WITH SIX-MEMBERED RINGS

Starting again with inorganic rings with π-electron sextet, the well-known “inorganic benzene” (borazine, $B_3H_6N_3$) has to be mentioned. Although it is formed by a variety of reactions [such as (i) treatment of BCl_3 with NH_3 followed by reduction of the resulting trichloroborazine by $NaBH_4$, (ii) heating ammonia-borane at around 150 °C, (iii) heating sodium borohydride with ammonium sulfate at around 130 °C, and (iv) heating $LiAlH_4$ with ammonium chloride at 400 °C], this liquid that has NBP 53 °C and is thermally stable until 400 °C, behaves chemically quite differently from benzene, reacting *via* addition: it adds readily HQ (Q = OH, OAlk, Hal), forming cyclic non-aromatic systems $(H_2N–BHQ)_3$, and having quite low aromaticity. The related $B_3P_3H_6$ has a higher, but still modest, aromaticity (98IC2110). A third $[X_3Z_3]$-type system is cyclotriphosphazene $N_3P_3R_6$, with $R = H, F, Cl, Br, CH_3, CF_3, NEt_2$ (94CCR137). Only the electron-withdrawing substituents give rise to NICS values showing modest aromaticity (05IC8407). The aromaticity of cyclophosphabenzenes has often been discussed (87MI2, 05IC8407).

5.1 Hexazine and hexaphosphine

Hexazine has constituted an intriguing fictitious molecule. It was studied theoretically in order to understand why it cannot be observed experimentally. Glukhovtsev and Schleyer concluded that among N_6 possible isomers, hexazine is less stable than a twist open-chain dimer of two azide radicals with C_2 symmetry (which, however, is thermodynamically unstable relative to the exothermal decomposition into $3N_2$ releasing 188.3 kcal/mol). In marked contrast to benzene, hexazine is calculated to be non-planar due to lone-pair repulsion into the σ system. Homodesmotic reactions:

$$Y_6 + 3H{-}Y{=}Y{-}H \rightarrow 3H{-}Y{=}Y{-}Y{=}Y{-}H$$

are calculated to result in positive energy for benzene ($Y = CH$), $\Delta E = 23.9$ kcal/mol, in good agreement with experiment, but in negative energy for hexazine ($Y = N$), namely $\Delta E = -17.6$ kcal/mol. Interestingly, two research groups claim to have observed a dimer of the azide radical in solid ethanol matrix at 77 K, but their reports on the UV maxima are conflicting (80AGE717). Several authors have reported ideas about N_6 in the 1970s and 1980s (70JA7486, 81CPL317, 82AGE64, 83JA1760, 84JMT(109)391).

Then in 1992, Glukhovtsev and Schleyer reported that the acyclic dimer of the azide radical was calculated to be 188 kcal/mol, and hexaazabenzene (hexazine) 211 kcal/mol higher in energy than three dinitrogen molecules, making it very unlikely to isolate valence isomers of hexazine (92CPL(198)547). The discussion is continuing (92JPC10879, 04CJC50).

If there is little chance for N_6 to be detected, still unknown pentazine derivatives may, however, be accessible by the same technique used earlier for pentazole, for example by trying to prepare 5-(4-aminophenylene)-pentazine. So far, only a few data for computed aromaticity indices (magnetic indices) of pentazine have been published (04JPO303).

An intriguing possibility is for trying to synthesize a pentazinium cation by a ring closure reminiscent of the formazan oxidation, starting from an arylhydrazone of aroylazide, with both aryl groups having donor substituents. One brief Japanese article reported the base-induced decomposition of *N*-(phenylsulfonyl)benzohydrazonoyl azide accompanied either by the formation of benzonitrile or by the cyclization to

1-benzenesulfonamido-2-phenyltetrazole (82CL59); it is not apparent, however, whether any oxidation was attempted.

An interesting discovery was made when Scherer and coworkers stabilized hexaphosphabenzene in the center of a triple-decker sandwich between two molybdenum atoms coordinated with two outer pentamethylcyclopentadienyl ligands (85AGE351). The P_6 hexagon is planar, aromatic and stable in this compound, and theoretical methods indicate that P_6 may be detected free in an inert matrix at low temperatures (unlike N_6) (86CC383, 86CPL(126)43, 88IC2219, 89CB2121, 92CB2687, 97PCA1409, 97JA12669, 02PCA10370, 05IC5266). It was calculated, however, that the order of energies for the five valence isomers of $(CH)_6$ and P_6 is different, with the planar hexagon having the lowest energy for $(CH)_6$ and the highest energy for P_6 (92JA5378, 99ACR751).

5.2 Pyrylium cations

Pyrylium cations occupy a privileged position among six-membered heteroaromatics with a single heteroatom because oxygen is the most electronegative among all Y-type atoms. Such a benzene ring with this strongest single perturbation reacts preferentially by adding a nucleophile in α (2- or 6-positions) followed by a thermally allowed electrocyclic ring opening, and finally by reclosure accompanied by water elimination forming a less perturbed six-membered aromatic ring. Such a series of reactions is known as Attention Nucleophilic–Ring Opening–Ring Closure (ANRORC). Thus, pyrylium salts can be converted into other aromatics (pyridinium or thiopyrylium salts, pyridines, pyridine-*N*-oxides, phosphabenzenes, etc.).

Several reviews exist on pyrylium salts (82MI1, 03MI6), which can easily be obtained by a variety of syntheses. Since the aromaticity is reduced by the oxygen's tendency to reduce delocalization, pyrylium salts are readily formed from acyclic starting materials involving two or three synthons, and are readily ring opened. Among the latter type of syntheses for pyrylium salts with aromatic substituents, Dilthey's reactions involve (i) two moles of aryl methyl ketone ($ArCOCH_3$) and one mole of acylating agent RCO^+ to afford 2,4-Ar_2-6-R-pyrylium, or (ii) two moles aryl methyl ketone ($ArCOCH_3$) and one mole of Ar′CHO yielding in the presence of dehydrogenating agents 2,6-Ar_2-4-Ar′-pyrylium. For alkyl-susbtituted pyrylium salts, the simplest three-synthon method is the diacylation of alkenes (Balaban–Nenitzescu–Praill synthesis).

With cold aqueous alkaline hydroxides, 2,6-diarylpyrylium salts form reversibly 1,5-enediones (pseudobases), but pseudobases of 2-methyl(ene) pyrylium salts react intramolecularly with hot alkali hydroxides affording phenolates. Another reversible reaction of methyl/methylene/methine groups in neutral or slightly acidic media is deprotonation to

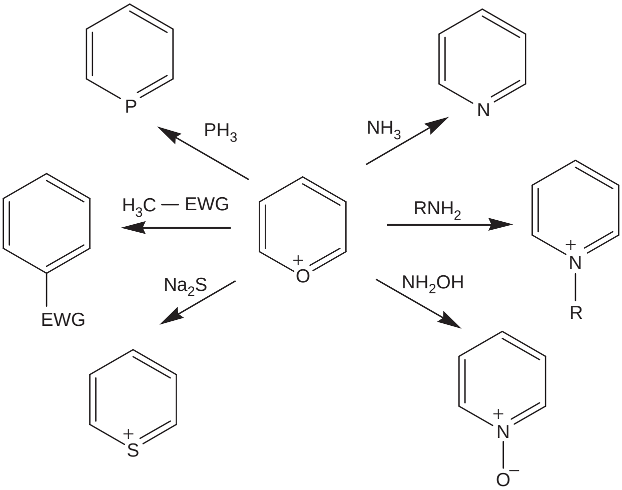


Figure 14 Reactions of pyrylium salts (usually 2,4,6-trisubstituted).

anhydrobases, as proved by deuterium exchange (in deuterium oxide or RCOOD solutions) in α (2- or 6-) or γ (4-position).

In the chart of converting pyrylium salts (usually with substituted α-positions) into other six-membered ring systems (Figure 14), there is an *increase in aromaticity.* For any conversion associated with *decreasing aromaticity* one must employ "energy-rich reagents". Thus, in the conversion of pyridine into pyrylium, which requires treatment of pyridine with sulfur trioxide or chlorosulfonic acid to afford a zwitterionic compound with EWG = SO_3^- followed by treatment with sodium methoxide affording the sodium salt of glutacondialdehyde, the final product is obtained by treatment with anhydrous strong acids such as a solution of perchloric acid in dichloromethane – caution is necessary because of the explosion danger associated with such solutions and with the unsubstituted pyrylium perchlorate.

N-Alkylpyridinium salts with linear alkyl chains have recently found interesting applications as ionic liquids, along with imidazolium cations. Another application of pyridinium salts with two hydrophobic tails is as non-viral gene transfer agents (cationic lipids) (06JMC3872).

5.3 Comparison between six-membered hetarenes with one heteroatom

It may be observed from Table 4 that there is a close parallelism between the proton NMR data of aromatic cations pyrylium and pyridinium;

Table 4 NMR chemical shifts (δ, ppm) of six-membered aromatic heterocycles with π-electron sextet (76JA5451)

Six-membered heterocycle	Proton NMR chemical shift						Carbon-13 NMR chemical shift					
	2	3	4	5	6	Solvent	2	3	4	5	6	Solvent
Pyrylium	9.22	8.08	8.91	8.08	9.22	tfa-D	169.2	127.7	161.2	127.7	169.2	D_3CCN
N-H-Pyridinium	9.23	8.50	9.04	8.50	9.23	tfa-D	142.5	129.0	148.4	129.0	142.5	D_3CCN
2*H*-Pyran-2-one	–	6.43	7.58	6.43	7.77	$CDCl_3$	162.0	116.7	144.3	106.8	153.3	Me_2CO
2-Pyridone	–	6.60	7.30	6.60	7.23	$CDCl_3$	162.3	119.8	140.8	104.8	135.2	dmso
4*H*-Pyran-4-one	7.88	6.38	–	6.38	7.77	$CDCl_3$	155.6	118.3	179.0	118.3	155.6	$CDCl_3$
4-Pyridone	7.98	6.63	–	6.63	7.98	$CDCl_3$	139.8	115.9	175.7	11.9	139.8	$CDCl_3$
Pyridine	8.59	7.38	7.75	7.38	8.59	$CDCl_3$	149.8	123.6	135.7	123.6	149.8	$CDCl_3$
Phosphabenzene	8.61	7.72	7.38	7.72	8.61	$CDCl_3$	154.1	133.6	128.8	133.6	154.1	$CDCl_3$
Arsabenzene	9.68	7.83	7.52	7.83	9.68	$CDCl_3$	167.7	133.2	128.2	133.2	167.7	$CDCl_3$
Stibabenzene	10.94	8.24	7.78	8.24	10.94	$CDCl_3$	178.3	134.4	127.4	134.4	178.3	$CDCl_3$
Bismabenzene	13.25	9.8	7.8	9.8	13.25	$CDCl_3$	–	–	–	–	–	–
Pyridazine	–	9.17	7.52	7.52	9.17	$CDCl_3$	–	153.0	130.3	130.3	153.0	$CDCl_3$
Pyrimidine	9.26	–	8.78	7.36	8.78	$CDCl_3$	158.4	–	156.9	121.9	156.9	$CDCl_3$
Pyrazine	8.60	8.60	–	8.60	8.60	$CDCl_3$	145.9	145.9	–	145.9	145.9	$CDCl_3$
1,2,3-Triazine	–	–	9.06	7.45	9.06	$CDCl_3$	–	–	149.7	117.9	149.7	$CDCl_3$
1,2,4-Triazine	–	9.73	–	8.70	9.34	$CDCl_3$	–	158.1	–	149.6	150.8	$CDCl_3$
1,3,5-Triazine	9.25	–	9.25	–	9.25	$CDCl_3$	166.1	–	166.1	–	166.1	$CDCl_3$
1,2,4,5-Tetrazine	–	11.05	–	–	11.05	Me_2CO	–	161.2	–	–	161.2	Me_2CO

however, the ^{13}C-NMR data show the appreciably higher deshielding of α- and γ-positions in the former cation, due to the higher electronegativity of oxygen as compared to nitrogen. If one compares the NMR data of benzene (^{1}H-NMR $\delta = 7.26$ ppm and ^{13}C-NMR $\delta = 128.5$ ppm) with those of pyridine and other pnictogena-hetarenes with Y = P, As, Sb, Bi), one can see the gradual sharp increase of chemical shifts for the α-proton and α-carbon atoms with increasing atomic number, due both to the higher nuclear charge and to the magnetic anisotropy of the heteroatom. A more detailed discussion will be found on page 89 and Table 6.

A strong deshielding observed for protons and ^{13}C-atoms situated between two heteroatoms is expected and observed for pyrimidine, 1,2,4-triazine, 1,3,5-triazine and 1,2,4,5-tetrazine, culminating for the ^{1}H-NMR chemical shift of the latter compound.

The only unsubstituted monocyclic heterocycles with aromatic π-electron sextet that absorb in the visible region of the electromagnetic field are the yellow 1,2,4-triazine and the crimson 1,2,4,5-tetrazine.

In Table 5 one may see experimental and calculated dipole moments for aromatic six-membered rings with one heteroatom [45]. Bond lengths increase and electronegativities decrease with increasing Period numbers, explaining the trends observed in this table. With Group-14 heteroatoms, the maximum dipole moment is attained for stannabenzene for the product of charges with distances. With Group-15 heteroatoms, pyridine has the highest dipole moment as a result of the high electronegativity of nitrogen.

Table 5 Dipole moments of six-membered π-electron sextet compounds that are isoelectronic with benzene [45]

Molecule	Formula	Dipole moment (D)	Method for obtaining the data
Benzene	C_6H_6	0.000	
Pyridine	C_5H_5N	2.150	Experimental
Phosphabenzene	C_5H_5P	1.844	AM1
Arsabenzene	C_5H_5As	1.575	AM1
Stibabenzene	C_5H_5Sb	1.534	AM1
Bismabenzene	C_5H_5Bi	1.306	PM3
Silabenzene	C_5H_6Si	0.139	AM1
Germabenzene	C_5H_6Ge	0.916	AM1
Stannabenzene	C_5H_6Sn	1.505	PM3
Plumbabenzene	C_5H_6Pb	1.097	PM3

6. OTHER 6-MEMBERED HETARENES. PNICTOGENABENZENES: PHOSPHABENZENE (λ^3-PHOSPHININE), ARSA-, STIBA-, BISMABENZENES

The first breakthrough for heterocycles related to pyridine but with other pnictogen heteroatoms instead of nitrogen occurred only in 1966 when Märkl prepared 2,4,6-triphenyl-phosphabenzene from 2,4,6-triphenylpyrylium salts and phosphine (PH_3) (66AGE846, 70TL4925). Higher yields were obtained on replacing PH_3 by $P(CH_2OH)_3$ or $P(SiMe_3)_3$. The common name phosphabenzene corresponds to the IUPAC name λ^3-phosphinine. The X-ray diffraction spectra of 2,4,6-triphenyl-phosphabenzene (yellow crystals that are relatively stable to air) show unambiguously the aromaticity of this heterocycle. It was therefore evident that ($3p$–$2p$) π-bonds can give rise to aromatic systems. Subsequently, K. Dimroth (73FCF1), Bickelhaupt (67AGE567) and Jutzi with their coworkers (69AGE991) provided additional evidence for substituted congeneric systems.

Then Ashe using a method based on tin derivatives (Figure 15) succeeded in synthesizing unsubstituted pnictogenabenzenes with Y = P and As (which proved to be distillable liquids, air sensitive, but stable to hydrolysis and to mild acids and bases). Stibabenzene with Y = Sb is stable below −70 °C, and bismabenzene with Y = Bi has a fleeting existence (proved spectroscopically and *via* chemical trapping) before it dimerizes (71JA3923, 71JA6691, 78ACR153, 82TCC125).

An interesting aspect of these heterobenzenes is the closer similarity between benzene and arsabenzene than between benzene and pyridine or phosphabenzene, possibly due to the combined effects of electronegativity, covalent radius and bond energy (nitrogen has a higher electronegativity than carbon, and phosphorus has a very high P–O bond energy). Thus, arsaphenol has $pK_a = 8.8$, close to the pK_a of phenol (9.9), smells like phenol, and does not tautomerize to a carbonyl derivative (as does the pyridine congener by contrast) (75AGE710). The colorless crystalline 4-arsabenzoic acid has $pK_a = 4.1$ similarly to benzoic acid ($pK_a = 4.2$), its ethyl ester has the same fruity aroma as ethyl benzoate, and 4-arsabenzaldehyde smells like almonds.

2,6-Dimethyl-4-phenyl- λ^3-phosphinine has a planar heterocyclic ring. Whereas pyridine has an almost regular hexagon, all the other

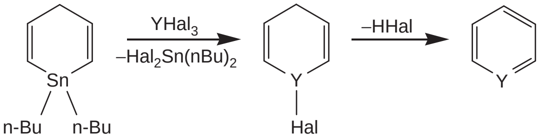


Figure 15 Formation of heterobenzenes (Y = P, As, Sb, Bi).

pnictogena-heteroaromatics have longer C–Y bond lengths and more acute C–P–C bond angles, but the planarity of the ring is conserved (78ACR153). According to spectral, structural, theoretical and energetic criteria, aromaticity indices for λ^3-phosphinine, pyridine and benzene have close values, as shown in a review by Nyulászi (01CRV1229).

The NMR spectra provide, like the X-ray data, strong evidence for the aromaticity of pnictogena-hetarenes. Table 6 presents chemical shifts for ^{1}H-NMR of six-membered ring systems with one or no heteroatom. The spectacular gradual increase of chemical shifts for the 2- and 6-hydrogen atoms for heavier heteroatoms is due not only to the diatropic ring current, but also to the magnetic anisotropy of the heteroatom. After correction for this effect, residual downfield shifts for α-H atoms (δ_0 relatively to benzene which has $\delta_0 = 7.37$ ppm) are $\delta_0 = 7.0$ ppm for phosphabenzene, 6.8 ppm for arsabenzene and 6.6 ppm for stibabenzene, indicating decreasing aromaticity in this order.

After having measured gas-phase dipole moments of pyridine, phosphabenzene and arsabenzene, (72JSP457), Ashe and coworkers checked the magnitude and direction of solution dipole moments by measuring them also for the 4-methyl-derivatives. It was found (75TL2749) that all these three heterobenzenes have the same direction of dipole moments, although nitrogen has a higher electronegativity than carbon, but phosphorus and arsenic have lower electronegativities. In solution, the dipole moments for C_5H_5N, C_5H_5P and C_5H_5As are 2.02, 1.46 and 1.02 D, respectively, whereas for the 4-methyl-derivatives the values are 2.57, 1.77 and 1.50 D, respectively.

The chemical behavior of this interesting family of heterobenzenes has both similarities and differences from pyridine. Interestingly, owing to the reduced electronegativity, electrophilic substitutions of arsabenzene (nitration with acetyl nitrate; acylation with acetyl chloride or benzoyl chloride, and deuteration with F_3C-COOD) take place with α, γ-regioselectivity instead of β-regioselectivity as in pyridine. Qualitatively, arsabenzene is even more reactive in electrophilic substitutions than benzene (82JA425). The chemistry of phosphabenzene and arsabenzene is more similar to that of benzene than to pyridine in the complexation with metal derivatives. Pyridine, which is a strong n-donor, forms σ-complexes (involving the lone pair of the heteroatom)

Table 6 Comparative ^{1}H-NMR data for benzene and pnictogena-hetarenes (δ in ppm)

Atom	C_6H_6	C_6H_5N	C_6H_5P	C_6H_5As	C_6H_5Sb	C_6H_5Bi
H-α	7.37	8.29	8.61	9.68	10.94	13.25
H-β	7.37	7.38	7.72	7.83	8.24	9.8
H-γ	7.37	7.75	7.38	7.52	7.78	7.8

with metal pentacarbonyls (M = Cr, Mo and W). Such complexes are also available from phosphabenzene and arsabenzene, but the weaker *n*-donor character of phosphabenzene and arsabenzene favors π-complexes when using $M(CO)_3(MeCN)_3$. The π-complex with stibabenzene is more stable than the original heterobenzene. A striking difference from pyridine is the lack of basicity and nucleophilicity for phosphabenzene and arsabenzene, which are protonated or deuterated at the α- and γ-carbon atoms. Neither alkyl halides nor trialkyloxonium salts can alkylate phosphabenzene, therefore there will be no discussion of quaternary salts for these pnictogena-hetarenes. Whereas pyridine can be oxidized to the zwitterionic *N*-oxide, phosphabenzene affords non-aromatic λ^5-oxidation products with tetracoordinated $P^{(V)}$ phosphorus atoms, similar to phosphin-oxides and phosphonic acids, respectively.

All pnictogena-hetarenes with Y = P, As, Sb and Bi react with dienophiles such as hexafluoro-2-butyne affording heterobarrelene derivatives (P-pnictogena-hetarenes at 100 °C, As- at 25 °C, Sb- and Bi-pnictogena-hetarenes at even lower temperatures). The low-temperature *dimerization* equilibrium of bismabenzene and stibabenzene (Y = Bi or Sb) also involve such cycloadditions (Figure 16).

Strong nucleophiles such as organolithium or organomagnesium derivatives do not react with substituted or unsubstituted phosphabenzene or arsabenzene (Y = P or As) by nucleophilic substitution as in the case of pyridines, but by addition to the heteroatom forming intermediate anions. These anions can then be converted into non-aromatic compounds by reaction with water yielding 1-alkyl-1,2-dihydro-derivatives, or they can be alkylated by an alkyl halide with the same or a different alkyl group, when two products may result: a 1,2-dialkyl-1,2-dihydro-derivative, or a λ^5-derivative (Figure 17). The former products are kinetically controlled, whereas the latter compounds are thermodynamically controlled.

Interestingly, the bond distances and angles of 1,1-dimethyl-2,4,6-triphenyl-λ^5-phosphorin determined by X-ray diffraction are similar to those of λ^3-derivatives (Figure 18), yet the physical and chemical properties show that the λ^5-phosphorins with electron-donor substituents (H, Me, SiH_3) at the P heteroatom are not aromatic, and that the tetracoordinated phosphorus atom interrupts the ring current in such compounds. However, when the P-substituents of λ^5-phosphorins have higher electronegativities (F, OH, Cl, Br) the NICS(1) values indicate aromaticity, but somewhat less than phosphabenzene (01HCA1578).

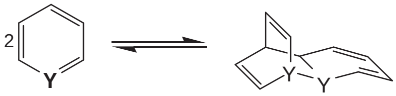


Figure 16 Dimerization equilibrium of bismabenzene and stibabenzene.

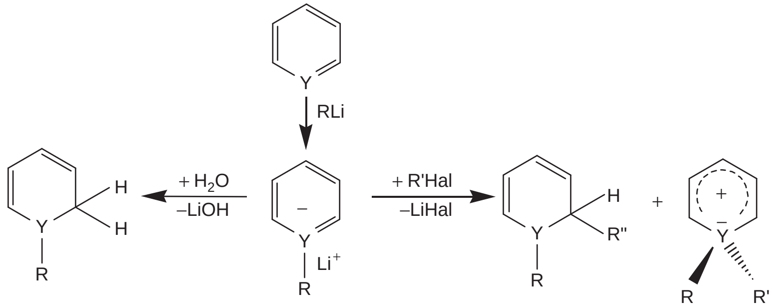


Figure 17 Reactions of phosphabenzene or arsabenzene initiated by RLi or RMgX.

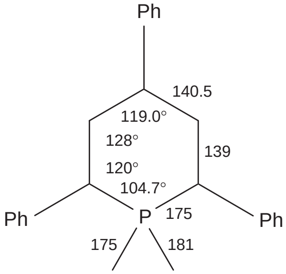


Figure 18 Geometry of 1,1-dimethyl-2,4,6-triphenyl-λ^5-phosphorin.

6.1 Silabenzene and germabenzene

Silabenzene and its congeners are unstable under normal conditions, and could be studied only at low temperatures or by trapping in solid matrices. However, after Tokitoh and coworkers introduced huge steric protecting groups (abbreviated as Tbt groups), with full name *tris*[bis (trimethylsilyl)methyl]phenyl, it was possible to stabilize six-membered aromatics (silabenzene and germabenzene) as crystalline compounds under normal conditions (04ACR86, 00AGE634). The kinetically stabilized Tbt-substituted silabenzene and germabenzene have planar rings, and bond lengths that attest their aromaticity (Figure 19). The geometry around the Si or Ge atom is completely trigonal.

T. J. Barton and coworkers had succeeded earlier to isolate in 1977 the first representative of this class, 1-methyl-silabenzene (silatoluene), and one year later the unsubstituted silabenzene (77JA5199, 78JA5246, 81JA6788). Both compounds could only be studied in solid argon matrices at 10–23 K. Maier and coworkers using a different synthetic approach also studied the very unstable unsubstituted silabenzene, which was shown to react photochemically in the argon matrix (86PAC95, 80AGE52). Previous attempts by Märkl for kinetic stabilization had led to the synthesis of (i) 1,4-di-*tert*-butyl-1-silabenzene, which

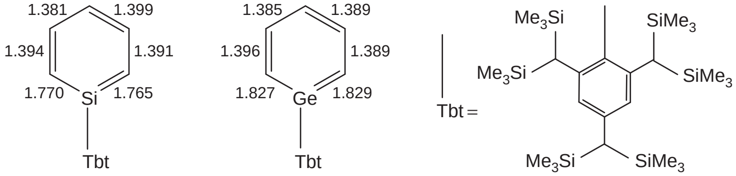


Figure 19 Bond distances in silabenzene and germabenzene with a Tbt substituent.

dimerized at 0 °C by a [2+2]-cycloaddition; (ii) 1,4-di-*tert*-butyl-2,6-bis (trimethylsilyl)-1-silabenzene, which was studied by NMR at low temperatures in special solvents; and (iii) 1 *tert*-butyl-2,6-bis(dimethylisopropylsilyl)-4-trimethylsilyl-1-silabenzene, which was stable also only at very low temperatures (79AGE789, 88AGE963). Similar germabenzene derivatives were also obtained, but they were also unstable under normal conditions. Among several theoretical calculations for such systems, one citation will be mentioned (83JOC3453). All theoretical models predict the instability of planar hexagonal hexasilabenzene $(SiH)_6$.

The aromaticity of rings containing Group-14 elements has been reviewed by Apeloig (89MI1, 98MI1). More recent reviews on this topic have been published by Sekiguchi, Lee et al., and by Tokitoh (07AGE6596, 00JOM228, 03CRV1429, 04BCJ429, 04ACR86).

6.2 Hetarenes containing Group-13 elements

Six-membered heteroaromatics with π-electron a sextet involving Z-type boron heteroatoms have been known for a long time, since borazine $B_3H_6N_3$ (“inorganic benzene”, wrongly called borazole) had been obtained by Stock in 1926; it is an X_3Z_3-type compound, with resonance formulas of type $X_2Y_2Z_2$, XY_4Z and Y_6. Its resonance energy is far lower than that of benzene, but it is planar and has equal bond lengths like benzene.

More recently, Dewar and Pettit prepared truly aromatic compounds (55CIL199, 56JCS2021, 56JCS2026) incorporating one boron atom along with one oxygen or nitrogen atom; they called such compounds borazarobenzene (derivatives of C_4H_5BN) or boroxarobenzene (derivatives of C_4H_4BO), respectively, but the IUPAC names are borazinine and boroxinine, respectively (with numbered polyhydro prefixes, which will be omitted for convenience in this review).

6.3 1,2-Azaborine

There are three possible monoaza-monoborinines, 11 diaza-diborinines, and three triaza-triborinines, with equal numbers of B and N heteroatoms, all structures of which are presented in (98PCA4679). Until recently, only borazine was known as an unsubstituted six-membered ring.

The second (simplest) such unsubstituted "borazaro-derivative", 1,2-dihydro-1,2-azaborinine C_4H_6BN (called for simplicity 1,2-azaborinine in the following) was obtained recently as a volatile liquid with a melting point (−45 °C) that is intermediate between that of benzene (+5 °C) and borazine (−58 °C). Its ^{1}H-NMR spectrum, calculated NICS and resonance stabilization energy are presented in Table 7 (09AGE973). It may be seen that on replacing sequentially a CH=CH group in benzene by a BH=NH group, the aromaticity is gradually reduced, becoming rather low in borazine. One term ($C_2H_6B_2N_2$) in the series of Table 7 is still missing.

On replacing an –RC=CR– bond in pyrylium cations by an –RB=O– bond, one should obtain boroxaropyrylium (1,3,2-dioxaborinium) cations. The crystalline perchlorates (64TL2721, 65TL3917, 65TL3925, 67SA1373, 68T2499), revealed by X-ray diffractometry, however, an unexpected feature, namely one of the perchlorate oxygens is attached covalently to the diazaborinium cation resulting in a neutral system (83ZNA1161, 06ZNA360).

6.4 Boratabenzene anions and related compounds with Group-13 elements

The first six-membered aromatic heterocycles containing one boron atom together with a second heteroatom (oxygen or nitrogen, namely boroxaro- and borazaro-derivatives, respectively) were prepared by Dewar and Pettit in 1955–1956 (55CIL199, 56JCS2021, 56JCS2026). Borabenzene C_5H_5B, *with the heteroatom having six electrons in the valence shell* is too reactive to exist in condensed phase, but if it is connected to a neutral Lewis base derived from a tertiary amine, phosphine or pyridine that becomes a positively charged group, then a stable zwitterionic (betainic) product results, where the boron has a formal negative charge (86PAC95). Thus, tradition conserves the name *borabenzene* that applies to a non-existent neutral molecule. However, *boratabenzene* C_5H_6B (or B-substituted derivatives thereof) as an independent ring is a stable aromatic anion, in agreement with Table 2.

There is a certain analogy between the aromatic anions of cyclopentadienide ($C_5H_5^-$) and boratabenzene ($C_5H_6B^-$). 1-Phenyl-1,4-dihydroborabenzene

Table 7 Comparison between benzene, azaborinine and borazine

Property	Benzene	Azaborinine	Borazine
^{1}H-NMR δ(N–H), ppm	–	8.44	5.63
^{1}H-NMR δ(B–H), ppm	–	4.9	4.4
NICS(0)	−8.76	−5.62	−2.02
NICS(1)	−10.39	−7.27	−3.01
RSE (kcal/mol)	34.1	21	10

has a more acidic proton connected to the sp^3-hybridized ring carbon atom than cyclopentadiene, due to the same tendency of aromatic anion formation (78JA3737, 71JA1804). It affords the lithium salt of 1-phenylboratabenzene on treatment with *tert*-butyllithium. Like metallic complexes such as ferrocene formed by cyclopentadiene, boratabenzene also forms such sandwich π-complexes with iron, which can be acetylated under Friedel–Crafts conditions.

The first cobalt metallic complexes of 1-phenyl- and 1-methyl-boratabenzene were prepared from $Co(C_5H_5)_2$ and R-$BHal_2$ by Herberich (70AGE805, 86AOC199, 95OM471). Then similar iron complexes were also obtained. Later, on treating such complexes with alkali cyanide, he prepared the first boratabenzene sodium and potassium salts. Complexes with Ru, Os, Rh and Pt have also been obtained. The sandwich complex can have two boratabenzene rings, or one boratabenzene ring and one cyclopentadienide ring (Figure 20).

The molecular structures obtained by X-ray crystallography for the cobalt sandwich complex with two B–Me- or B–OMe-containing rings show that both molecules have planar and parallel rings arranged centrosymmetrically (74CB3786). Similar structures were found for metallic complexes with M = Fe or Mn, and R = Me or Ph (72CB3484).

The molecular structure of the lithium 1*H*-boratabenzene obtained by treating borabenzene–PMe_3 with $LiAlH_4$ indicates that the ring is planar, with the four C–C bond distances within the range 138–141 pm, but with slightly longer B–C bond distances (141–148 pm). On treating borabenzene–PMe_3 with a variety of nucleophiles such as lithium trimethylsilylacetylide, lithium dimethylamide, sodium ethoxide and potassium diphenylphosphide, an associative mechanism *via* attack at the boron atom results in a nucleophilic substitution of the hydrogen attached to boron (96JA6329).

Starting from stannacyclohexadienes and $BHal_3$, Ashe and coworkers reported in 1971 a general synthesis of lithium boratabenzenes, which can easily be converted into other metal complexes (75PAC513). The zirconium(IV) complexes with two boratabenzene rings and two halogen

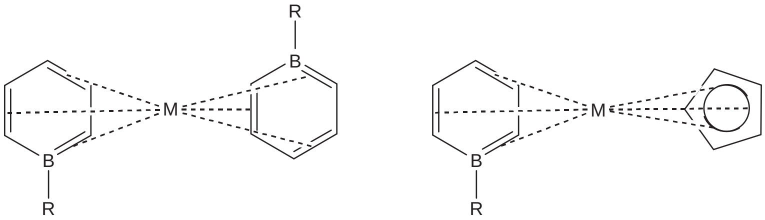


Figure 20 Sandwich complexes with one or two boratabenzene rings.

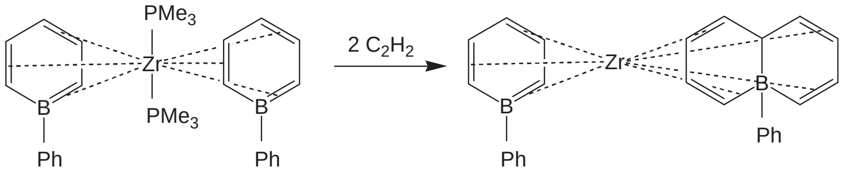


Figure 21 Complexes of boratabenzene with zirconium.

atoms have an electrophilic zirconium that is a good catalyst for alkene polymerization. The zirconium(II) complexes that have phosphine ligands instead of halogens catalyze the incorporation of alkynes leading to the formation of boratanaphthalene systems, as shown in Figure 21 (99JOM99).

Calculations indicate that persubstitution of boratabenzene with acceptor groups such as CN or CF_3 would allow the preparation of conjugate acids behaving as superacids (09CPC499).

Ashe et al. have obtained even a 1-arylgallatabenzene, a gallium congener, with the aryl group being 2,4,6-tri-*tert*-butylphenyl. ^{1}H-NMR and ^{13}C-NMR spectra confirm the aromatic delocalization. The acidity of the gallata-cyclohexadiene precursor is lower than that of the boron analogue or cyclopentadiene, but higher than that of indene (95AGE1357).

6.5 Metallabenzenes

Roald Hoffmann's 1982 Nobel Prize lecture (82AGE711) was centered on the idea that transition metals are able to give rise to groups that are isolobal to common organic groups. The term "isolobal" had been introduced in a paper by Elian et al. (76IC1148). Groups with a metal M coordinated to halides (Hal) or to two-electron neutral ligands (such as CO or PR_3), for instance ML_3 or ML_2Hal_2 groups with M = Co, Rh, Ir, or also ML_4 groups with M = Mn, Re, which are isolobal to sp^2-hybridized CH groups, were predicted in 1979 to be able to become part of six-membered aromatic rings (79NJC39). Indeed, 3 years later Roper and coworkers obtained the first metallabenzene having an octahedrally coordinated osmium atom (82CC811, 89IS184) from the pentacoordinated complex $Os(CO)(CS)(PPh_3)_3$ and two acetylene molecules, *via* the loss of one triphenylphosphine molecule and incorporation of the CS ligand. An iodo-derivative with a true osmabenzene ring was also obtained (Figure 22). The X-ray crystallographic data show that the rings are planar, and the two phosphine ligands are on a line that is perpendicular to this plane. Bond lengths denote aromatic electronic delocalization.

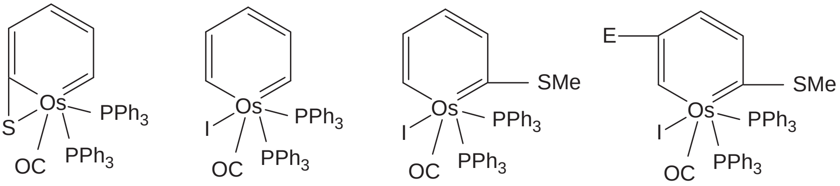


Figure 22 Osmabenzene derivatives.

So far, the metals that have successfully been incorporated into metallabenzenes are Os, Ir and Pt (also with Ru as a lighter metal) (87OM1578, 89JA4118, 97JA8503, 97OM1103, 07OM1986). Comprehensive reviews have been published recently by Landorf and Haley (06AGE3914), by Bleeke (91ACR271, 01CRV1205), by Wright (06JCD1821) and by Fernandez and Frenking (07CEJ5873).

7. SEXTET π-ELECTRON HETEROAROMATICS WITH SEVEN-MEMBERED RINGS

Borepin (Figure 23) was predicted to be aromatic before it was prepared (in a paper (59MI257) that inspired Vol'pin to include this seven-membered heterocyclic system in his comprehensive review on aromaticity (60RCR129), which enjoyed a much larger circulation than the former paper). As early as in 1955, private exchange of information between the author of this chapter and M. J. S. Dewar, who was at that time at Queen Mary College (London), had centered on boron-containing aromatics, before being announced in the same year by Dewar and Pettit (55CIL199).

The first borepin to be reported was heptaphenyl-borepin in 1975 (75JA4436, 88JA6599) but Ashe reported many syntheses of less heavily substituted borepins (87JA1879, 88JA4082). He reviewed this field with his coworkers in 1990 providing a list of relevant references for many substituted borepins that they had prepared (90PAC513). The unsubstituted 1*H*-borepin is extremely oxygen and heat sensitive. Water converts it rapidly into a mixture of 1-hydroxyborepin and a B–O–B anhydride. Methanol converts it into 1-methoxyborepin in 73% yield. Although it was not isolated in pure form, 1*H*-borepin was characterized by NMR spectra (92AGE1255).

1-Chloroborepin and its tricarbonyl-molybdenum semi-sandwich complex are definitely planar and aromatic, as proved by X-ray diffraction (93AGE1065). However, electron-donor or sterically demanding substitution causes non-planarity of the seven-membered ring: 1-dimethylaminoborepin was shown experimentally and theoretically to

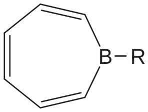


Figure 23 Borepin with an R-substituent attached to the heteroatom.

have a pronounced non-planar structure; permethylated 1-aminoborepin is even more distorted (00OM2932).

8. CONCLUSIONS

The fuzzy but fundamental concept of aromaticity has been called a cornerstone of heterocyclic chemistry (04CRV2777). It can be evaluated quantitatively by several criteria and numerical indices: (i) thermodynamic energy scales, (ii) geometry of bond lengths – harmonic oscillator model or HOMA, and (iii) magnetic criteria obtained experimentally from NMR data, or theoretically – nucleus-independent chemical shifts or NICS(*d*) values at distance $d = 0$ or 1 Å from the molecular plane. However, principal component analysis has revealed that aromaticity is multidimensional and scale dependent, so that there is little hope of finding an all-encompassing yardstick for measuring aromaticity, which is thus rendered even fuzzier.: Recently a universal scale of aromaticity based on neural networks was proposed (10JCC000). Nevertheless, there is a consensus that there are three types of conjugated chemical systems, aromatic, non-aromatic and anti-aromatic, and that aromaticity can be defined quantitatively according to specified criteria (01CRV1421 08JCC1543, 09MI2).

Five- and six-membered aromatic heterocycles can accommodate a π-electron sextet without appreciable strain, and are therefore most frequently encountered, although four- and seven-membered aromatic heterocycles exist also, but never reaching high values of aromaticity indices. Monocyclic systems with a π-electron doublet or decet exist, but again they have lower aromaticity indices.

The bottom line on monocyclic aromatic compounds with π-electron sextet is that so far, among six-membered systems only benzene, the azines with 1 through 4 nitrogen atoms, phosphabenzene and arsabenzene, pyrylium, azapyrylium, chalcogenopyrylium cations (with or without exocyclic groups such as hydroxy, amino and corresponding tautomeric or prototropic forms), and the metallabenzenes with platinum family metals have been proved to afford stable molecules under normal conditions. The list is richer for five-membered systems.

Life as we know it could not exist without aromatic heterocycles, as shown by the fact that biological evolution has ended up in selecting many aromatic heterocyclics for playing important roles in living organisms, that is the five DNA and RNA bases, two essential amino acids, namely tryptophan and histidine, several porphyrins, namely chlorophyll, heme, cytochromes. The list could be continued, but the idea is that there must be something special in the compromise of stability *versus* reactivity for aromatic heterocycles to be eligible for being leading actors in the game of life on this planet.

REFERENCES

54HCA798 K. Clusius and H. Hurzeler, *Helv. Chim. Acta*, **37**, 798 (1954).

54JA3203 W. v. E. Doering and L. H. Knox, *J. Am. Chem. Soc.*, **76**, 3203 (1954).

55CIL199 M. J. S. Dewar and R. Pettit, *Chem. Ind. (London)*, 199 (1955).

56AGE466 I. Ugi, R. Huisgen, K. Clusius, and M. Vecchi, *Angew. Chem., Int. Ed.*, **24**, 466 (1956).

56JCS2021 M. J. S. Dewar and R. Pettit, *J. Chem. Soc.*, 2021 (1956).

56JCS2026 M. J. S. Dewar and R. Pettit, *J. Chem. Soc.*, 2026 (1956).

57CB2914 R. Huisgen and I. Ugi, *Chem. Ber.*, **90**, 2914 (1957).

58CB2324 I. Ugi, H. Perlinger, and L. Behringer, *Chem. Ber.*, **91**, 2324 (1958).

58CB531 I. Ugi and R. Huisgen, *Chem. Ber.*, **91**, 531 (1958).

59MI1 D. Ginsburg (ed.), "*Non-Benzenoid Aromatic Compounds*" Interscience, New York (1959).

59MI257 A. T. Balaban, *Studii si cercetari chim., Acad. R. P. Romania*, **7**, 257–295 (1959).

60JA1515 C. G. Krespan, B. C. McKusick, and T. L Cairns, *J. Am. Chem. Soc.*, **82**, 1515 (1960).

60RCR129 M. E. Vol'pin, *Russ. Chem. Rev. (Engl. Transl.)*, **29**, 129 (1960).

61JA3434 C. G. Krespan, *J. Am. Chem. Soc.*, **83**, 3434 (1961).

63AGE633 R. Huisgen, *Angew. Chem., Int. Ed.*, **2**, 633 (1963).

63IC641 R. B. King, *Inorg. Chem.*, **2**, 641 (1963).

63JA1584 R. B. King, *J. Am. Chem. Soc.*, **85**, 1584 (1963).

63JA1587 R. B. King, *J. Am. Chem. Soc.*, **85**, 1587 (1963).

64AHC373 I. Ugi, *Adv. Heterocycl. Chem.*, **3**, 373 (1964).

64IC814 A. Davison, N. Edelstein, R. H. Holm, and A. H. Maki, *Inorg. Chem.*, **3**, 814 (1964).

64TL2721 A. T. Balaban, E. Barabas, and A. Arsene, *Tetrahedron Lett.*, **5**, 2721 (1964).

65TL3917 A. T. Balaban, A. Arsene, I. Bally, A. Barabas, M. Paraschiv, and M. Romas, *Tetrahedron Lett.*, 3917 (1965).

65TL3925 A. Barabas, C. Mantescu, D. Duta, and A. T. Balaban, *Tetrahedron Lett.*, 3925 (1965).

66AGE846 G. Märkl, *Angew. Chem., Int. Ed. Engl.*, **5**, 846 (1966).

66MI1 D. M. G. Lloyd, "*Carbocyclic Non-Benzenoid Aromatic Compounds*", Elsevier, Amsterdam (1966).

67AGE567 P. deKoe and F. Bickelhaupt, *Angew. Chem., Int. Ed. Engl.*, **6**, 567 (1967).

67SA1373 A. Arsene, A. T. Balaban, I. Bally, A. Barabas, M. Paraschiv, and C. N. Rentea, *Spectrochim. Acta A*, **23**, 1373 (1967).

67TFS801 R. C. Sahni, *Trans. Faraday Soc.*, **63**, 801 (1967).

68PIC49 J. A. McCleverty, *Prog. Inorg. Chem.*, **10**, 49 (1968).

68T2499 A. Trestianu, H. Niculescu-Majewska, I. Bally, A. Barabas, and A. T. Balaban, *Tetrahedron*, **24**, 2499 (1968).

69AGE991 P. Jutzi and K. Deuchert, *Angew. Chem., Int. Ed. Engl.*, **8**, 991 (1969).

69JA5286 D. J. Bertelli, T. G. Andrews, Jr., and P. O. Crews, *J. Am. Chem. Soc.*, **91**, 5286 (1969).

69MI1 J. P. Snyder (ed.), *"Non-Benzenoid Aromatics"* Vol. 1, Academic Press, New York (1969).

70AGE805 G. E. Herberich, G. Greiss, and H. F. Heil, *Angew. Chem., Int. Ed. Engl.*, **9**, 805 (1970).

70JA7486 E. Hayon and M. Simic, *J. Am. Chem. Soc.*, **92**, 7486 (1970).

70TL4925 G. Märkl and D. E. Fischer, *Tetrahedron Lett.*, **11**, 4925 (1970).

71ACR413 R. J. Gillespie and J. Passmore, *Acc. Chem. Res.*, **4**, 413 (1971).

71CCA3254 A. F. Berniaz, G. Hunter, and D. G. Tuck, *J. Chem. Soc. (A)*, 3254 (1971).

71IC1410 J. Miller and A. L. Balch, *Inorg. Chem.*, **10**, 1410 (1971).

71JA1804 A. J. Ashe, III and P. Shu, *J. Am. Chem. Soc.*, **93**, 1804 (1971).

71JA3923 A. J. Ashe, III, *J. Am. Chem. Soc.*, **93**, 3923 (1971).

71JA6691 A. J. Ashe, III, *J. Am. Chem. Soc.*, **93**, 6691 (1971).

71MI1 J. P. Snyder (ed.), *"Non-Benzenoid Aromatics"* Vol. 2, Academic Press, New York (1971).

71MI2 E. D. Bergmann and B. Pullman (eds.), *"Aromaticity, Pseudo-Aromaticity, Anti-Aromaticity"* The Israel Academy of Sciences and Humanities, Jerusalem (1971).

72CB3484 G. Huttner, B. Krieg, and W. Gartzke, *Chem. Ber.*, **105**, 3424 (1972).

72CC365 J. S. McKennis, L. Brener, J. R. Schweiger, and R. Pettit, *J. Chem. Soc., Chem. Commun.*, 365 (1972).

72JSP457 R. L. Kuczkowski and A. J. Ashe, III, *J. Mol. Spectrosc.*, **42**, 457 (1972).

72T5299 B. A. Hess, Jr., L. J. Schaad, and C. W. Holyoke, Jr., *Tetrahedron*, **28**, 5299 (1972).

73FCF1 K. Dimroth, *Fortschr. Chem. Forsch.*, **38**, 1 (1973).

74CB3786 G. Huttner and W. Gartzke, *Chem. Ber.*, **107**, 3786 (1974).

75AGE710 G. Märkl, H. Baier, and S. Heinrich, *Angew. Chem., Int. Ed.*, **14**, 710 (1975).

75IC2011 J. S. Miller, *Inorg. Chem.*, **14**, 2011 (1975).

75JA4436 J. J. Eisch and J. E. Galle, *J. Am. Chem. Soc.*, **97**, 4436 (1975).

75PAC513 A. J. Ashe, III, F. J. Drone, C. M. Kausch, J. Kroker, and S. M. Al-Taweel, *Pure Appl. Chem.*, **62**, 513 (1975).

75TL2749 A. J. Ashe, III, and W. Chan, *Tetrahedron Lett.*, **16**, 2749 (1975).

76IC1148 M. Elian, M. M.-L. Chen, D. M. P. Mingos, and R. Hoffmann, *Inorg. Chem.*, **15**, 1148 (1976).

76JA5451 A. J. Ashe, III, R. B. Sharp, and J. W. Tolan, *J. Am. Chem. Soc.*, **98**, 5451 (1976).

76MI1 A. T. Balaban (ed.), *"Chemical Applications of Graph Theory"* Academic Press, London (1976).

76T315 A. T. Balaban and Z. Simon, *Tetrahedron*, **18**, 315 (1962).

77IC2482 A. Cisar and J. D. Corbett, *J. D. Inorg. Chem.*, **16**, 2482 (1977).

77JA5199 T. J. Barton and D. S. Banasiak, *J. Am. Chem. Soc.*, **99**, 5199 (1977).

78ACR153 A. J. Ashe, III, *Acc. Chem. Res.*, **11**, 153 (1978).

78JA3737 S. A. Sullivan, H. F. Sandford, J. L. Beauchamp, and A. J. Ashe, III, *J. Am. Chem. Soc.*, **100**, 3737 (1978).

78JA5246	T. J. Barton and G. T. Burns, *J. Am. Chem. Soc.*, **100**, 5246 (1978).
79AGE789	G. Märkl and P. Hofmeister, *Angew. Chem., Int. Ed. Engl.*, **18**, 789 (1979).
79NJC39	D. R. Thorn and R. Hoffmann, *Nouv. J. Chem.*, **31**, 39 (1979).
79TL437	A. T. Balaban, A. Dinculescu, H. N. Koutrakis, and F. Chiraleu, *Tetrahedron Lett.*, **20**, 437 (1979).
80AGE52	G. Maier, G. Mihm, and H. P. Reisenauer, *Angew. Chem., Int. Ed. Engl.*, **19**, 52 (1980).
80AGE717	A. Vogler, R. E. Wright, and H. Kunkley, *Angew. Chem., Int. Ed.*, **19**, 717 (1980).
80PAC1409	A. T. Balaban, *Pure Appl. Chem.*, **52**, 1409 (1980).
81CPL317	T.-K. Ha, R. Cimiraglia, and M. T. Nguyen, *Chem. Phys. Lett.*, **83**, 317 (1981).
81CS230	A. T. Balaban, A. Dinculescu, F. Iordache, F. Chiraleu, and D. Patrascoiu, *Chem. Scripta*, **18**, 230 (1981).
81JA6788	T. J. Barton and M. Vuper, *J. Am. Chem. Soc.*, **103**, 6788 (1981).
82AGE64	H. Huber, *Angew. Chem., Int. Ed.*, **21**, 64 (1982).
82AGE711	R. Hoffmann, *Angew. Chem., Int. Ed. Engl.*, **21**, 711 (1982).
82CC811	G. P. Elliott, W. R. Roper, and J. M. Waters, *J. Chem. Soc., Chem. Commun.*, 811 (1982).
82CL59	S. Ito, Y. Tanaka, and A. Kakeki, *Chem. Lett.*, 59 (1982).
82JA425	P. D. Burrow, A. J. Ashe, III, D. J. Bellville, and K. D. Jordan, *J. Am. Chem. Soc.*, **104**, 425 (1982).
82MI1	A. T. Balaban, A. Dinculescu, G. N. Dorofeenko, G. W. Fischer, A. V. Koblik, V. V. Mezheritskii, and W. Schroth, Pyrylium salts. Syntheses, reactions and physical properties, in "*Advances in Heterocyclic Chemistry*" (A. R. Katritzky, ed.), Suppl. Vol. 2, Academic Press, New York (1982).
82TCC125	A. J. Ashe, III, *Top. Curr. Chem.*, **105**, 125 (1982).
83CC910	J. D. Wallis and J. D. Dunitz, *J. Chem. Soc., Chem. Commun.*, 910 (1983).
83JA1760	P. Saxe and H. P. Schaefer, Jr., *J. Am. Chem. Soc.*, **105**, 1760 (1983).
83JOC3453	J. Chandrasekhar, P. v. R. Schleyer, R. O. W. Baumgärtner, and M. T. Reetz, *J. Org. Chem.*, **48**, 3453 (1983).
83ZNA1161	C. K. Narula and H. Nöth, *Z. Naturforsch. A*, **61**, 360 (2006).
84CHEC1	A. R. Katritzky and C. W. Rees (eds.), "*Comprehensive Heterocyclic Chemistry (covering the literature till 1982)*" Elsevier, Amsterdam (1984).
84IC770	S. C. Critchlow and J. D. Corbett, *J. D. Inorg. Chem.*, **23**, 770 (1984).
84JMT(109)391	H. Huber, T.-K. Ha, and M. T. Nguyen, *J. Mol. Struct. Theochem.*, **109**, 391 (1984).
84JOC4475	K. Jug, *J. Org. Chem.*, **49**, 4475 (1984).
84MI1	R. Huisgen, in "*1,3-Dipolar Cycloaddition Chemistry*" (A. Padwa, ed.), vol. 1, p. 1, Wiley, New York (1984).
84MI2	D. M. G. Lloyd, "*Non-Benzenoid Conjugated Carbocyclic Compounds*", Elsevier, Amsterdam (1984).
85AGE351	O. J. Scherer, H. Sitzmann, and G. Wolmershäuser, *Angew. Chem., Int. Ed. Engl.*, **24**, 351 (1985).
85AGE513	R. Müller, J. D. Wallis, and W. v. Philipsborn, *Angew. Chem., Int. Ed. Engl.*, **24**, 513 (1985).
86AOC199	G. E. Herberich and H. Ohst, *Adv. Organomet. Chem.*, **25**, 199 (1986).

86CC383 M. T. Nguten and A. F. Hegarty, *J. Chem. Soc., Chem. Commun.*, 383 (1986).

86MI1 P. J. Garratt, *"Aromaticity"*, Wiley, New York (1984).

86CPL(126)43 S. Nagase and K. Ito, *Chem. Phys. Lett.*, **126**, 43 (1986).

86PAC95 G. Maier, *Pure Appl. Chem.*, **58**, 95 (1986).

87JA1879 A. J. Ashe, III and F. J. Drone, *J. Am. Chem. Soc.*, **109**, 1879 (1987).

87JA6290 P. H. M. Budzelaar, D. Cremer, M. Wallasch, E.-U. Würthwein, and P. von R. Schleyer, *J. Am. Chem. Soc.*, **109**, 6290 (1987).

87MI1 I. Haiduc and D. B. Sowerby, in "*The Chemistry of Inorganic Homo- and Heterocycles*" (I. Haiduc and D. B. Sowerby, eds.), vol. 1, chapter 1, p. 1, Academic Press, London (1987).

87MI2 I. Haiduc, in "*The Chemistry of Inorganic Homo- and Heterocycles*" (I. Haiduc and D. B. Sowerby, eds.), vol. 2, chapter 17, p. 419, Academicv Press, London (1987).

87MI3 A. T. Balaban, M. Banciu, and V. Ciorba, "*Annulenes, Benzo-, Hetero-, Homo-Derivatives and their Valence Isomers*", vol. 3, p. 1. CRC Press, Boca Raton, FL (1986).

87OM1578 J. W. Egan, Jr., R. P. Hughes, and A. L. Rheingold, *Organometallics*, **6**, 1578 (1987).

88AGE963 G. Märkl and W. Schlosser, *Angew. Chem., Int. Ed. Engl.*, **27**, 963 (1988).

88IC2219 G. Ohanessian, P. C. Hiberty, J. M. Lefour, J. P. Flement, and S. S. Shaik, *Inorg. Chem.*, **27**, 2219 (1988).

88JA4082 A. J. Ashe, III and F. J. Drone, *J. Am. Chem. Soc.*, **10**, 4082 (1988).

88JA6599 J. J. Eisch and J. E. Galle, *J. Am. Chem. Soc.*, **110**, 6599 (1988).

89CB2121 R. Janoschek, *Chem. Ber.*, **122**, 2121 (1989).

89IS184 G. P. Elliott, N. M. McAuley, and W. R. Roper, *Inorg. Synth.*, **26**, 184 (1989).

89JA4118 J. R. Bleeke, Y.-F. Xie, W.-J. Peng, and M. Chiang, *J. Am. Chem. Soc.*, **111**, 4118 (1989).

89MI1 Y. Apeloig, in "*The Chemistry of Organic Silicon Compounds*", Part 1 (Z. Patai and Z. Rappoport, eds.), Chapter 2, Wiley, Chichester (1989).

90JA4155 G. Van Zandwijk, R. A. J. Janssen, and H. M. Buck, *J. Am. Chem. Soc.*, **112**, 4155 (1990).

90JA7529 H. Yu, W. Chan, and J. D. Goddard, *J. Am. Chem. Soc.*, **112**, 7529 (1990).

90PAC423 B. M. Gimarc, *Pure Appl. Chem.*, **62**, 423 (1990).

90PAC513 A. J. Ashe, III, F. J. Drone, C. M. Kausch, J. Kroker, and S. M. Al-Taweel, *Pure Appl. Chem.*, **62**, 513 (1990).

91ACR271 J. R. Bleeke, *Acc. Chem. Res.*, **24**, 271 (1991).

91CPL175 V. Jonas and G. Frenking, *Chem. Phys. Lett.*, **177**, 175 (1991).

91TL3949 R. S. Hosmane and J. F. Liebman, *Tetrahedron Lett.*, **32**, 3949 (1991).

92AGE1255 A. J. Ashe, III, J. W. Kampf, Y. Nakadaira, and J. M. Pace, *Angew. Chem., Int. Ed. Engl.*, **31**, 1255 (1992).

92CB2687 R. Janoschek, *Chem. Ber.*, **125**, 2687 (1992).

92CPL(198)547 M. N. Glukhovtsev and P. v. R. Schleyer, *Chem. Phys. Lett.*, **198**, 547 (1992).

92JA5378 D. S. Warren and B. M. Gimarc, *J. Am. Chem. Soc.*, **114**, 5378 (1992).

92JPC10879 R. Engelke, *J. Phys. Chem.*, **96**, 10879 (1992).

92TL2303	R. S. Hosmane and J. F. Liebman, *Tetrahedron Lett.*, **33**, 2303 (1992).
93AGE1065	A. J. Ashe, III, J. W. Kampf, W. Klein, and R. Rousseau, *Angew. Chem., Int. Ed. Engl.*, **32**, 1065 (1993).
93JPC6384	R. A. J. Janssen, *J. Phys. Chem.*, **97**, 6384 (1993).
94CCR137	C. W. Allen, *Coord. Chem. Rev.*, **130**, 137 (1994).
94MI1	V. I. Minkin, M. N. Glukhovtsev, and B. Ya. Simkin, "*Aromaticity and Antiaromaticity: Electronic and Structural Aspects*", Wiley, New York (1994).
94MI2	R. Huisgen, "*The Adventure Playground of Mechanisms and Novel Reactions*", Am. Chem. Soc., Washington, D. C., pp. 79–82, 94–110 (1994).
95AGE1357	A. J. Ashe, III, S. Al-Ahmad, and J. W. Kampf, *Angew. Chem., Int. Ed.*, **34**, 1357 (1995).
95OM471	G. E. Herberich, B. Schmidt, and U. Englert, *Organometallics*, **14**, 471 (1995).
95SR371	S. B. Nielson and A. Senning, *A. Sulfur Rep.*, **16**, 371 (1995).
96CHEC2(4)897	R. N. Butler, in "*Comprehensive Heterocyclic Chemistry*" 2nd ed. (A.R. Katritzky, C. W. Rees, and E. F. Scriven, eds.), vol. 4, p. 897, Elsevier, New York (1996).
96CHEC2-1	A. R. Katritzky, C. W. Rees, and E. F. V. Scriven (eds.), "*Comprehensive Heterocyclic Chemistry*" Elsevier, Amsterdam (1996) (covering 1982–1995).
96CPL407	L. Gonzalez, O. Mo, and M. Yanez, *Chem. Phys. Lett.*, **263**, 407 (1996).
96IJQ859	M. Mann and J. Fabian, *Int. J. Quant. Chem.*, **60**, 859 (1996).
96JA6329	S. Qiao, D. A. Hoic, and G. C. Fu, *J. Am. Chem. Soc.*, **119**, 6329 (1996).
96JPC13447	M. N. Glukhovtsev, A. Dransfeld, and P. v. R. Schleyer, *J. Phys. Chem.*, **100**, 13447 (1996).
96JP2-801	R. N. Butler, S. Collier, and A. F. M. Fleming, *J. Chem. Soc., Perkin Trans. 2*, 801 (1996).
96PAC209	P. v. R. Schleyer, *Pure Appl. Chem.*, **68**, 209 (1996).
97JA8503	J. R. Bleeke and R. Behm, *J. Am. Chem. Soc.*, **119**, 8503 (1998).
97JA12669	P. v. R. Schleyer, H. Jiao, N. J. R. v. E. Hommes, V. G. Malkin, and O. L. Malkina, *J. Am. Chem. Soc.*, **119**, 12669 (1997).
97OM1103	J. R. Bleeke, R. Behm, and A. M. Beatty, *Organometallics*, **16**, 1103 (1997).
97PCA1409	P. W. Fowler and E. Steiner, *J. Phys. Chem. A*, **101**, 1409 (1997).
98ACS967	A. Skancke, R. S. Hosmane, and J. F. Liebman, *Acta Chem. Scand.*, **52**, 967 (1998).
98IC2110	E. D. Jemmis and B. Kiran, *Inorg. Chem.*, **37**, 2110 (1998).
98JEM119	M. A. Hiskey, N. Goldman, and J. R. Stine, *J. Energ. Mat.*, **16**, 119 (1998).
98LA(303)57	J. Thiele, *Liebigs Ann. Chem.*, **303**, 57 (1898).
98MI1	Y. Apeloig and Z. Karni, in "*The Chemistry of Organic Silicon Compounds*" (Z. Rappoport and Y. Apeloig, eds.), Vol. 2, Part 1, Chapter 1, Wiley, Chichester (1998).
98PCA4679	R. J. Doerksen and A. J. Thakkar, *J. Phys. Chem. A*, **102**, 4679 (1998).
99ACR751	O. J. Scherer, *Acc. Chem. Res.*, **32**, 751 (1999).
99JCP7705	J. D. Goddard and G. Orlova, *J. Chem. Phys.*, **111**, 7705 (1999).

99JOM99	A. J. Ashe, III, S. Al-Ahmad, and X. Fang, *J. Organometall. Chem.*, **581**, 99 (1999).
00AGE634	K. Wakita, N. Tokitoh, R. Okazaki, and S. Nagase, *Angew. Chem., Int. Ed.*, **39**, 634 (2000).
00AHC(77)221	J. Nakayama and A. Ishii, *Adv. Heterocycl. Chem.*, **77**, 221 (2000).
00JA5652	A. Sekiguchi, T. Matsuo, and H. Watanabe, *J. Am. Chem. Soc.*, **122**, 5652 (2000).
00JCP8430	A. Timoshkin and G. Frenking, *J. Chem. Phys.*, **113**, 8430 (2000).
00JMT181	C. Jakins and E. Lewars, *J. Mol. Struct. Theochem.*, **531**, 181 (2000).
00JOM106	T. Shimizu and N. Kamigata, *J. Organomet. Chem.*, **611**, 106 (2000).
00JOM228	V. Ya. Lee, A. Sekiguchi, M. Ichinohe, and N. Fukaya, *N. J. Organomet. Chem.*, **611**, 228 (2000).
00OM2932	J. M. Schulman and R. L. Disch, *Organometallics*, **19**, 2932 (2000).
00PCA1246	M. Balci, M. L. McKee, and p. v. R. Schleyer, *J. Phys. Chem. A*, **104**, 1246 (2000).
01AGE2004	H. C. Kolb, M. G. Finn, and K. B. Sharpless, *Angew. Chem., Int. Ed.*, **40**, 2004 (2001).
01CRV1115	P. v. R. Schleyer (Guest Ed.), *Chem. Rev.*, **101**, 1115 (2001).
01CRV1205	J. R. Bleeke, *Chem. Rev.*, **101**, 1205 (2001).
01CRV1229	L. Nyulászi, *Chem. Rev.*, **101**, 1229 (2001).
01CRV1421	A. R. Katritzky, K. jug, and D. C. Oniciu, *Chem. Rev.*, **101**, 1421 (2001).
01HCA1578	Z.-X. Wang and P. v. R. Schleyer, *Helv. Chim. Acta*, **84**, 1578 (2001).
01JA5356	K. Ishii, N. Kobayashi, T. Matsuo, M. Tanaka, and A. Sekiguchi, *J. Am. Chem. Soc.*, **123**, 5356 (2001).
01SCI859	X. Li, X. A. E. Kuznetsov, H.-F. Zhang, A. I. Boldyrev, and L.-S. Wang, *Science*, **291**, 859 (2001).
02JA366	G. S. Harbison, *J. Am. Chem. Soc.*, **124**, 366 (2002).
02JA1119	T. Sommerfeld, *J. Am. Chem. Soc.*, **124**, 1119 (2002).
02JOC1333	M. K. Cyranski, T. M. Krygowski, A. R. Katritzky, and P. v. R. Schleyer, *J. Org. Chem.*, **67**, 1333 (2002).
02PCA10370	S. Sakai, *J. Phys. Chem. A*, **106**, 10370 (2002).
02MI1	A. Hassner and C. Stumer, *"Organic Syntheses Based on Name Reactions"*, 2nd edition, p. 17. Pergamon-Elsevier, Amsterdam (2002).
02RCR869	V. I. Minkin, R. M. Minyaev, and R. Hoffmann, *Russ. Chem. Rev.*, **71**, 869 (2002).
03CRV1429	A. Sekiguchi and V. Ya. Lee, *Chem. Rev.*, **103**, 1429 (2003).
03DDT1128	H. C. Kolb and K. B. Sharpless, *Drug Disc. Today*, **8**, 1128 (2003).
03MI	T. Eicher and S. Hauptmann, *"The Chemistry of Heterocycles"*, 2nd edition, Wiley-VCH, Weinheim (2003).
03MI6	T. S. Balaban and A. T. Balaban, in *"Science of Synthesis; Houben-Weyl Methods of Molecular Transformations"*, Vol. 14, p. 11, Thieme, Stuttgart (2003).
03OBC3410	K. Najafian, P. v. R. Schleyer, and T. T. Tidwell, *Org. Biomol. Chem.*, **1**, 3410 (2003).
04ACR86	N. Tokitoh, *Acc. Chem. Res.*, **37**, 86 (2004).
04ACR9549	F. Mathey, *Acc. Chem. Res.*, **37**, 9549 (2004).
04BCJ429	N. Tokitoh, *Bull. Chem. Soc. Jpn.*, **77**, 429 (2004).
04CJC50	J. Fabian and E. Lewars, *Can. J. Chem.*, **82**, 50 (2004).

04CPL192 D. Vijay, U. D. Priyakumar, and G. N. Sastry, *Chem. Phys. Lett.*, **383**, 192 (2004).

04CRV2125 A. R. Katritzky (Guest Ed.), *Chem. Rev.*, **104**, 2125 (2004).

04CRV2777 A. T. Balaban, D. C. Oniciu, and A. R. Katritzky, *Chem. Rev.*, **104**, 2777 (2004).

04IC6490 I. Todorov and S. C. Sevov, *Inorg. Chem.*, **43**, 6490 (2004).

04JPO303 N. Sadlej-Sosnowska, *J. Phys. Org. Chem.*, **17**, 303 (2004).

05AGE1078 S. Ehrardt, G. Frenking, Z. Chen, and P. v. R. Schleyer, *Angew Chem., Int. Ed.*, **44**, 1078 (2005).

05AGE5188 S. Bräse, C. Gil, K. Knepper, and V. Zimmermann, *Angew. Chem., Int. Ed.*, **44**, 5188 (2005).

05CCR2740 C. A. Tsipis, *Coord. Chem. Rev.*, **249**, 2740 (2005).

05CRV3433 P. v. R. Schleyer (Guest Ed.), *Chem. Rev.*, **105**, 3433 (2005).

05CRV3436 A. T. Balaban, P. v. R. Schleyer, and H. S. Rzepa, *Chem. Rev.*, **105**, 3436 (2005).

05CRV3716 A. L. Boldyrev and L.-S. Wang, *Chem. Rev.*, **105**, 3716 (2005).

05IC5266 J. J. Engelberts, R. W. A. Havenith, J. H. v. Lenthe, L. W. Jenneskens, and P. W. Fowler, *Inorg. Chem.*, **44**, 5266 (2006).

05IC8407 A. B. Chaplin, J. A. Harrison, and P. J. Dyson, *Inorg. Chem.*, **44**, 8407 (2005).

05JMT(728)61 B. A. Shainyan and A. Sekiguchi, *J. Mol. Struct. Theochem.*, **728**, 1 (2005).

05JMT(732)71 D. Vijay and G. N. Sastry, *J. Mol. Struct. Theochem.*, **732**, 71 (2005).

05PCA236 B. M. Elliott and A. I. Boldyrev, *J. Phys. Chem. A*, **109**, 236 (2005).

06AGE3914 C. W. Landorf and M. M. Haley, *Angew. Chem., Int. Ed. Engl.*, **45**, 3914 (2006).

06CRV4681 T. Baumgartner and R. Rau, *Chem. Rev.*, **106**, 4681 (2006).

06EJO51 V. D. Bock, H. Hiemstra, and J. H. van Maarseveen, *Eur. J. Org. Chem.*, 51 (2006).

06JA11026 D. J. Harrison, N. Nguyen, A. J Lough, and F. Ulrich, *J. Am. Chem. Soc.*, **128**, 11026 (2006).

06JCD1821 L. G. Wright, *J. Chem. Soc., Dalton Trans.*, 1821 (2006).

06JMC3872 M. A. Ilies, W. A. Seitz, B. H. Johnson, E. L. Ezell, A. L. Miller, E. B. Thompson, and A. T. Balaban, *J. Med. Chem.*, **49**, 3872 (2006).

06JOM4359 J. O. C. Jiménez-Halla, E. Matito, J. Robles, and M. Solà, *J. Organometal. Chem.*, **691**, 4359 (2006).

06ZNA360 H. Hartmann, *Z. Naturforsch. A*, **61**, 360 (2006).

07AGE6596 V. Ya. Lee and A. Sekiguchi, *Angew. Chem., Int. Ed.*, **46**, 6596 (2007).

07AM2197 H. Nandivada, X. Jiang, and J. Lahann, *Adv. Mat.*, **19**, 2197 (2007).

07CAJ700 A. Dondoni, *Chem. Asian J.*, **2**, 700 (2007).

07CEJ5873 I. Fernandez and G. Frenking, *Chem. Eur. J.*, **13**, 5873 (2007).

07CSR1249 J. E. Moses and A. D. Moorhouse, *Chem. Soc. Rev.*, **36**, 1249 (2007).

07CSR1369 D. Fournier, R. Hoogenboom, and U. S. Schubert, *Chem. Soc. Rev.*, **36**, 1369 (2007).

07OM1986 J. Zhu, G. Jia, and Z. Lin, *Organometallics*, **26**, 1986 (2007).

08AGE3330 G. Steinhauser and T. M. Klapötke, *Angew. Chem., Int. Ed.*, **47**, 3330 (2008).

08CHEC3-1 A. R. Katritzky, C. A. Ramsden, E. F. V. Scriven, and R. J. K. Taylor (eds.), "*Comprehensive Heterocyclic Chemistry*" Elsevier, Amsterdam (2008) (covering 1995–2007).

08CHEC3-739 T. M. Klapötke and A. Hammerl, in "*Comprehensive Heterocyclic Chemistry*" 3rd edn. (A. R. Katritzky, C. A. Ramsden, E. F. V.

Scriven, and R. J. K. Taylor, eds.), Elsevier, Amsterdam (2008) (covering 1995–2007).

08JCC1543 F. Feixas, E. Matito, J. Poater, and M. Solà, *J. Comput. Chem.*, **29**, 1543 (2008).

08JOC1354 R. N. Butler, J. M. Hannify, J. C. Stephens, and L. A. Burke, *J. Org. Chem.*, **73**, 1354 (2008).

08PR2216 C. D. Hein, X.-M. Liu, and D. Wong, *Pharm. Res.*, **25**, 2216 (2008).

09AGE973 A. J. V. Marwitz, M. H. Matus, L. N. Zakharov, D. A. Dixon, and S. Liu, *Angew. Chem., Int. Ed.*, **48**, 973 (2009).

09CPC499 A. Kütt, I. Koppel, I. A. Koppel, and I. Leito, *ChemPhysChem*, **10**, 499 (2009).

09MI1 L. Nyulászi and Z. Benkö, in "*Aromaticity in Heterocyclic Compounds*" (T. M. Krygowski and M. K. Cyrański, eds.), p. 27, Springer, Berlin (2009).

09MI2 A. T. Balaban, in "*Aromaticity in Heterocyclic Compounds*" (T. M. Krygowski and M. K. Cyranski, eds.), p. 203, Springer, New York (2009).

09OL1587 F. Zhang and J. E. Moses, *Org. Lett.*, **11**, 1587 (2009).

10JCC000 M. Alonzo and B. Herradón, *J. Comput. Chem.* DOI 10.1039/b917343a

CHAPTER 4

Biologically Active Silacyclanes

Edmunds Lukevics†, **Edgars Abele** and **Luba Ignatovich**

Contents

1. INTRODUCTION

Organosilicon chemistry opens a new and promising way to potent pharmaceutical substances (05MDMD83, 03CODD526, 07CODD654). Nine organosilicon compounds already entered clinical trials. Five of them belong to sila-heterocycles containing not only a silicon atom but also another heteroatom in the ring. It may be oxygen – as in anticancer drug cisobitan (**1**) and conjonctyl (**2**) proposed for the treatment of painful polycystic mastopathies, nitrogen – as in silicon phthalocianine Pc-4 (**3**) suitable for cancer photodynamic therapy, or both oxygen and nitrogen – as in the muscle relaxant Sandoz 58-112 (**4**) (05MDMD83) and hair growth stimulant 1-chloromethylsilatrane (**5**) (05SMA123).

Interesting biological properties have been found also for the sila-heterocycles containing a silicon atom as a single heteroatom.

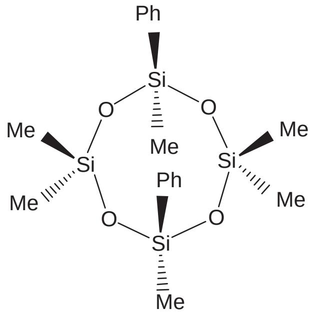
Latvian Institute of Organic Synthesis, 21 Aizkraukles, Riga, LV-1006, Latvia
†Deceased

Advances in Heterocyclic Chemistry, Volume 99
ISSN 0065-2725, DOI 10.1016/S0065-2725(10)09904-6

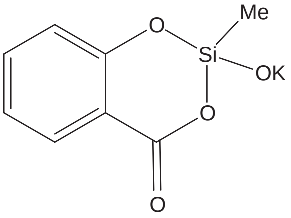
These compounds have been prepared in two ways:

(1) Substitution of one or more carbon atoms for silicon atoms (silicon switches) to obtain the silicon analogues of known drugs (03CODD526, 89COSC1143, 03DDT551, 05DDRO467, 06MRMC1169).
(2) Introduction of a silacycloalkyl group as a substituent into the biologically active organic compound (C-modification) (05MDMD83, 02MBD45, 03BCA299, 02MBD307, 05AOC1109).

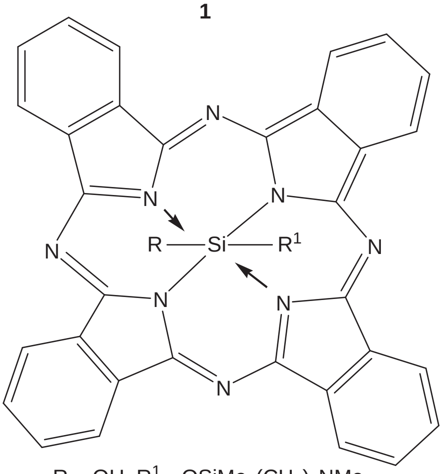
In this review, we are describing the synthesis and biological properties of such silacyclanes which contain one or more silicon atoms in the ring and no other heteroatoms.



1

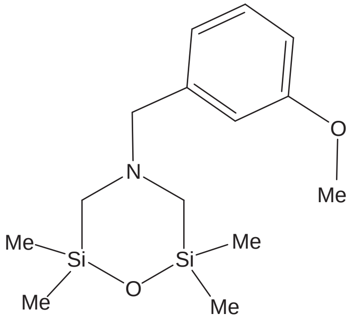


2

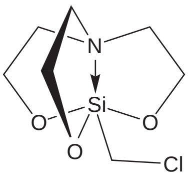


R = OH, $R^1 = OSiMe_2(CH_2)_3NMe_2$

3



4



5

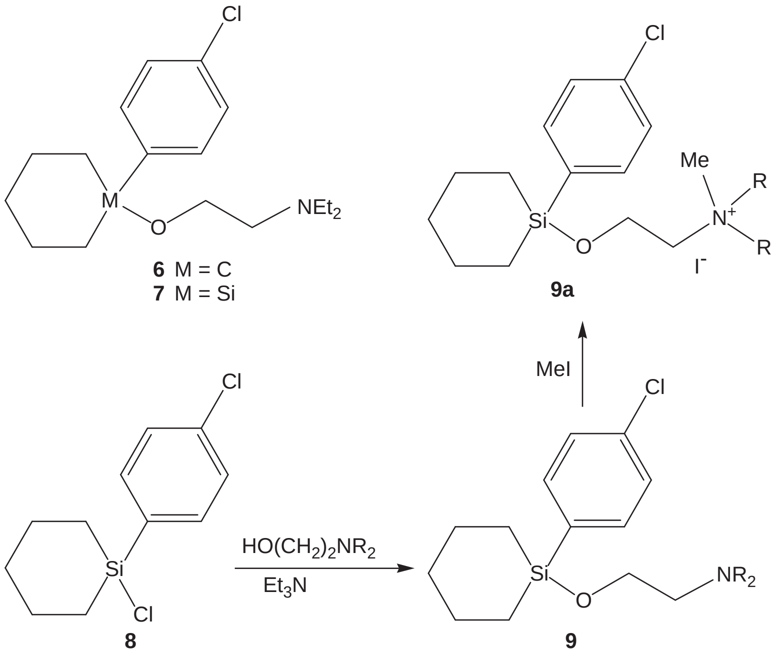
2. NEUROTROPIC SUBSTANCES

Silacycloalkanes have been widely investigated as agents acting on the nervous system.

One of the first articles in this field was dedicated to the synthesis and investigation of the biological activity of sila analogues **7** and **9** of the known CNS drug chlorphencyclane **6** and their methiodides **9a**. Compounds **9** were synthesized from 1-chloro-1-(4-chlorophenyl)silacyclohexane **8**, obtained from $SiCl_4$ by stepwise Grignard reactions with amino alcohols in the presence of Et_3N (80AP(313)129) (Scheme 1).

The spasmolytic activity of **7** on isolated guinea-pig ileum was comparable to that of chlorphencyclane **6**. They had the same effects on contractility and on refractory period of the left guinea-pig atria, similar antitremorine activity and comparable acute toxicity in mice. The shorter duration of action observed for the sila analogues containing a Si–O–C group may be connected with their hydrolytic inactivation (80AP(313)129).

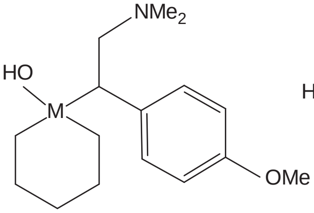
Venlafaxine **10** is a serotonin-noradrenaline reuptake inhibitor used in the treatment of depression. Several sila analogues of venlafaxine have been prepared: the silacyclohexylderivative **11** (04WOP200494436), its desmethoxy derivative **12** (06JOM(691)3589) and silacyclopentyl



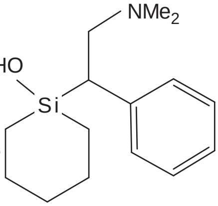
$NR_2 = NMe_2, NEt_2$, morpholino

Scheme 1

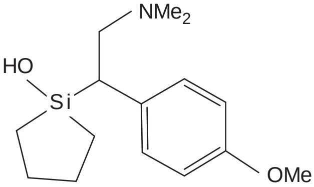
analogue **13** (06OM1188) containing a five-membered silacycle instead of the six-membered ring.



10 M =C
11 M =Si



12



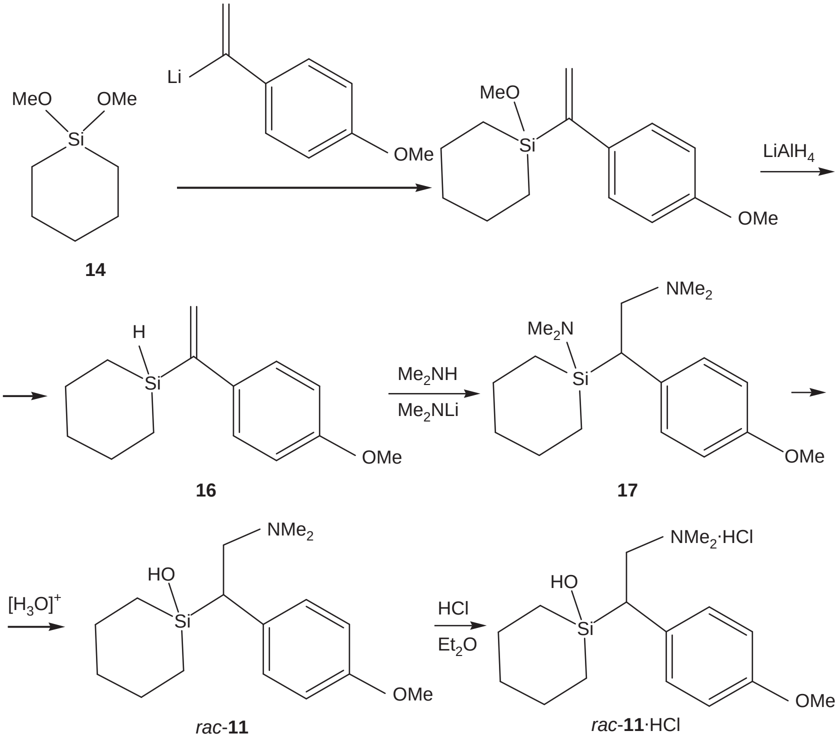
13

Sila-venlafaxine **11** was obtained in racemic form and resolved into (*R*)- and (*S*) -enantiomers (04OM4987, 06OM1188, 07CODD654, 03OSC575, 03WOP03037905, 06BMCL2555, 08TAP369, 04WOP200494436).

Two general schemes have been proposed for its synthesis from 1,1-dimethoxy-1-silacyclohexane **14** (06OM1188) (Scheme 2) or 1,1-dichloro-1-silacyclohexane **15** (Scheme 3) (04OM4987). Thus, treatment of dimethoxysilane **14** with [1-(4-methoxyphenyl)vinyl]lithium and further reduction of the SiOMe group with lithium aluminum hydride gave 1-[1-(4-methoxyphenyl)vinyl]-1-silacyclohexane **16**. When it reacted with dimethylamine in the presence of lithium dimethylamide substitution of the Si–H bond for an Si-NMe$_2$ group and addition of dimethylamine to the C=C double bond of the vinyl group took place to afford diamin **17**. Further hydrolysis with a potassium acetate/acetic acid buffer gave *rac*-sila-venlafaxine **11** (Scheme 2) which was converted to the hydrochloride with ethereal hydrogen chloride.

Silanols **12** and **13** were prepared similarly using (1-phenylvinyl) magnesium bromide instead of the methoxy derivative in the first case and starting from the 1,1-dimethoxy-1-silacyclopentane in the second case.

The application of the acid labile 2,4,6-trimethoxyphenyl protecting group (Scheme 3) avoided reduction by highly flammable LiAlH$_4$ in the preparation of the target in multigram quantities (04OM4987). The interaction of dichlorosilane **15** with 2,4,6-trimethoxyphenyllithium gave selectively the monosubstitution product, its further methanolysis and reaction with 1-(4-methoxyphenyl)vinyllithium afforded **18** that was deprotected by HCl in Et$_2$O to obtain chlorosilane **19**. When it reacted with dimethylamine and lithium dimethylamide in THF substitution of the Si–Cl bond for an Si-NMe$_2$ group and addition of dimethylamine to the vinyl group took place. Further hydrolysis afforded *rac*-sila-venlafaxine **11**. The (*R*)-enantiomer was obtained from *rac*-**11** by

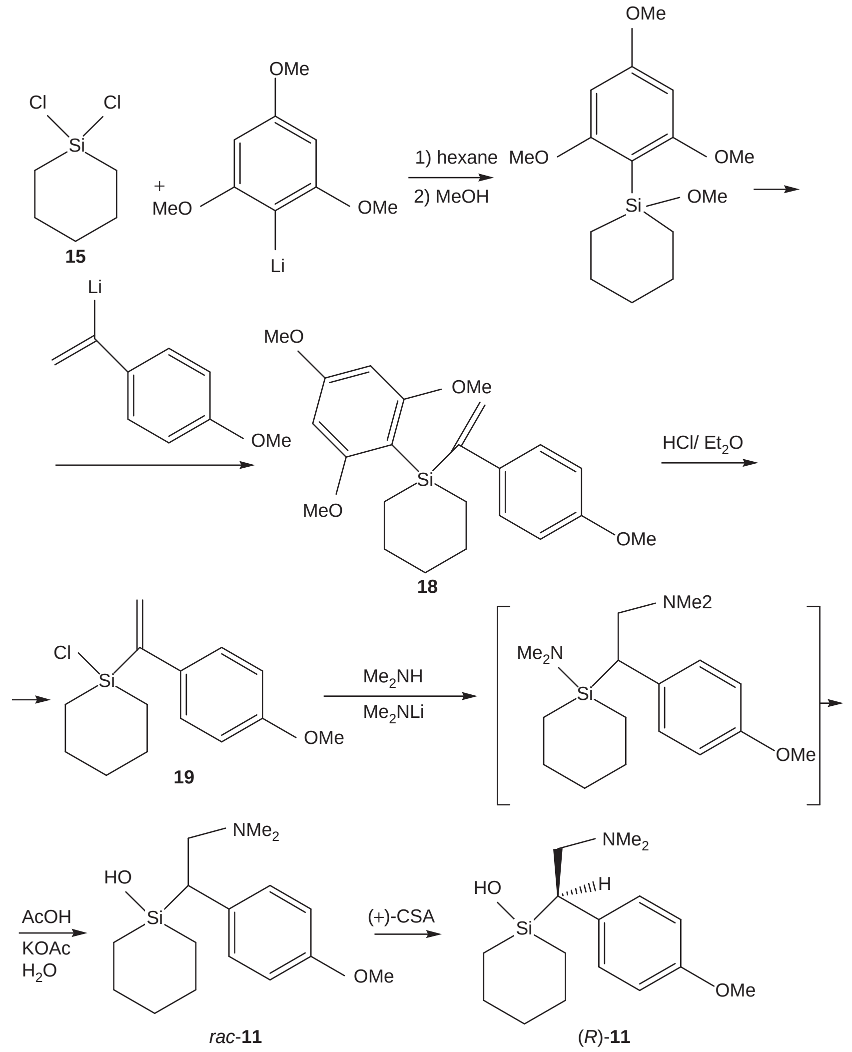


Scheme 2

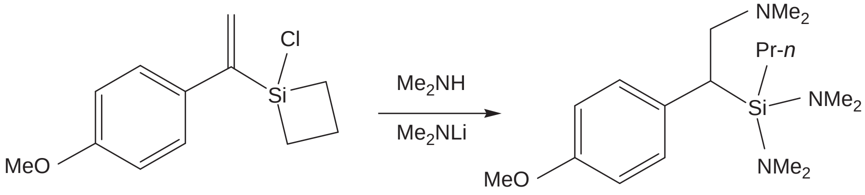
fractional crystallization of its (+)-10-camphorsulfonic acid salt. The (*S*)-enantiomer was prepared from the mother liquor obtained in the preparation of the (*R*)-enantiomer using (−)-10-camphorsulfonic acid resolving agent.

This scheme was also used for the synthesis of a venlafaxine analogue containing a four-membered silacycle instead of a six-membered ring but Si–C bond cleavage with silacyclobutane ring opening took place in the amination step (Scheme 4) (04OM4987).

Rac-venlafaxine **10** and its sila analogue *rac*-**11** have similar physicochemical properties ($pK_a = 9.7$, log $P = 3.1$ in *n*-octanol/water, log $P = 0.9$ at pH 7.4) indicating that venlafaxine and sila-venlafaxine could have a similar brain penetration profile. The *in vitro* pharmacological studies of venlafaxine, sila-venlafaxine and their enantiomers (used as hydrochlorides) for their efficacy in monoamine reuptake inhibition demonstrated differences in activity and also in inhibition profile (06JOM(691)3589, 06OM1188). With respect to serotonin, noradrenaline and dopamine reuptake inhibition potency these



Scheme 3



Scheme 4

compounds can be placed in the following order of decreasing activity:

serotonin reuptake transporter
(*S*)-**10** > *rac*-**10** > (*R*)-**10** > (*S*)-**11** > *rac*-**11** > *rac*-**13** > (*R*)-**11** > *rac*-**12**

noradrenaline reuptake transporter
(*R*)-**10** > *rac*-**11** > *rac*-**10** > (*R*)-**11** > *rac*-**13** > (*S*)-**10** > *rac*-**12** > (*S*)-**11**

dopamine reuptake transporter
rac-**13** > *rac*-**11** > *rac*-**10** > (*R*)-**11** > (*S*)-**10** > (*R*)-**10** > *rac*-**12** > (*S*)-**11**

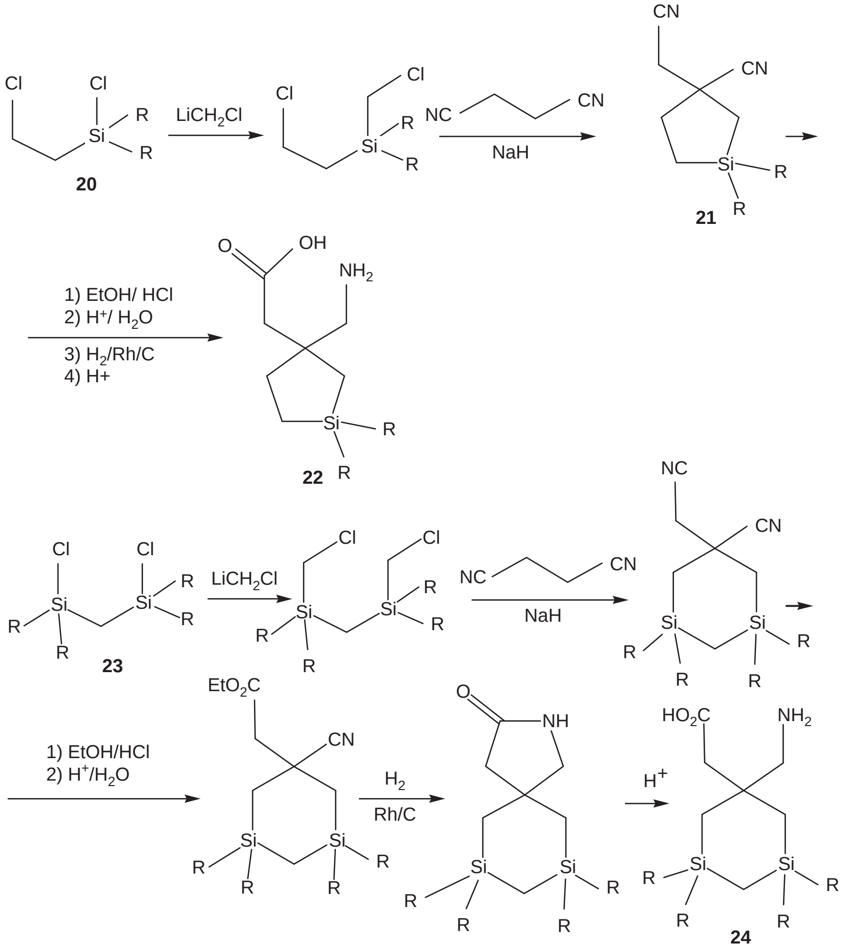
(*S*)-Venlafaxine (*S*)-**10** is a potent and selective serotonin reuptake inhibitor while its (*R*)-enantiomer was found to be a mixed serotonin/noradrenaline reuptake inhibitor. The serotonin reuptake inhibition was significantly reduced by sila-substitution. It changed also the monoamine reuptake inhibition profile. If (*S*)-sila-venlafaxine (*S*)-**11** may be considered a serotonin/noradrenaline-reuptake inhibitor, then (*R*)-**11** and *rac*-**11** exhibited quite different profiles with dominating noradrenaline reuptake inhibition. The potency at serotonin receptors has been reduced also by *rac*-**13** containing a five-membered ring but the dopamine transporter selectivity in this case increased (06OM1188). Elimination of the methoxy group from position 4 of the benzene ring (compound **12**) leads to a significant reduction in activity (06JOM(691)3589).

One of the adverse effects of clinically used venlafaxine **10** is nausea that may be connected with its mixed serotonin/noradrenaline profile. The selective noradrenaline-reuptake inhibitor sila-velafaxime (*R*)-**11** at oral administration effectively inhibited emetic episodes caused by emetogen (morphine) in the ferret emesis model (06BMCL2555). Intraperitoneally administered sila-venlafaxine (*R*)-**11** was able to reduce cisplatin-induced acute and delayed emesis (08TAP369).

Silicon derivatives of venlafaxine were also proposed for the treatment or prevention of psoriasis and panic disorder (04WOP2004075902).

Silacyclopentyl and silacyclohexyl analogues of the known antiepileptic gabapentin have been synthesized (04GBP2397576). Silacyclopentyl analogues **22** were prepared starting from 2-chloroethyl (chloro)silanes **20**. The interaction of chlorosilanes **20** with chloromethyl lithium and then with 1,2-dicyanoethane/NaH led to silacyclopentanes **21,** which after hydrolysis and hydrogenation gave **22**. Disilylmethanes **23** under similar conditions afforded 1,3-disilacyclohexanes **24** (Scheme 5).

Successful sila-modification of several peptides leading to new protease inhibitors (03CODD526) stimulated the elaboration of synthetic methods for the preparation of silicon-containing amino acids. Among these compounds α-amino acids-containing silacycles were synthesized

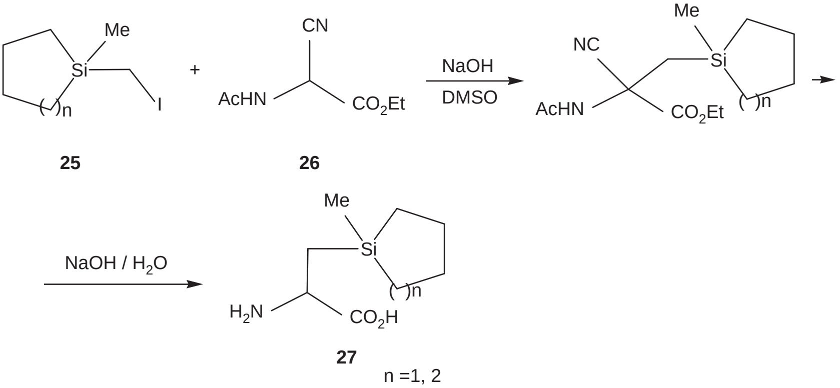


R = alkyl

Scheme 5

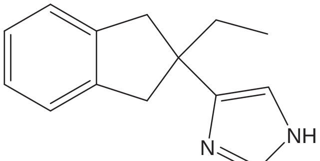
and investigated as potential pharmacokinetic agents. These silicon-containing amino acids are more lipophilic than their natural counterparts, and can be more resistant to proteases. Silacycloalkyl substituted amino acids **27** were prepared in 73–86% yield from iodomethylsilanes **25** and ethyl *N*-acetamidocyanoacetate **26** with alkali, followed by hydrolysis (Scheme 6) (97TE13695).

Silicon analogues **31** of α_2-adrenergic antagonist atipamezole **28** used in veterinary medicine were synthesized from *N*-protected 4-iodoimidazole derivatives. They were converted to their 4-imidazolyl anion with RMgX and then reacted with dichloro- or dimethoxysilaindane **30** to substitute one of the functional groups at the silicon atom. The alkyl

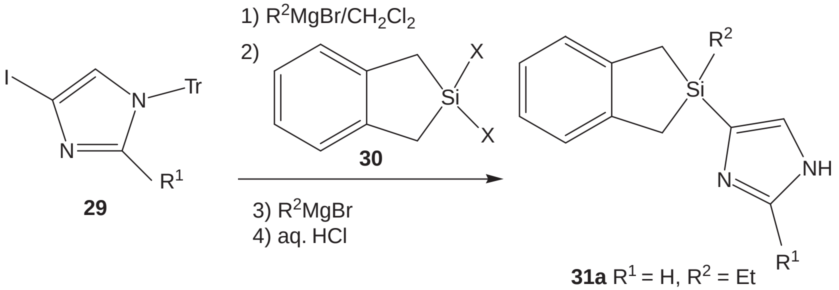


n =1, 2

Scheme 6



28



31a R^1 = H, R^2 = Et
31b R^1 = H, R^2 = Me
31c R^1 = Me; R^2 = Et

X = Cl, OMe

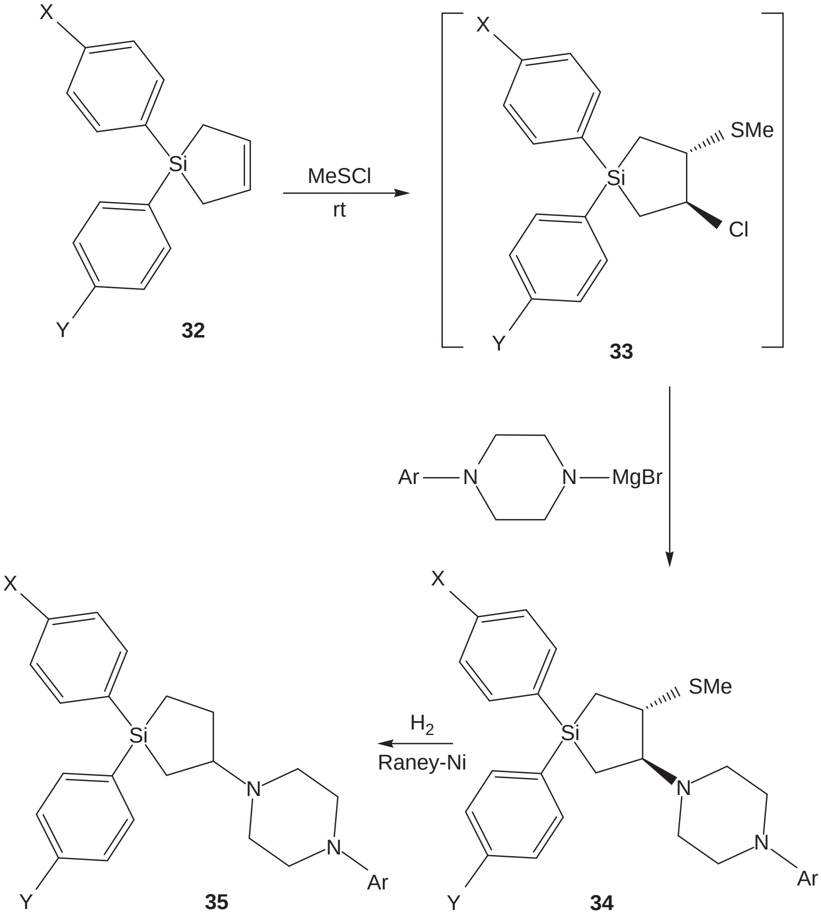
Scheme 7

substituent then was introduced by another Grignard reaction. Finally, N-deprotection gave **31** (Scheme 7) (96EJMC725).

Pharmacological studies showed that sila-substitution materials retained significant affinity to human α_2 adrenoreceptor subtypes α_{2A}, α_{2B} and α_{2C} but by one order of magnitude lower than that for the parent **28**.

Sila derivative **31a** and atipamezole **28** had similar pK_a values (5.70 ± 0.03 and 5.79 ± 0.02) and comparable pharmacokinetic properties in rats (96EJMC725).

3-(4-Arylpiperazino)-1-silacyclopentanes **35** were investigated as 5-hydroxytryptamine 5-HT_{2A} antagonists (93FRP2689892, 93FRP2689893, 93FRP2689894, 94BMCL415). They were prepared from 1,1-diaryl-1-silacyclopent-3-enes **32** by the addition of methanesulfenyl chloride followed by nucleophilic substitution of the chlorine atom in the intermediate **33** by various 4-arylpiperazines leading to the 3-(4-arylpiperazino)-4-methylthiosilacyclopentanes **34** in 22–63% yields. Hydrogenation of **34** over Raney nickel catalyst gave **35**. Analogous 4-arylpiperidyl and 4-aryl-1,2,5,6-tetrahydropyridyl derivatives were prepared in the same way (Scheme 8).



X, Y = H, F; Ar = Ph, 3- and 4-MeC_6H_4, 2-, 3- and 4-FC_6H_4, 4-ClC_6H_4, 4-HOC_6H_4, 2-Py, 2-pyrimidyl

Scheme 8

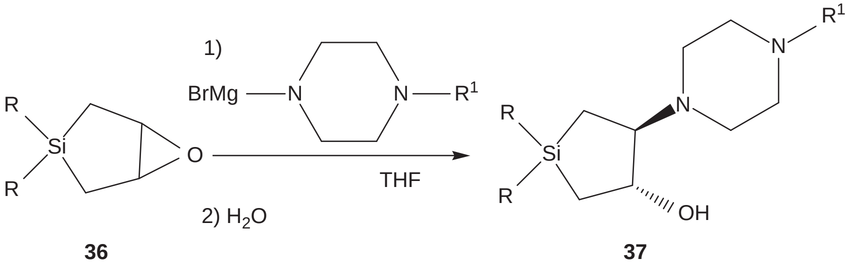
The diphenyl derivatives **35** (X = Y = H, Ar = Ph, 4-FC_6H_4) and di(4-fluorophenyl)derivative **35** (X = Y = F, Ar = Ph) exhibited the highest 5-HT_{2A} binding activity. The latter showed also the highest *in vivo* activity with a long duration of action at low dose and displayed a potent antagonist activity after oral administration against both mescaline and 1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane (DOI)-induced head-twitches in mice and rats.

6-Oxa-3-silabicyclo[3.1.0]hexanes with nitrogen and oxygen nucleophiles afforded antidepressant and anxiolytic *trans*-3,4-bifunctional silacyclopentanes (94JOM(484)119). For example, bicyclic **36** and magnesium piperazides gave *trans*-4-piperazino-1-silacyclopentan-3-ols **37** in 56–71% yield (Scheme 9). Compound **37** (R = Ph, R^1 = 4-FC_6H_4) showed high affinity for the 5-HT_{2A} receptor. The inhibitory concentration IC_{50}, the concentration required to cause a reduction of 50% in the amount of specific binding of [^{3}H] ketanserin, is 2.2 nM and after oral administration it effectively protected mice against mescaline-induced head-twitches.

Some silacycles containing a triazaspirodecenone fragment were investigated as β-secretase inhibitors for the treatment of Alzheimer's disease (07WOP20071183). The synthesis of cyclic silicon derivatives used dichlorodimethylsilane **38** and vinyl magnesium bromide in the presence of bis(cyclopentadienyl)titanium dichloride. Subsequent aziridination of intermediate 1,1-dimethyl-1-silacyclopent-3-ene **39** with Chloramine-T gave aziridine **40**. Its reduction followed by N-deprotection and isocyanide synthesis afforded isocyanide **41**. A further four component condensation gave a racemic product, which was subsequently resolved using chiral column chromatography on Chiralpack AD to optically active **42** and **43** (Scheme 10).

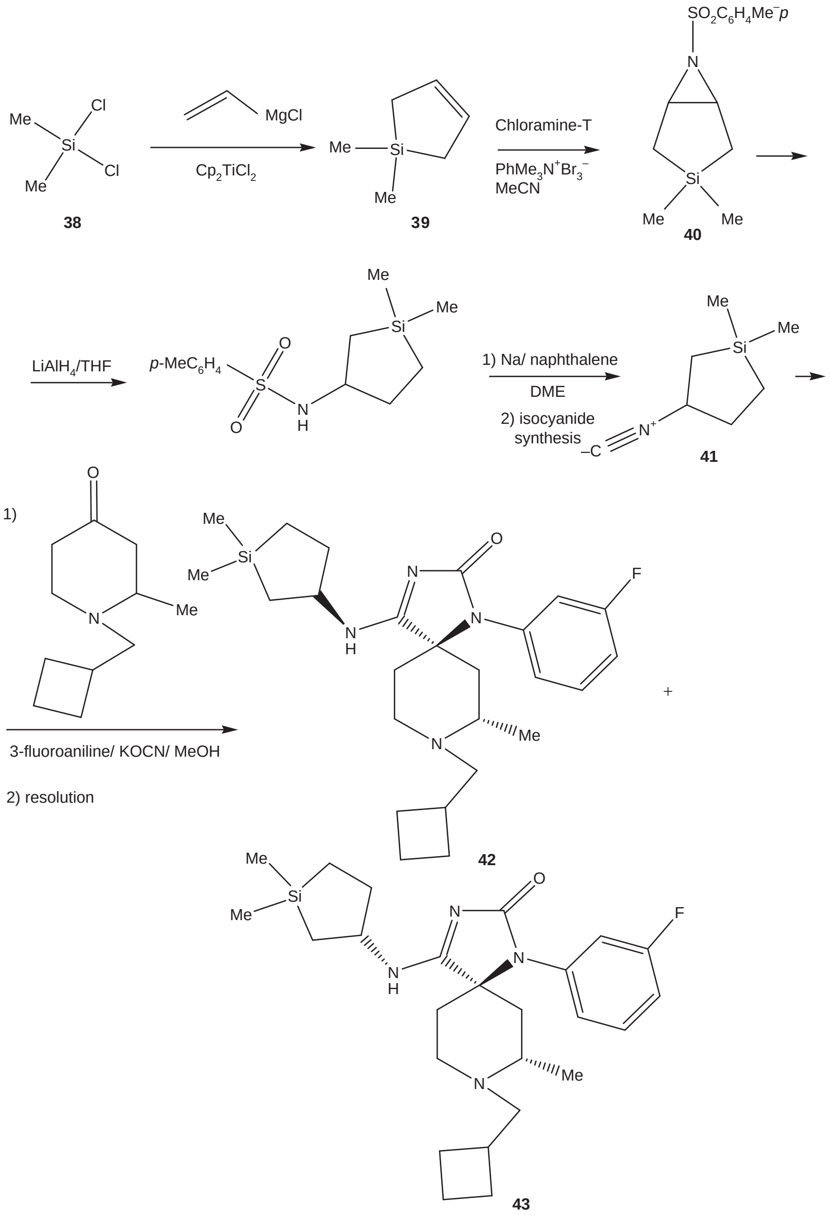
The structures of new potential cyclooxygenase (COX-2) inhibitors containing sila rings have been designed using theoretical methods (05MC215).

Silaantracenes **44**, **46** (78JOM(153)127) and 10,11-dihydro-5*H*-dibenzo[*b*, *f*]silepins **45**, **47** (78JOM(153)15, 76CCCC910) have been synthesized and



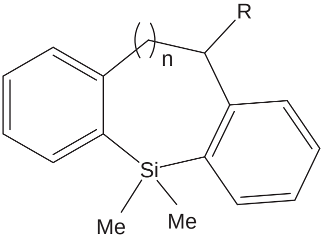
R, R^1 = Me, Ph, 4-FC_6H_4

Scheme 9

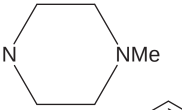


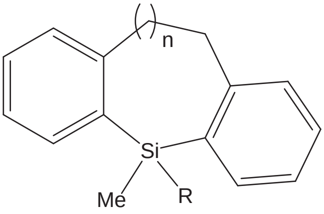
Scheme 10

tested for CNS activity. Compounds **44a**, **45a** (R = H) were converted to bromoderivatives **44b**, **45b** (R = Br) by *N*-bromosuccinimide and then heated with *N*-methylpiperazine to afford *N*-methylpiperazinoderivatives **44c**, **45c**. 3-Dimethylaminopropylsilanes **46b**, **47b** were obtained by the hydrosilylation of *N,N*-dimethylallylamine with hydrosilanes **46a**, **47a** (R = H). 3-Bromopropylsilane **47d** was brominated in position 10 by *N*-bromosuccinimide, dehydrobrominated by diazabicyclonene and aminated with diethylamine to give 5-methyl-5-(3-dimethylaminopropyl)-5*H*-dibenzo[*b,f*]silepine **48** (78JOM(153)15).

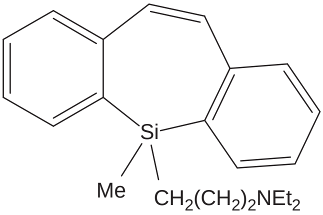


44 n = 0
45 n = 1
a R = H; **b** R = Br
c R =





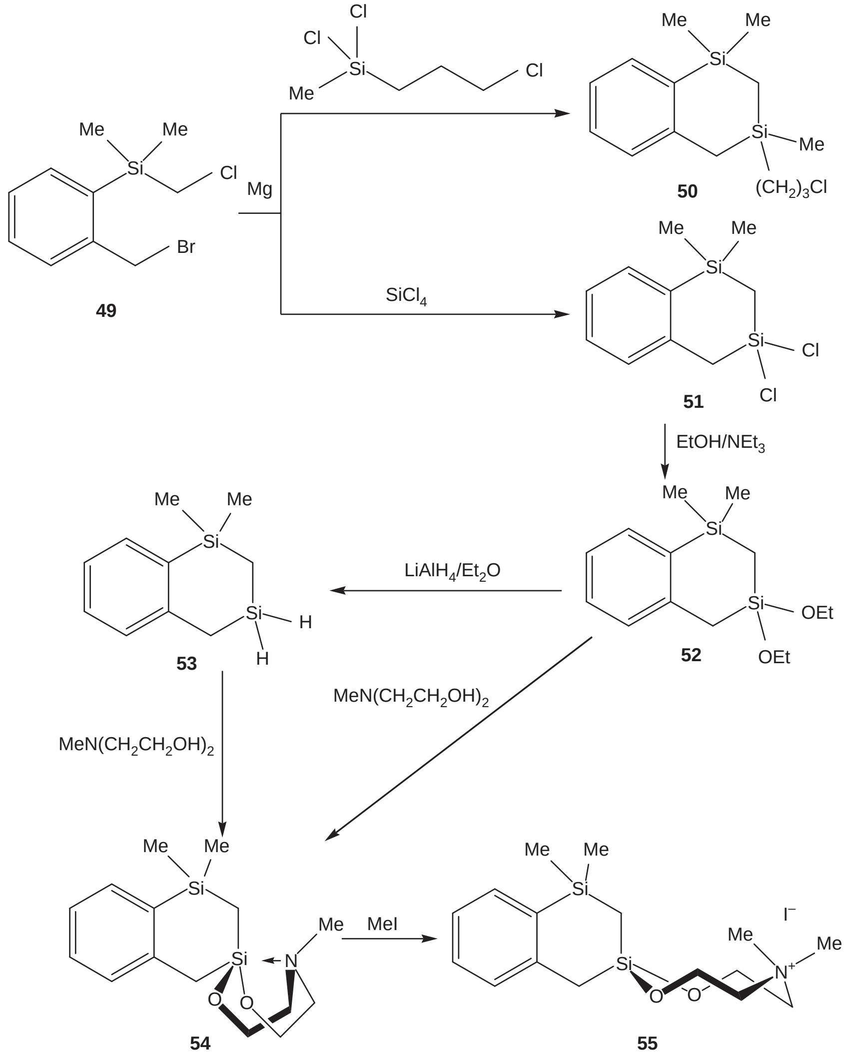
46 n = 0
47 n = 1
a R = H; **b** R = $(CH_2)_3NMe_2$
c R = $(CH_2)_3NEt_2$; **d** R = $(CH_2)_3Br$



48

Hydrochloride salts of **46b**, **47b**, **47c**, **48**, and maleate and fumarate salts of **45c** have been tested for CNS activity and exhibited a similar pattern but their potency was less than that of standard pharmacological agents (78JOM (153)127, 78JOM(153)15, 76CCCC910) and **44c** was inactive. In the catalepsy test, **45c** showed no effect even at the dose 10 mg kg^{-1} (76CCCC910).

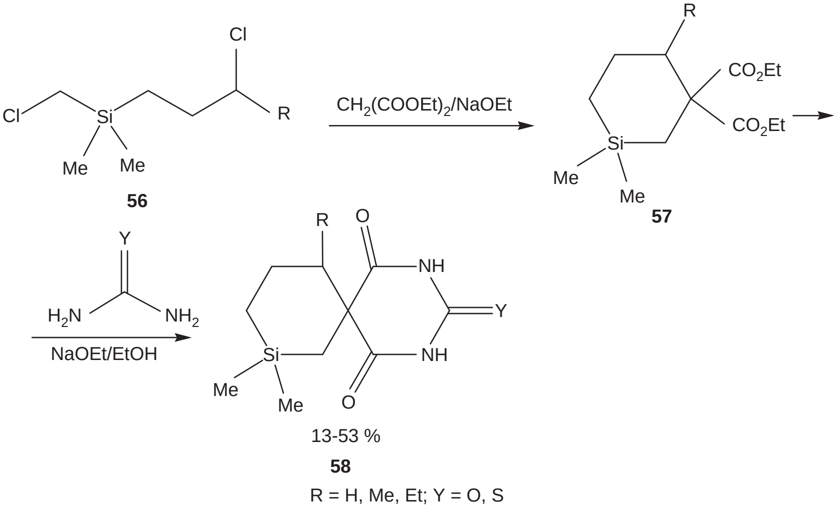
Derivatives of 1,3-disilabenzo[5,6]cyclohexene have been tested as psychotropic agents (03CHC813) (Scheme 11). (*o*-Bromomethylphenyl) dimethylchloromethylsilane (**49**) with magnesium and (3-chloropropyl) methyldichlorosilane or tetrachlorosilane afforded disilabenzocyclohexenes **50** or **51**, correspondingly. Ethanolysis of dichloroderivative **51** gave diethoxysilane **53**, which was converted into spirocyclic **54** containing a coordinative N→Si bond *via* dihydrosilane **53** or directly with *N*-methyldiethanolamine. Phenamine antagonists **50**, **54** and **55** also exhibit pronounced anticonvulsant activity while **54** has also a strong antistress activity.



Scheme 11

A series of silicon-containing spirobarbiturates **58** has been synthesized from 3,3-di(ethoxycarbonyl)-1-silacycloalkanes **57**, prepared from chloromethyl(3-chloropropyl)silanes **56** and diethyl malonate in the presence of sodium ethylate, and urea or thiourea (64JMC695) (Scheme 12). Analogous silacycloheptyl derivatives were prepared from (4-chlorobutyl)chloromethylsilanes similarly.

The acute toxicity for white mice and loss of their righting reflex after intraperitoneal injection of these compounds were investigated. The



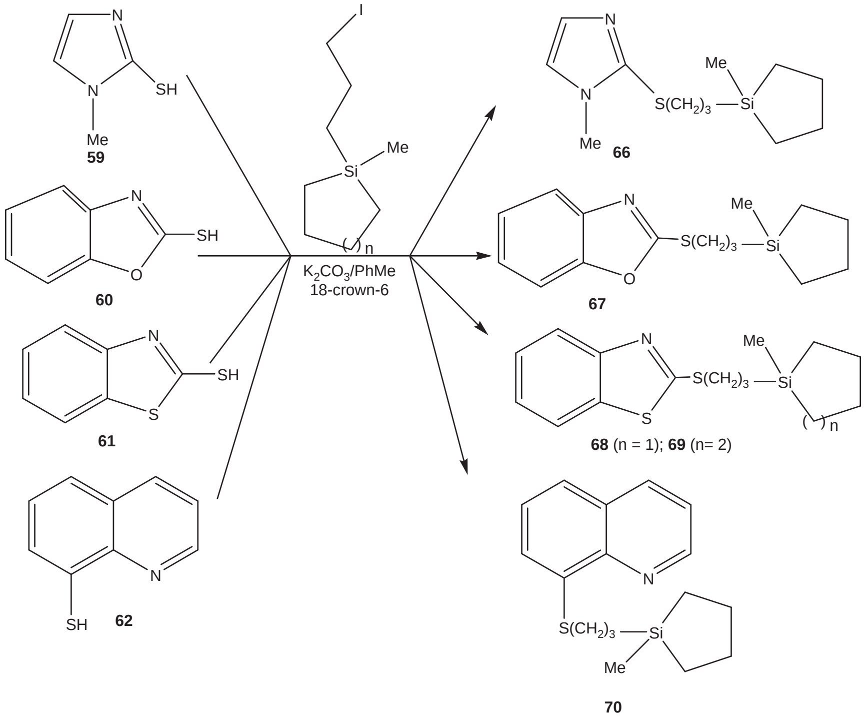
Scheme 12

therapeutic ratio of **58** was lower than that of cyclohexylspirobarbiturates. The silacycloheptyl derivative (Y = O) showed the shortest induction period and the highest therapeutic ratio among the silaspirobarbiturates. Sulfur analogues were the most toxic in this group (64JMC695).

3. CHOLESTEROL LEVEL LOWERING AND HYPOTENSIVE AGENTS

A simple method for the preparation of silacyclic derivatives of the *N*-, *O*- and *S*-heterocyclic thiols **59–65** was developed using the phase transfer catalytic system solid K_2CO_3/18-crown-6/toluene (02MBD307) (Scheme 13). The stronger base (KOH) led to the destruction of the alkylating agents. Substances **66–70** were obtained in yields up to 70% in a short time under mild conditions. The alkylation of thiols **63–65** simultaneously containing SH and NH bonds led to the S-, N-disubstituted derivatives **71–73**. 1,2,4-Triazole thiol **65** gave two isomeric products on alkylation: 1-[3-(1-methyl-1-silacyclopentyl) propyl]-5-[3-(1-methyl-1-silacyclopentyl)propyl]thio-1,2,4-triazole (**73a**) (32%) and 3-[3-(1-methyl-1-silacyclopentyl)propyl]thio-4-[3-(1-methyl-1-silacyclopentyl)propyl]-1,2,4-triazole (**73b**) (34%), correspondingly.

Benzoxazole and triazole derivatives **67** and **73b** showed the highest antiatherosclerotic activity among all the investigated silacyclic S-substituted heterocycles in mice maintained on high-cholesterol diet. They protected against an increase in serum low-density lipoprotein level and

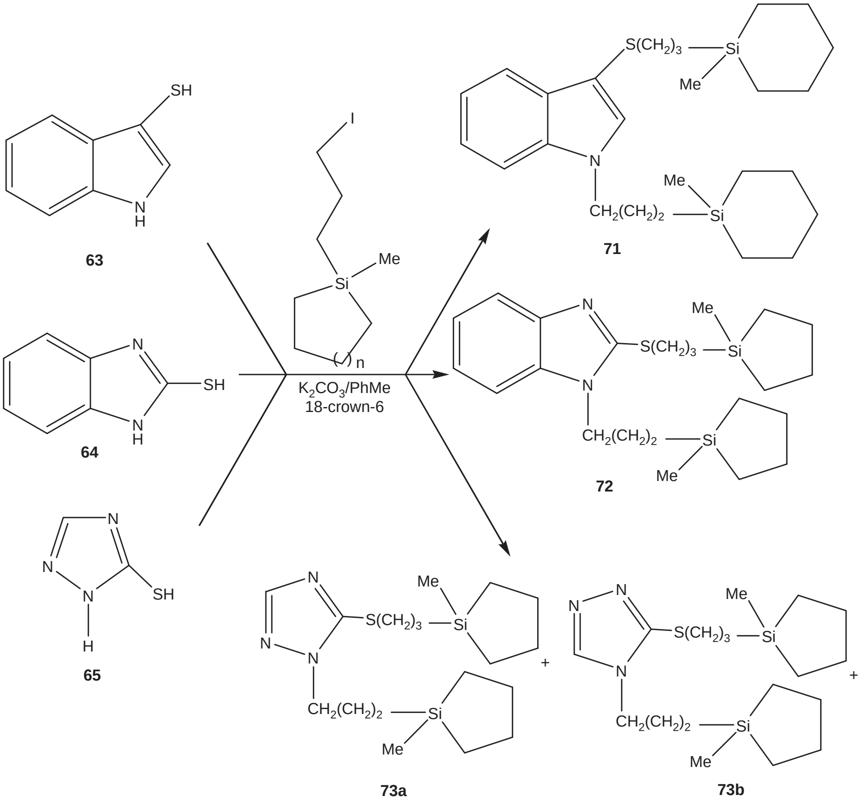


had the lowest atherogenecity coefficients K (0.073 and 0.091, correspondingly). A strong influence of the silacyclic substituent on the triazole ring on the cholesterol lowering action has been found. Compound **73a** has a slight effect on the atherosclerotic coefficient ($K = 0.799$). However, 4-N-substitution leads to a considerable increasing of activity: 3-[3-(1-methyl-1-silacyclopentyl)propyl]thio-4-[3-(1-methyl-1-silacyclopentyl)propyl]-1,2,4-triazole (**73b**) is nine times more active ($K = 0.091$) than isomer **73a**.

The silacyclopentyl derivative of imidazole **66** exhibited a high K ($K = 0.111$) and additionally showed a tendency to increase the high-density lipoprotein level. The insertion of an additional methylene group into the five-membered silacyclopentane ring leads to decrease of activity ($K = 0.200$ for **68** and 0.401 for **69**) while benzoxazole **67** is three times more active than benzothiazole **68**.

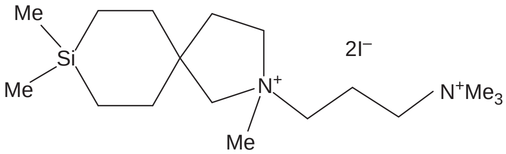
These silacyclic compounds had a weak influence on vasodilatation on the isolated perfused rabbit ear blood vessels even in at $50\,\mu\text{g}\,\text{ml}^{-1}$ dose. The highest relaxation effect (18% at $10\,\mu\text{g}\,\text{ml}^{-1}$) was found for imidazole **66** (02MBD307).

The dimethiodide of *N*-(3-dimethylaminopropyl)-8,8-dimethyl-8-sila-2-azaspiro[4.5]decane (**74**) (see synthesis in Scheme 15) when administered



Scheme 13

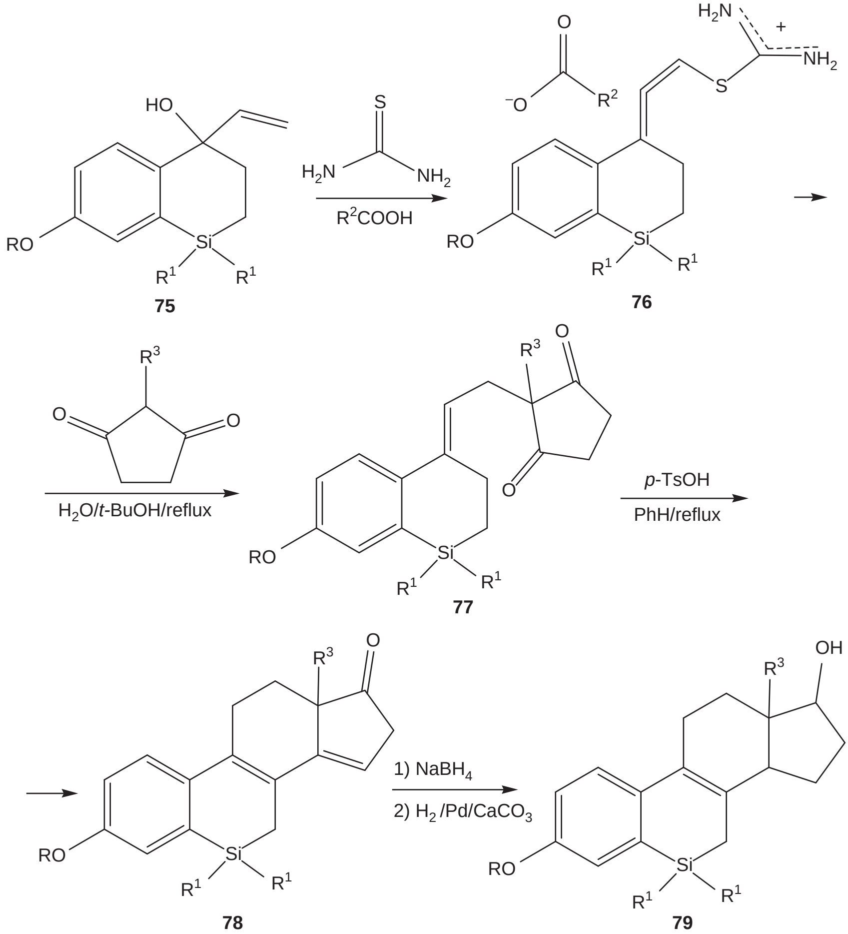
intravenously in anaesthetized dogs lowered their blood pressure by 40% at a dosage of 10 mg kg^{-1} (73JHC737).



74

4. SILA-STEROIDS

Silicon-containing steroids were synthesized as potential estrogenic agents (70USP3529005, 72USP3637782, 75TE2363), antiestrogenic and antifertility agents (75TE2369). However, none of the studied compounds showed significant activity. Generally, vinyl derivatives **75** with thiourea and aliphatic carboxylic acids gave isothiuronium salts **76**. These intermediates and cyclic *β*-diketones at reflux led to silicon-containing diketones **77**, which in the presence of an acidic catalyst (e.g., *p*-toluene sulfonic acid) were cyclized to silasteroid ring **78** (yields up to 40%). The reduction of the carbonyl group by $NaBH_4$ and further hydrogenation in the presence of palladium on calcium carbonate gave 3-alkoxy-6,6-dimethyl-6-sila-17*β*-hydroxyestra-1,3,5(10),8-tetraenes **79** (Scheme 14).

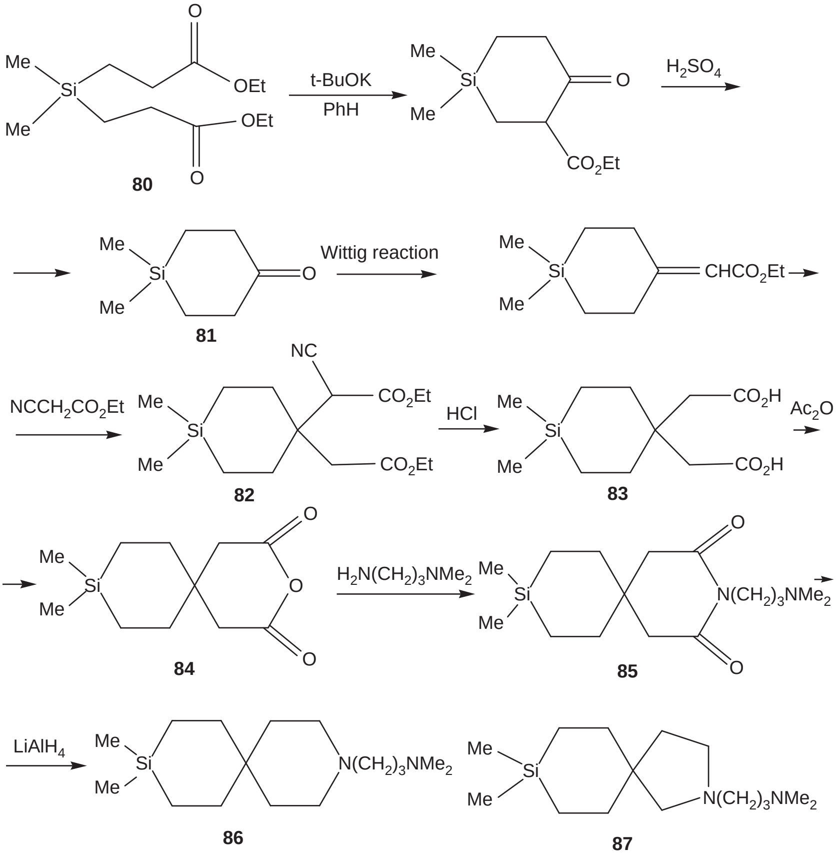


R-R^3 =alkyl

Scheme 14

5. CYTOTOXIC AGENTS

The first investigation of silacyclic derivatives as cytotoxic agents was published in 1973 (73JHC737, 73GEP2243550) where synthesis of silicon analogues of known antineoplastic agents azaspiranes (73JHC731) was described. Thus, diester **80** with *t*-BuOK and then with sulfuric acid led to ketone **81** that underwent a Witting reaction, followed by conjugate addition of ethyl cyanoacetate leading to diester **82**. Its hydrolysis and decarboxylation with HCl gave the diacid **83** that was converted to anhydride **84**. Treatment of this anhydride with 3-dimethylaminopropylamine afforded spiroimide **85**. Further reduction with LiAlH$_4$ produced *N*-(3-dimethylaminopropyl)-9,9-dimethyl-9-sila-3-azaspiro[5.5]undecane **86** (Scheme 15).



Scheme 15

A similar scheme was used to prepare compounds with ethyl groups at the silicon atom and the compounds containing a five-membered aza-ring instead of the six-membered ring **87**.

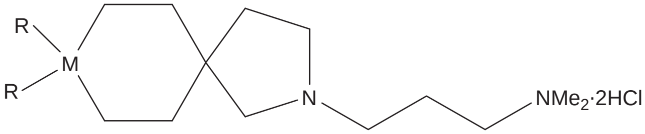
The dihydrochloride salt of silaazaspirane **86** inhibited completely human mammary cancer cell growth at a concentration of 1 μg ml^{-1}. The analogue with the five-membered aza-ring **87** was 10 times less active (73JHC737).

A comparison of cytotoxic and immunomodulating properties of azaspiranes is presented in Table 1 (85IP201, 87IJI621, 89ADD231, 90JMC2963).

Cytotoxic and immunomodulating activities of azaspiranes strongly depend on the nature of the element M in position 8 and on the type of substituents R bound to it. Ethyl derivatives were found to be more active than methyl, the germanium-containing compound being the most active in these tests.

Silacycloalkyl substituted heteroaromatic aldehydes (05AOC1109), ketones (07CHC143) thiosemicarbazones (05AOC1109), oximes (03BCA299) and sulfides (02MBD45) have been synthesized and investigated *in vitro* against human fibrosarcoma (HT-1080) and mouse hepatoma (MG-22A) cells. Silicon-containing heterocyclic aldehydes were prepared from furan- and thiophenecarbaldehydes using lithium *N*-methylpiperazide (LNMP)/ butyl lithium/chlorocyclosilane/water as the sequence of reagents. The second route to silyl-substituted aldehydes proceeded by carbonyl blocking on conversion to a diethylacetal, metallation with *n*-BuLi and substitution of lithium atoms for the corresponding electrophile. Deprotection of the

Table 1 Cytotoxic and immunomodulating properties of azaspiranes

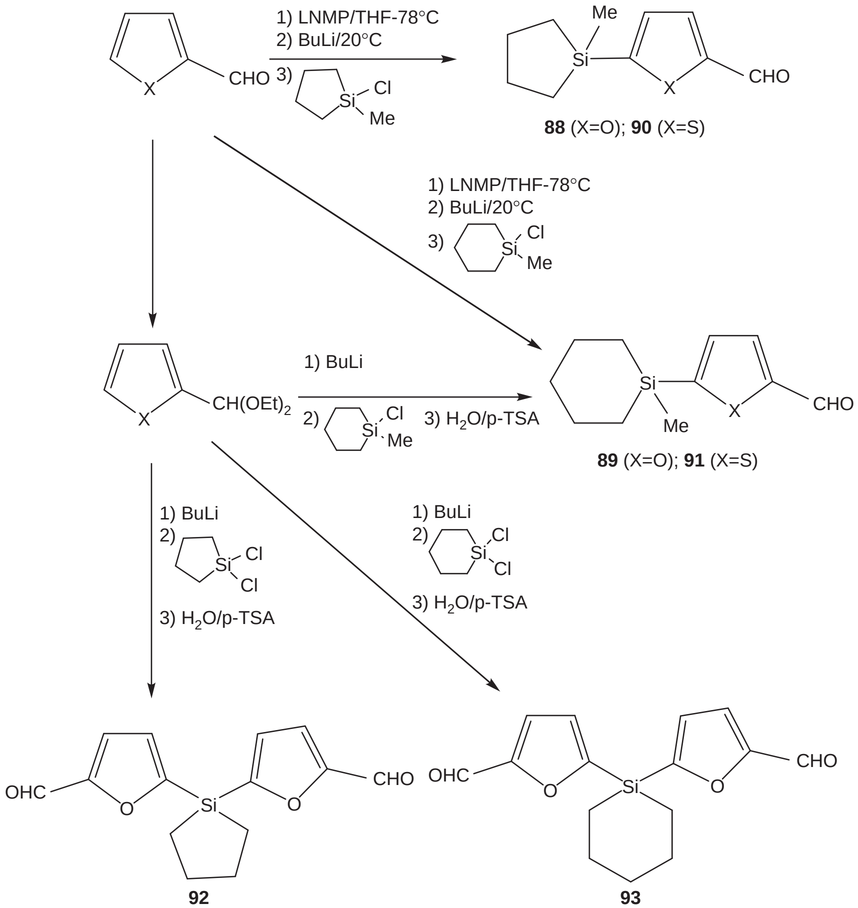


Activity	R	M		
		C	Si	Ge
Antiarthritic, % (in rats)	Me	12	0	–
	Et	57	92	100
Induction of suppressors, %	Me	0	0	–
	Et	88	63	100
IC_{50}[a](μM) HT-29 colony-formation	Me	170	80	–
	Et	19	–	12

[a] IC_{50} – dose required to inhibit human colon carcinoma cells HT-29 colony formation by 50% relative to control.

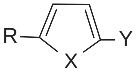
aldehyde used a catalytic amount of *p*-toluenesulfonic acid (*p*-TSA) (Scheme 16). Aldehydes **88–93** were converted to thiosemicarbazones by condensation with thiosemicarbazide.

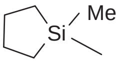
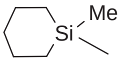
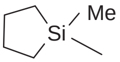
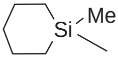
The highest cytotoxic activity on HT-1080 cells was recorded for thiosemicarbazones of furan aldehydes **88** and **89** (IC_{50} 2.7 or 1 μg ml^{-1}, correspondingly). The latter also was the most active against M-22A cells and readily increased the NO concentration in the cultural medium of the HT-1080 line (05AOC1109). High cytotoxicity (1–3 μg ml^{-1}) was observed for the nitrovinyl derivatives (Table 2), while the compounds containing two heteroaromatic substituents at the silicon atom were less active (Table 3). In most cases silacyclohexyl derivatives exhibited higher cytotoxicity against HT-1080 and MG-22A cells than silacyclopentyl derivatives (Tables 2 and 3).



Scheme 16

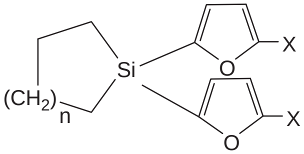
Table 2 Influence of a silacycloalkyl substituent on cytotoxicity (LC_{50}, $\mu g\,ml^{-1}$, CV[a]) against human fibrosarcoma HT-1080 (08ISOC112)



Y	X = O		X = S	
	R		R	
				
CHO	3	29	5	4
$CH=NNHCSNH_2$	2.7	1	100	17
$CMe=NOH$	14	1	10	1
$CH=N(O)Me$	50	31	34	35
$CH=CHNO_2$	1	3	3	3

[a] LC_{50} – concentration providing 50% cell killing effect; CV – crystal violet coloration.

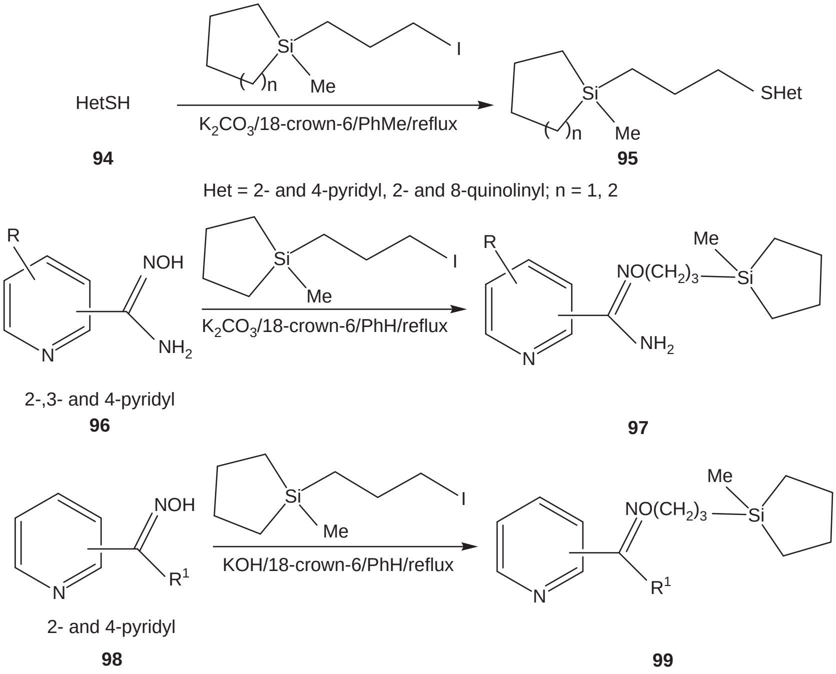
Table 3 Cytotoxicity (LC_{50}, $\mu g\,ml^{-1}$)[a] of heterocyclic dialdehydes and their thiosemicarbazones (05AOC1109)



n	X	HT-1080		MG-22A	
		CV	MTT	CV	MTT
1	CHO	59	44	29	29
2	CHO	15	11	24	10
1	$CH=NNHCSNH_2$	34	34	100	61
2	$CH=NNHCSNH_2$	5.7	4.5	6.4	5.2

[a] HT-1080 – human fibrosarcoma; MG-22A – mouse hepatoma; LC_{50} – concentration providing 50% cell killing effect; CV – crystal violet coloration; MTT – 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-2*H*-tetrazolium bromide coloration.

Silacycloalkyl pyridine and quinoline sulfides **95** have been prepared in yields up to 81% using a phase transfer catalyst (PTC) consisting of thiol **94** (1-(3-iodopropyl)-1-methylsilacycloalkane) and solid K_2CO_3/



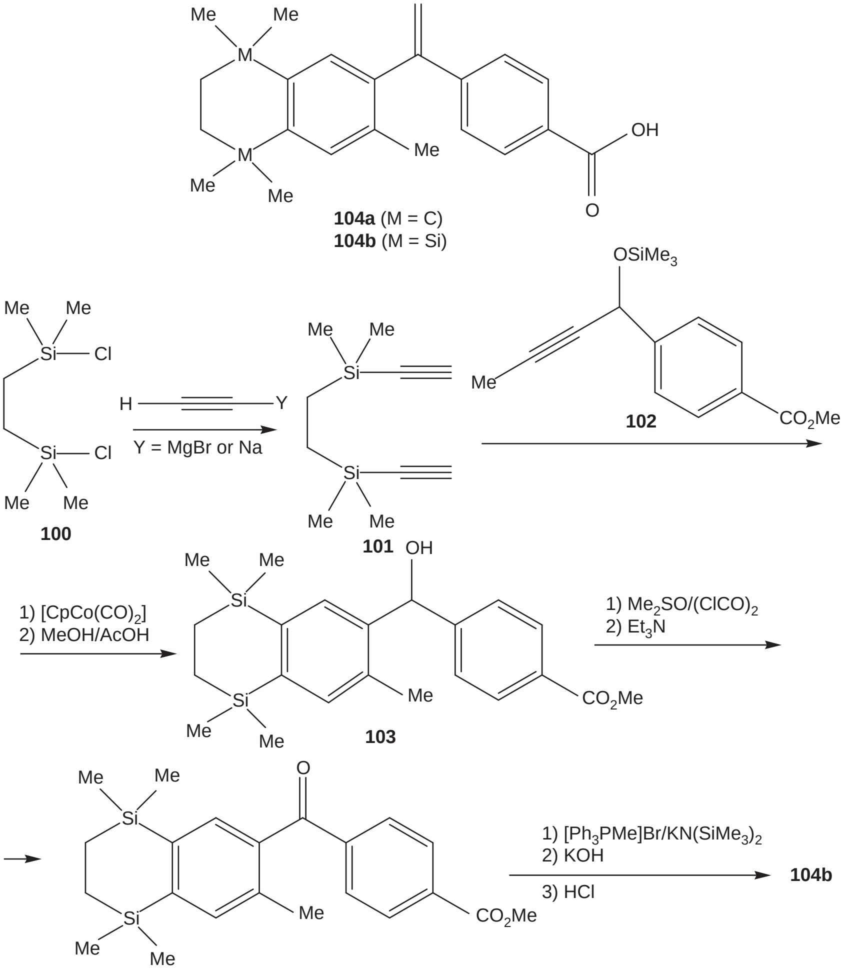
Het = 2- and 4-pyridyl, 2- and 8-quinolinyl; n = 1, 2

R, R^1 = H, Me

Scheme 17

18-crown-6/PhMe (02MBD45). Similarly *O*-[3-(1-methyl-1-silacyclalkyl)-propyl] oximes **97** were prepared from the corresponding amidoximes **96**. For oxime **98** (1-(3-iodopropyl)-1-methylsilacyclopentane)/solid KOH/18-crown-6/PhH was the most efficient PTC in the synthesis of aldoxime and ketoxime *O*-ethers **99** (03BCA299) (Scheme 17). Compound **95** (Het = 4-pyridyl; $n = 1$) exhibited high cytotoxicity on HT-1080 (IC_{50} $3\,\mu g\,ml^{-1}$) and M-22A cells ($IC_{50} < 1\,\mu g\,ml^{-1}$). Among oxime derivatives 2-pyridyl aldoxime *O*-ether **99** ($R^1 = H$) showed high activity (IC_{50} $1.85\,\mu g\,ml^{-1}$) on the HT-1080 cell line.

Bexarotene (Targretin®, **104a**) is a selective agonist of retinoid receptors (RXR) that is in therapeutic use for treatment of cutaneous T-cell lymphoma. Two-fold sila-substitution (C/Si exchange) in the saturated ring of the tetrahydronaphthalene skeleton leads to disila-bexarotene **104b**. Its synthesis starts with the conversion of 1,2-bis(chlorodimethylsilyl) ethane (**100**) to dialkyne **101**, which underwent alkyne trimerization with ester **102** in the presence of a cobalt catalyst leading to silacycle **103**. The

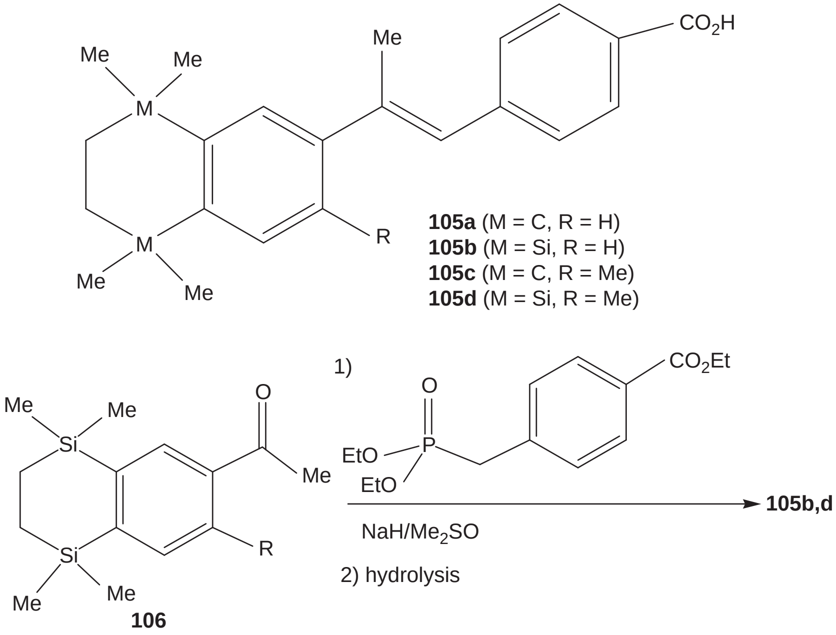


Scheme 18

oxidation and olefination of this intermediate afforded after hydrolysis **104b** (Scheme 18). Disila-bexarotene **104b** showed a high RXR agonist activity comparable to that of bexarotene (05OM3192).

Silicon analogues **105b,d** of known pan-RAR selective retinoid agonist TTNPB **105a** were synthesized from ketones **106** by a Wittig reaction followed by hydrolysis (07CBC1688) (Scheme 19).

Compounds **105b** and **105d** showed strong RARα agonist binding similar to that of carbon analogues **105a,c**, and induced differentiation

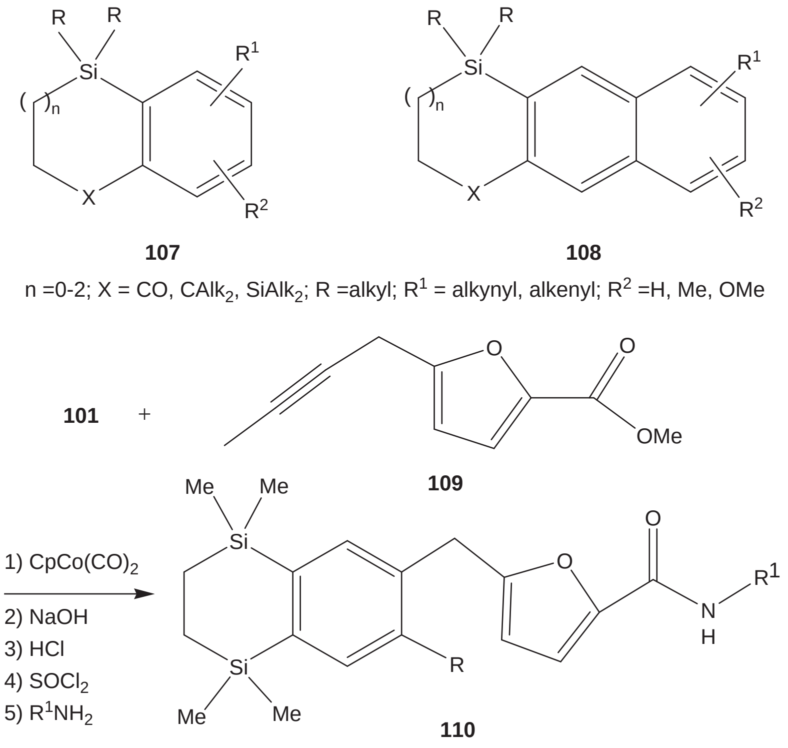


Scheme 19

and apoptosis of promyelotic leukemia NB4 cells. The 3-methyl derivatives had some reduced pan-RAR activation efficacy but they displayed RXR agonist activity and also similar differentiation and apoptosis induction in NB4 cells.

The crystal structures of **104a** and **104b** bound to a complex consisting of the RARβ ligand binding domain with the second nuclear receptor box peptide of the SRC-1 coactivator show different contacts with helix H11 (07CBC1688).

Silacyclic compounds **107** and **108** were synthesized as new ligands for retinoid receptors generally by the above method (04WOP2004048390, 04WOP2004048391). Cobalt-catalyzed cyclotrimerization used for the synthesis of disila-bexarotene (Scheme 18, **101–103**) was extended to prepare diverse sila-heterocycles. Thus, amides **110** have been synthesized from diethynyl compound **101** and alkyne **109** in the presence of CpCo (CO)$_2$, followed by hydrolysis and amination (Scheme 20). They were gonadotropin-releasing hormone (GnRH) antagonists potentially useful for the treatment of diseases related to GnRH, such as cancer (leukemia therapy), HIV and Alzheimer's disease (04WOP2004045625, 05WOP2005005443).



n =0-2; X = CO, $CAlk_2$, $SiAlk_2$; R =alkyl; R^1 = alkynyl, alkenyl; R^2 =H, Me, OMe

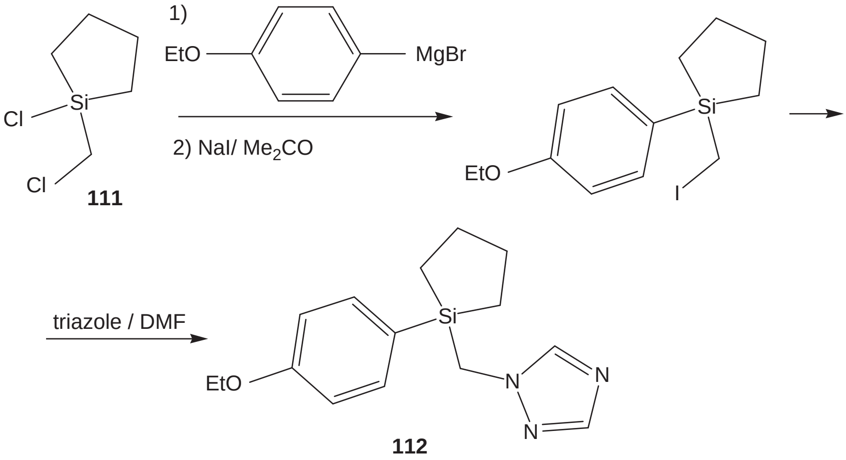
R = H, alkyl, hal; R^1 = alkyl, cycloalkyl, aryl, hetaryl

Scheme 20

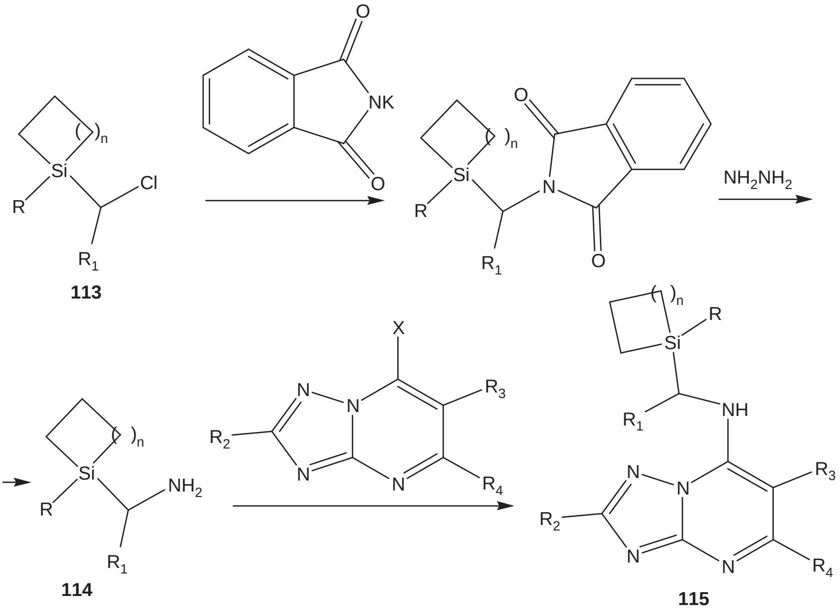
6. FUNGICIDES AND BACTERICIDES

Triazolyl derivatives of five- and six-membered silacyclanes exhibited a broad spectrum of fungicidal activity. For example, silacyclopentane **112** protected plants against *Alternaria mali* at 50 ppm. It has been synthesized from 1-chloro-1-chloromethyl-1-silacyclopentane **111** and 4-ethoxyphenyl magnesium bromide and then with the triazole (94JPP06256357, 98BKCS358, 98PS138) (Scheme 21). The fungicidal activity of this type of compounds is strongly dependent upon the phenyl para-substituent and increases in the following order H< EtO< Ph< Cl< F. The *p*-fluorophenyl derivative showed significant activity *in vitro* with a broad spectrum comparable to flusilazole (98PS138).

1-Haloalkyl-1-silacycloalkanes were also used in the synthesis of fungicidal triazolopyrimidines (06WOP2006066873). Thus, **113** on treatment with potassium phthalimide in DMF, followed by hydrazinolysis afforded amines **114**. Their reaction with 7-halotriazolo[1,5-*a*]pyrimidines gave **115** (Scheme 22).



Scheme 21



n = 1- 4; R = alkyl, R^1 = H, Me, CF_3, R^2 = H, SH; R^3= Ar; R^4 = H, F, Cl, Me

Scheme 22

Products **115** protected tomato plants against *Alternaria solani* and *Botrytis cinerea*, grape against powdery mildew, wheat against brown rust and Septoria leaf spot, barley against net blotch and rice plants against rice blast. For example, silacyclopentane derivative **115** ($n = 2$, R = Me, $R^1 = R^2 = H$, R^3 = 2,4,6-trifluorophenyl, R^4 = Cl) at 200 ppm inhibited *Pyricularia oryzae* infestation on 3-weeks-old rice plants to at least 80% (06WOP2006066873).

The dimaleate salt of 5,5-dimethyl-10-(4-methylpiperazino)-10,11-dihydro-5*H*-dibenzo[*b*,*f*]silepin (**45c**) exhibited some antibacterial activity *in vitro* toward *Mycobacterium tuberculosis* H37Rv (minimum inhibitory concentration 12,5 $\mu g\,ml^{-1}$), *Streptococcus* β-*haemolyticus* (25 $\mu g\,ml^{-1}$) and *Staphylococcus pyogenes aureus* (25 $\mu g\,ml^{-1}$) (76CCCC910).

7. ODORANTS

Organosilicon compounds, particularly silacyclic, have been investigated as odorants (04CAB1921). Usually they have a very similar odor to that of their organic analogues. But recently more data appear showing quite different olfactory properties, both in quality and intensity, for silicon and carbon analogues, opening new possibilities for the fragrance industry.

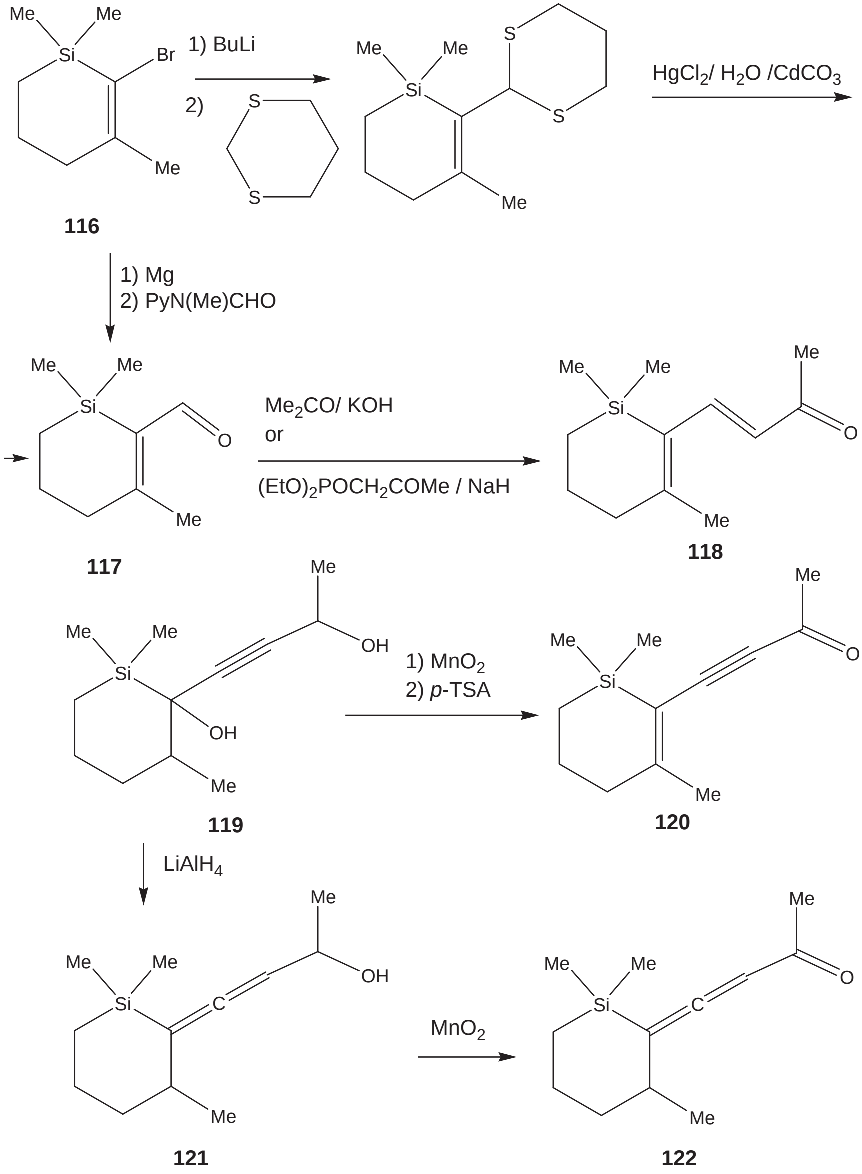
Sila analogues of the natural perfumes *β*-cyclocitral and *β*-ionone have been synthesized from 2-bromo-1,1,3-trimethyl-1-silacyclohex-2-ene **116**. Thus, **116** with 1,3-dithian-2-yllithium and then with $HgCl_2$/H_2O in the presence of $CdCO_3$ gave sila-*β*-cyclocitral **117** in 30% yield. A higher yield (40%) has been achieved by conversion of **116** into a Grignard reagent followed by formylation with 2-[formyl(methyl)amino]pyridine (85LA950). Condensation of sila-*β*-cyclocitral **117** with acetone and KOH or a Wittig reaction led to sila-*β*-ionone **118** in 44% and 52% yields, respectively (Scheme 23).

Compound **117** had a camphoric odor with additional green notes while its carbon analogue smells like mint and even turpentine. The sila-*β*-ionone **118** and *β*-ionone have similarly strong violet and freesia odors.

Oxidation of pentynediol **119** by MnO_2 followed by interaction with *p*-TSA led to acetylenic derivative **120** that possesses extremely strong and diffusive violet and freesia, raspberry, woody, odors similar to *β*-ionone. But the odor of allene derivative **122**, also prepared from diol **119** by dehydration with $LiAlH_4$ and further oxidation with MnO_2, was rather unpleasant (85LA950).

Silicon analogues **124** of the powerful musk odorant Versalide **123** were synthesized by a cobalt-catalyzed cyclization of 1,2-bis(ethynyldimethylsilyl)ethane (**101**) and alkynes (07OM1295) (Scheme 24).

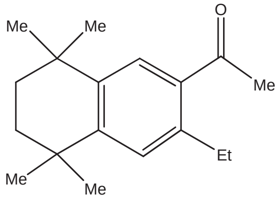
Versalide **123** possesses a typical strong and distinct musk odor. Disila-versalide **124b** still smells musky, but much less than **123**. The silicon compound **124a** containing a methyl group instead of an ethyl group in position 3 smells too weak to be considered as an odorant. The musk odor also completely disappears for the versalide derivative unsubstituted in position 3. However, its silicon analogue **124c** has a



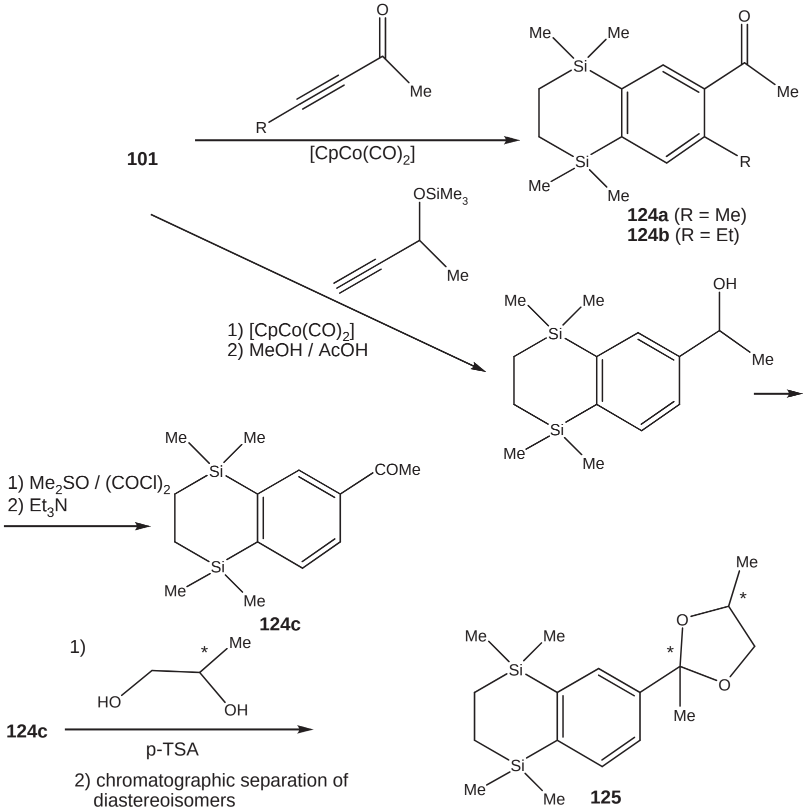
Scheme 23

weak, slightly musky and fruity odor with the fruity aspects in the direction of blackberries (07CBC1447, 08CBD920).

Compound **124c** was converted to silicon analogue **125**, related to natural odorant Okoumal **126**, by interaction with *R*- or *S*-propane-1,2-diol and *p*-TSA (Scheme 24).



123 (versalide)

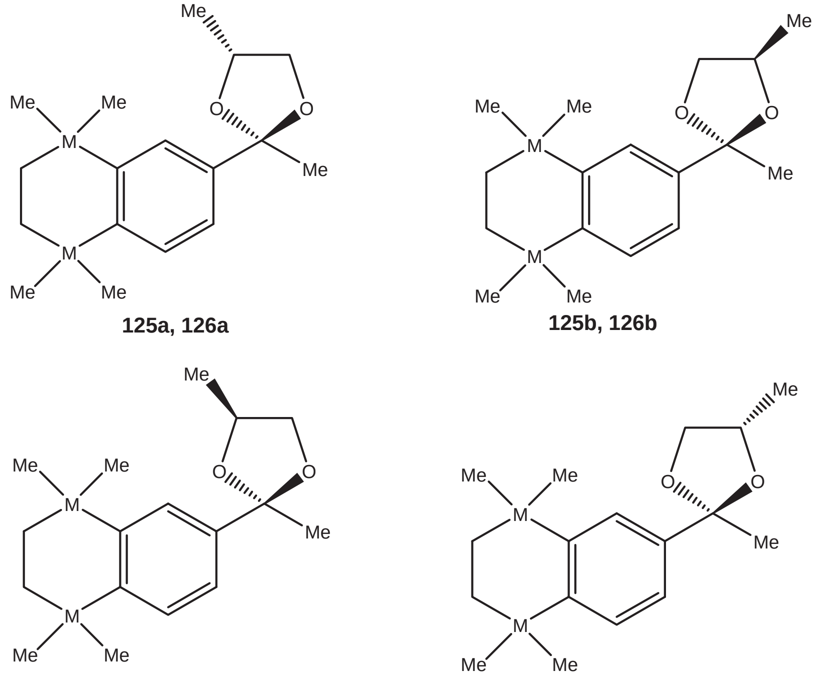


Scheme 24

Okoumal **126**, a powerful ambergris odorant, has two stereogenic centers in the 1,3-dioxolane ring and therefore there are four stereoisomers of **126a–d**. The four stereoisomers of disila-okoumal **125** were obtained by chromatographic separation of the racemate prepared by Scheme 24.

Compound **126a** has a strong, pronounced, typical ambery odor of the okoumal-karanal family. Disila analogue **125a** possesses a pronounced, typically ambery odor with woody aspects. It was the strongest disila-okoumal odorant enantiomer, but clearly weaker than **126a**. Compound **125b** was very weak to odorless, with only a slightly ambery-woody odor. The odor of **126b** is also very weak and ambery with woody facets. Compound **125c** has an ambery odor with woody aspects, characteristically okoumal-like, very close in intensity to **125a**. Compound **126c** shows ambery odor, typical in the okoumal-karanal family, with woody aspects stronger than that of **126d**. The odor of **125d** is very weak to odorless, only faintly ambery-woody. Finally, **126d** possesses weak, ambery, with a woody facets odor, somewhat okoumal-like. Disila-okoumal stereoisomers **125a** and **125c** with an *R* configuration at the 2-position had the lowest odor threshold values (0.31 ng per liter of air) among all eight tested compounds (Scheme 25).

1,3,5,7-Tetrasilaadamantanes **127** exhibit mosquito repellent properties (71GEP2123343, 71GEP2123345). For example, silaadamantane **127** (R = Me), prepared by heating cyclic dimethylsilylmethylene trimer with $AlBr_3$ at 100 °C for 2 h with distillation of Me_4Si, was active against *Aedes aegypti*.



125a, 126a

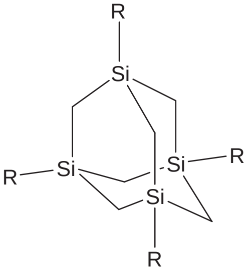
125b, 126b

125c, 126c

125d, 126d

125a-d (M = Si); **126a-d** (M = C)

Scheme 25



127

R=Cl, Br, Me

8. TOXICITY OF SILACYCLANES

The toxicity of silacyclanes depends on the type of cyclic compound and varies from toxic salts of diamines **46c** (LD_{50} 49 mg kg^{-1}) [3], **86** (73JHC737, 89ADD231) and **87** (LD_{50} 100–137 mg kg^{-1}) (73JHC737) to slightly toxic disilaspirocyclic **54** (LD_{50} 5000 mg kg^{-1}). The toxicity of its methiodide **55** is higher and is similar to that of 3-chloropropylderivative **50** (LD_{50} 355 mg kg^{-1}) (03CHC813).

The toxicity of another group of spirocyclic compounds, the silaspirobarbiturates **58** (LD_{50} 140–1000 mg kg^{-1}), depends on the size of the silacycle and on the type of heteroatom in the barbiturate ring. Those containing a seven-membered ring are more toxic than those with a six-membered ring, and thiobarbiturates are even more toxic than the corresponding barbiturates. The seven-membered silaspirothiobarbiturate (LD_{50} 140 mg kg^{-1}) is the most toxic of this class (64JMC695).

Silacycloalkyl(hetaryl)sulfides **67–73** showing high-cholesterol lowering activity have low acute toxicity (LD_{50} 580–800 mg kg^{-1}). Only *N*-methylimidazole **66** exhibits medium toxicity (LD_{50} 375 mg kg^{-1}).

5-Silacycloalkyl substituted 2-acetylfurans (LD_{50} 960–1000 mg kg^{-1}) are less toxic than analogous thiophene derivatives (LD_{50} 718–930 mg kg^{-1}) (07CHC143). They are also less toxic than the corresponding furans **88**, **89** (LD_{50} 227–625 mg kg^{-1}) and thiophenes **90**, **91** (LD_{50} 319–370 mg kg^{-1}) aldehyde derivatives. The cytotoxic thiosemicarbazones of these aldehydes are less toxic (LD_{50} 800–1900 mg kg^{-1}) (05AOC1109).

REFERENCES

64JMC695	R. J. Fessenden, J. G. Larsen, M. D. Coon, and J. S. Fessenden, *J. Med. Chem.*, **7**, 695 (1964).
70USP3529005	S. Barcza, *US Pat.* 3529005 (1970) [*Chem. Abstr.*, **73**, 120818b (1970)].

71GEP2123343 A. J. Barry and J. M. Klosowski, *Ger. Pat.* 2123343 (1971) [*Chem. Abstr.*, **76**, 72650d (1972)].

71GEP2123345 C. L. Frye, D. R. Weyenberg, and J. M. Klosowski, *Ger. Pat.* 2123345 (1971) [*Chem. Abstr.*, **76**, 85918x (1972)].

72USP3637782 S. Barcza, *US Pat.* 3637782 (1972) [*Chem. Abstr.*, **76**, 154021p (1972)].

73GEP2243550 L. M. Rice, *Ger. Pat.* 2243550 (1973) [*Chem. Abstr.*, **79**, 42680h (1973)].

73JHC731 L. M. Rice, B. S. Sheth, and J. W. Wheeler, *J. Heterocycl. Chem.*, **10**, 731 (1973).

73JHC737 L. M. Rice, B. S. Sheth, and J. W. Wheeler, *J. Heterocycl. Chem.*, **10**, 737 (1973).

75TE2363 S. Barcza and C. W. Hoffman, *Tetrahedron*, **31**, 2363 (1975).

75TE2369 C. G. Pitt, A. E. Friedman, D. Rector, and M. C. Wani, *Tetrahedron*, **31**, 2369 (1975).

76CCCC910 K. Šindelaž, J. O. Jilek, V. Bartl, J. Metyšova, B. Kakaè, J. Holubek, E. Svatek, J. Pomykaèek, and M. Protiva, *Collect Czech. Chem. Commun.*, **41**, 910 (1976).

78JOM(153)15 J. Y. Corey and R. L. Farrell, *J. Organomet. Chem.*, **153**, 15 (1978).

78JOM(153)127 J. Y. Corey, M. J. Dye, R. L. Farrell, and M. V. Mitchell, *J. Organomet. Chem.*, **153**, 127 (1978).

80AP(313)129 J. Ackermann, R. Tacke, U. Wannagat, U. Koke, and F. Meyer, *Arch. Pharm.*, **313**, 129 (1980).

85IP201 A. M. Badger, C. K. Mirabelli, and M. J. DiMartino, *Immunopharmacology*, **10**, 201 (1985).

85LA950 U. Wannagat, R. Münstedt, and U. Harder, *Liebigs Ann. Chem.*, 950 (1985).

87IJI621 A. M. Badger, M. J. DiMartino, T. C. Schmitt, B. A. Swift, and C. K. Mirabelli, *Int. J. Immunopharm.*, **9**, 621 (1987).

89ADD231 C. K. Mirabelli, A. M. Badger, C.-P. Sung, L. Hillegass, C.-M. Sung, R. K. Johnson, D. Picker, D. Schwartz, J. Dorman, and S. Martellucci, *Anti-Cancer Drug Des.*, **3**, 231 (1989).

89COSC1143 R. Tacke and H. Linoh, in "*The Chemistry of Organic Silicon Compounds*" (S. Patai and Z. Rappoport, eds.), p. 1143, Wiley, Chichester (1989).

90JMC2963 A. M. Badger, D. A. Schwartz, D. H. Picker, J. W. Dorman, F. C. Bradley, E. N. Cheeseman, M. J. DiMartino, N. Hanna, and C. K. Mirabelli, *J. Med. Chem.*, **33**, 2963 (1990).

93FRP2689892 D. Damour and S. Mignani, *France Pat.* 2689892 (1993) [*Chem. Abstr.*, **120**, 323854x (1993)].

93FRP2689893 D. Damour and S. Mignani, *France Pat.* 2689893 (1993) [*Chem. Abstr.*, **121**, 9696f (1993)].

93FRP2689894 D. Damour and S. Mignani, *France Pat.* 2689893 (1993) [*Chem. Abstr.*, **120**, 323853w (1993)].

94BMCL415 D. Damour, M. Barreau, G. Dutruc-Rosset, A. Doble, O. Piot, and S. Mignani, *Bioorg. Med. Chem. Lett.*, **4**, 415 (1994).

94JOM(484)119 R. Boukherroub, G. Manuel, S. Mignani, and D. Damour, *J. Organomet. Chem.*, **484**, 119 (1994).

94JPP06256357 Korean Institute of Science and Technology, *Jpn. Pat.* 06256357 (1994) [*Chem. Abstr.*, **123**, 199137m (1995)].

96EJMC725	P. Heinonen, H. Sipilä, K. Neuvonen, H. Lönnberg, V. B. Cockcroft, S. Wurster, R. Virtanen, M. K. T. Savola, J. S. Salonen, and J. M. Savola, *Eur. J. Med. Chem.*, **31**, 725 (1996).
97TE13695	R. J. Smith, S. Bratovanov, and S. Bienz, *Tetrahedron*, **53**, 13695 (1997).
98BKCS358	B. R. Yoo, M. Y. Suk, Y.-M. Yu, S.-G. Hong, and I. N. Jung, *Bull. Korean Chem. Soc.*, **19**, 358 (1998).
98PS138	B. R. Yoo, M. Y. Suk, S. J. Han, Y.-M. Yu, S.-G. Hong, and I. N. Jung, *Pestic. Sci.*, **52**, 138 (1998).
02MBD45	E. Lukevics, E. Abele, P. Arsenyan, R. Abele, K. Rubina, I. Shestakova, I. Domracheva, and V. Vologdina, *Metal Based Drugs*, **9**, 45 (2002).
02MBD307	E. Abele, K. Rubina, R. Abele, O. Dzenitis, P. Arsenyan, J. Popelis, M. Veveris, D. Meirena, and E. Lukevics, *Metal Based Drugs*, **9**, 307 (2002).
03BCA299	E. Abele, R. Abele, P. Arsenyan, I. Shestakova, I. Kanepe, I. Antonenko, J. Popelis, and E. Lukevics, *Bioinorg. Chem. Appl.*, **1**, 299 (2003).
03CHC813	E. Lukevics, A. Zablotskaya, I. Segal, S. Germane, and J. Popelis, *Chem. Heterocycl. Comp.*, **36**, 813 (2003).
03CODD526	W. Bains and R. Tacke, *Curr. Opin. Drug Discov. Devel.*, **6**, 526 (2003).
03DDT551	G. A. Showel and J. S. Mills, *Drug Discov. Today*, **8**, 551 (2003).
03OSC575	J. O. Dai*ß*, B. Müller, C. Burschka, R. Tacke, W. Bains, and J. Warneck, in "*Organosilicon Chemistry*" (N. Auner and J. Weis, eds.), vol. VI, pp. 575–581, Wiley, (2003).
03WOP03037905	R. Tacke and J. Daiss, *PCT Int. WO Pat.* 03037905 (2003) [*Chem. Abstr.*, **138**, 354097d (2003)].
04CAB1921	L. Doszczak, T. Gasperi, A. Saint-Dizier, M. A. Loreto, and D. Enders, *Chem. Biodivers.*, **1**, 1921 (2004).
04GBP2397576	R. Tacke, J. Daiss, G. A. Showell, and A. Richards, *GB Pat.* 2397576 (2004) [*Chem. Abstr.*, **141**, 145697t (2004)].
04OM4987	J. O. Daiss, M. Penka, C. Burschka, and R. Tacke, *Organometallics*, **23**, 4987 (2004).
04WOP2004045625	J. G. Montana, I. Fleming, R. Tacke, and J. Daiss, *PCT Int. WO Pat.* 2004045625 (2004) [*Chem. Abstr.*, **141**, 7278k (2004)].
04WOP2004048390	J. G. Montana, G. A. Showell, I. Fleming, R. Tacke, and J. Daiss, *PCT Int. WO Pat.* 2004048390 (2004) [*Chem. Abstr.*, **141**, 23724h (2004)].
04WOP2004048391	J. G. Montana, G. A. Showell, and R. Tacke, *PCT Int. WO Pat.* 2004048391 (2004) [*Chem. Abstr.*, **141**, 17657x (2004)].
04WOP2004075902	G. A. Showell, *PCT Int. WO Pat.* 2004075902 (2004) [*Chem. Abstr.*, **141**, 265967g (2004)].
04WOP200494436	G. A. Showell, D. Miller, A. K. Mandal, R. Tacke, and J. Daiss, *PCT Int. WO Pat.* 2004094436 (2004) [*Chem. Abstr.*, **141**, 395661p (2004).
05AOC1109	E. Lukevics, L. Ignatovich, I. Sleiksha, I. Shestakova, I. Domracheva, and J. Popelis, *Appl. Organomet. Chem.*, **19**, 1109 (2005).
05DDRO467	P. Englebienne, A. Van Hoonacker, and C. V. Herst, *Drug Design Rev.-Online*, **2**, 467 (2005).
05MC215	P. Englebienne, *Med. Chem.*, **1**, 215 (2005).

05MDMD83 E. Lukevics and L. Ignatovich, in *"Metallotherapeutic Drugs and Metal-Based Diagnostic Agents"* (M. Gielen and E. R. T. Tiekink, eds.), p. 83, Wiley, Chichester (2005).

05OM3192 J. O. Daiss, C. Burschka, J. S. Mills, J. G. Montana, G. A. Showell, I. Fleming, C. Gaudon, D. Ivanova, H. Gronemeyer, and R. Tacke, *Organometallics*, **24**, 3192 (2005).

05SMA123 M.G. Voronkov and V.P. Baryshok, *"Silatranes for Medicine and Agriculture"*, Publ. House Siberian Branch of Russian Acad. Sci., Novosibirsk, 123 (2005).

05WOP2005005443 D. J. Miller, G. A. Showell, R. Conroy, J. Daiss, R. Tacke, and D. Tebbe, *PCT Int. WO Pat.* 2005005443 (2005) [*Chem. Abstr.,* **142**, 134728c (2004)].

06BMCL2555 G. A. Showell, M. J. Barnes, J. O. Daiss, J. S. Mills, J. G. Montana, R. Tacke, and J. B. H. Warneck, *Bioorg. Med. Chem. Lett.*, **15**, 2255 (2006).

06JOM(691)3589 J. O. Daiss, C. Burschka, J. S. Mills, J. G. Montana, G. A. Showell, J. B. H. Warneck, and R. Tacke, *J. Organomet. Chem.*, **691**, 3589 (2006).

06MRMC1169 P. K. Pooni and G. A. Showel, *Mini-Rev. Med. Chem.*, **6**, 1169 (2006).

06OM1188 J. O. Daiss, C. Burschka, J. S. Mills, J. G. Montana, G. A. Showell, J. B. H. Warneck, and R. Tacke, *Organometallics*, **25**, 1188 (2006).

06WOP2006066873 K. Nebel, S. W. Wandeborn, C. Lamberth, P. J. Crowley, and F. Cederbaum, *PCT WO Pat.* 2006066873 (2006) [*Chem. Abstr.,* **145**, 103836u (2006)].

07CBC1447 M. W. Büttner, C. Burschka, K. Junold, P. Kraft, and R. Tacke, *ChemBioChem*, **8**, 1447 (2007).

07CBC1688 M. W. Büttner, C. Burschka, J. O. Daiss, D. Ivanova, N. Rochel, S. Kammerer, C. Peluso-Iltis, A. Bindler, C. Gaudon, P. Germain, D. Monas, H. Gronemeyer, and R. Tacke, *ChemBioChem*, **8**, 1688 (2007).

07CHC143 E. Lukevics, L. Ignatovich, I. Sleiksha, V. Romanov, S. Grinberga, J. Popelis, and I. Shestakova, *Chem. Heterocycl. Comp.*, **43**, 143 (2007).

07CODD654 A. K. Franz, *Curr. Opin. Drug Discov. Devel.*, **10**, 654 (2007).

07OM1295 M. W. Büttner, M. Penka, L. Doszczak, P. Kraft, and R. Tacke, *Organometallics*, **26**, 1295 (2007).

07WOP20071183 C. A. Coburn, M. S. Egbertson, S. L. Graham, G. B. Mcgaugley, S. R. Stauffer, H. A. Rajapakse, P. G. Nantermet, S. R. Stachel, W. Yang, W. Lu, and B. Fahr, *PCT Int. WO Pat.* 2007011833 (2007) [*Chem. Abstr.,* **146**, 184469x (2007)].

08CBD920 R. Tacke and S. Metz, *Chem. Biodivers.*, **5**, 920 (2008).

08ISOC112 L. Ignatovich, V. Muravenko, J. Popelis, S. Grinberga, I. Shestakova, and E. Lukevics, in *The 15th International Symp. Organosilicon Chem., Progr. Abstr. List Partic.*, p. 112, Jeju, Korea (2008).

08TAP369 J. B. Warneck, F. H. M. Cheng, M. J. Barnes, J. S. Mills, J. G. Montana, R. J. Naylor, M.-P. Ngan, M.-K. Wai, J. O. Daiss, R. Tacke, and J. A. Rudd, *Toxicol. Appl. Pharmacol.*, **232**, 369 (2008).

CHAPTER 5

Positional Selectivity in Electrophilic Substitution in π-Excessive Heteroaromatics

L.I. Belen'kii

Contents

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

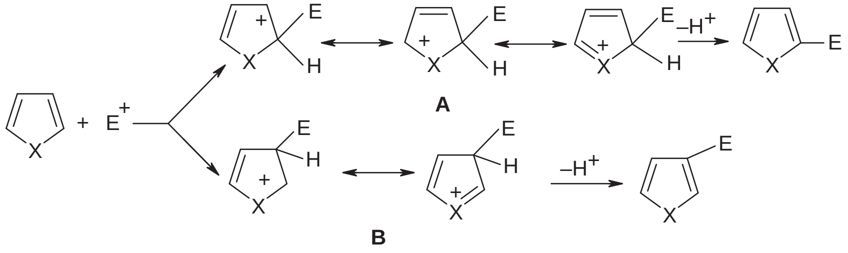
Advances in Heterocyclic Chemistry, Volume 99
ISSN 0065-2725, DOI 10.1016/S0065-2725(10)09905-8

1. INTRODUCTION

Electrophilic substitution is an important type of reactions for five-membered heterocycles with one heteroatom and enables compounds with various substituents to be obtained. The present work is devoted to certain features of substrate and positional selectivities in electrophilic substitution reactions of derivatives of pyrrole, furan, thiophene and selenophene, and also the corresponding benzannulated systems, which had not been explained until recently. In a recent review (05RKZ(6)59), these problems were mainly discussed for thiophenes, while in a previous review (94H(37)2029) only monocyclic pyrrole, furan and thiophene derivatives were considered.

The effect of a heteroatom is displayed in an increased reactivity of α-positions, which is usually interpreted to be the result of the higher stability of the corresponding σ-complex (**A**) due to better charge delocalization compared with its isomer (**B**) formed on attack at a β-position (Scheme 1).

The higher stability of hetarenium ions of the type **A** as compared with their isomers **B** is confirmed not only by circumstantial evidence but also by direct observation, mainly using NMR spectroscopy. This review does not include an exhaustive citation of the literature concerning reactions of five-membered heterocycles with electrophiles. Substantial additional information can be found in CHEC-I (84CHEC(4)40, 84CHEC(4)201, 84CHEC(4)599, 84CHEC(4)742, 84CHEC(4)936), CHEC-II (96CHEC-II(2)40, 96CHEC-II(2)297, 96CHEC-II(2)492, 96CHEC-II(2)731)



Scheme 1

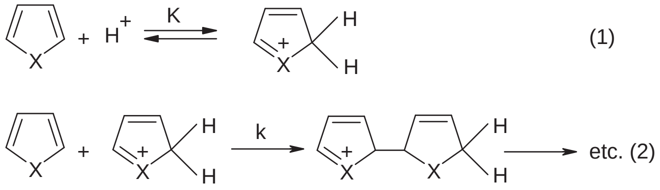
and CHEC-III (08CHEC-III(3)45, 08CHEC-III(3)407, 08CHEC-III(3)741, 08CHEC-III(3)975).

2. GENERATION AND STABILITY OF HETARENIUM IONS

Many features of reactions of pyrrole, furan, thiophene and their derivatives bearing electron-releasing substituents with electrophiles are governed by their ready formation and the high stability of corresponding 2*H*-hetarenium ions, mainly α-C-protonation products like **A** ($E = H$). The reversible formation of such σ-complexes (Scheme 2, reaction 1) competes with acid-catalyzed oligomerization (reaction 2), which is practically irreversible and starts from the attack of an hetarenium cation on the neutral five-membered heterocycle analogously to the first step of electrophilic substitution.

Taking into account the relative strengths of the parent heterocycles as bases (76T1767), which depends on the nature of heteroatom $K_{NH}:K_O:K_S \approx 10^9:1:1$, it is evident that pyrrole derivatives must undergo protonation most readily. However, the stability of σ-complexes **A** depends not only on the pK_a values of heterocycles but also on their oligomerization rate, the latter might be estimated using data of (71AHC(13)235) for electrophilic substitution as $K_{NH}:K_O:K_S \approx 10^8:10^2:1$. As the result, the hetarenium ions are quite stable at ordinary temperature for an unsubstituted pyrrole (59CJC1859, 63JA26, 63JA2763, 81LA789) and thiophene (66RTC1072, 73TL3929, 75ZOR424, 78ZOR641, 79ZOR1289, 84T2471, 86T759), whereas with furan derivatives the cations are only stable for the sterically hindered di- and trialkyl-substituted compounds (67TL2951, 70RTC553, 72RTC1359, 72KGS1594). Stable selenophenium ions are unknown, the instability of selenophenes to acids being clearly defined (84CHEC(4)936).

The high "acidophoby" of furans and their relatively low aromaticity led to the development of some peculiar procedures for the generation of stable furanium ions, which do not use furans as starting compounds. Thus, the 3,5-dimethyl-2*H*-furanium ion was generated from mesityl oxide in $FSO_3H–SbF_5$ (70RTC553), and several sterically hindered



Scheme 2

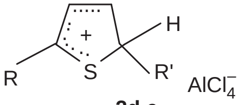
furanium ions were formed by protonation of *tert*-butylated methylenedihydrofurans (75TL3619), and stable 3,5-disubstituted 2,2-dimethylfuranium salts were prepared from alkynyl-substituted aliphatic 1,2-diols or 5,5-dimethylfuran-2-ones (61ZOK1958, 63ZOK3768, 66RZC1657, 66MC1088, 67RZC251).

Pyrrolium ions are stable in strongly acidic solution (59CJC1859, 63JA26, 63JA2763). β-Protonated species were indicated by ^{1}H NMR as minor products (59CJC1859) and this can be regarded as the result of the super high activity of pyrroles in reactions with electrophiles. Ion cyclotron experiments have shown that in the gas phase the preferability for α-protonation is substantially lower for a pyrrole molecule than for a furan and a thiophene (81NJC505). Several sterically overcrowded di- and trialkyl-substituted pyrrolium salts can be isolated as crystalline tetrafluoroborates (81LA789). Taking into account the high basicity of pyrroles (e.g., for 2,5-dimethylpyrrole $pK_a = -1.0$ (76T1767)), it is not surprising that polyalkylated carbonyl-containing pyrroles undergo protonation at an α-carbon rather than at a CO group (71ZOK179, 72KGS336). Interesting data were obtained in NMR studies of the protonation of *N*-vinylpyrrole (98MI1), particularly those concerning HBr addition to 1-vinyl-2*H*-pyrrolium ions (94BCJ1161, 94BCJ1872) and the unexpected protonation of furan ring as well as "normal" formation of the 5-(2-furyl)-1-vinyl-2*H*-pyrrolium ion from 5-(2-furyl)-1-vinylpyrrole (95ZOR801).

The appropriate pK_a values and oligomerization rate constants k (see above) leads to the stability of numerous thiophenium ions in solution at room temperature (66RTC1072, 73TL3929, 75ZOR424, 78ZOR641, 79ZOR1289, 84T2471, 86T759) even in the presence of an equimolar amount of acid (75ZOR424, 84T2471, 86T759). In pioneering studies, the generation of C-protonated thiophenes was conducted using conventional procedures known from the chemistry of arenium ions, such as the action of excess HF, $HF-BF_3$ and $HF-SbF_5$ (66RTC1072, 76JCS(P2)323, 78JA4326, 79JOC3917) as well as fluorosulfonic acid and its mixtures with Lewis acids, which also played the role of solvent (73TL3929, 76JCS (P2)323, 78JA4326, 79JOC3917). Thiophenium ions were thoroughly characterized by ^{1}H NMR spectra (66RTC1072, 00AHC(76)85).

The high stability of hetarenium ions allows their generation under nonconventional conditions. Thus, on acylation of thiophene and its homologs with acyl chlorides and aluminum chloride in 1,2-dichloroethane or methylene dichloride, along with ketones (as nv-complexes with $AlCl_3$ **1a–c**), thiophenium ions of type **A** (σ-complexes **2a–c** formed from starting thiophenes) unexpectedly were found (75ZOR424). The latter cations proved to be stable under acylation conditions and were formed in the absence of any added proton acid from the hydrogen chloride eliminated on acylation, HCl being consumed practically completely. Acylthiophenes in *ca*. 50% yield were formed as well as equimolar quantities of thiophenium ions (Scheme 3).

The formation of σ-complexes **2** was confirmed by model reactions of thiophenes with HCl and $AlCl_3$ in the same solvents to give the same products **2a–c** from thiophene, 2-methylthiophene and 2,5-dimethylthiophene, respectively, as well as σ-complexes **2d** from 2-(methylthio) thiophene and **2e** from 2-methyl-5-(methylthio)thiophene (75ZOR424).

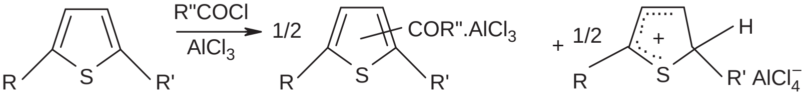


2d,e

d R = MeS, R' = H; **e** R = MeS, R' = Me

This method was exploited repeatedly by our group (78ZOR641, 84T2471, 86T759, 90G365) and other investigators (81CL813, 83BCJ2208, 86BCJ83) for the generation of thiophenium ions and their use in synthesis (see reviews concerning mainly preparative aspects of the chemistry of thiophenium ions (92KGS733, 03MI1, 08MI1)). σ-Complexes **2a–e** could be stored in solution at room temperature without visible changes (^{1}H NMR) for several days to several weeks (75ZOR424). 2,5-Dimethyl-2*H*-thiophenium ion **2c** is especially stable and transforms into the more stable isomeric 3,5-dimethyl-2*H*-thiophenium ion only after storage of a **2c** solution in a sealed ampoule at room temperature over several years (84T2471).

The stability of σ-complexes **2** and their easy formation are substantially governed by the nature of the counter anion. Thus, in HF solution, thiophene and alkylthiophenes form cations stable at temperatures below −40 °C, in HF−BF_3 the same cations are stable up to −20 °C and 2,5-dimethyl-2*H*-thiophenium ion, generated in HF−SbF_5 is sufficiently stable even at +60 °C (66RTC1072). The high stability of 2*H*-thiophenium ions formed by protonation in the presence of $AlCl_3$ in dichloroalkanes as solvents (75ZOR424) is undoubtedly caused by the $AlCl_4^-$ counterions as well as by favorable solvation conditions. The stability of thiophenium ions is mainly caused by their peculiar structure,



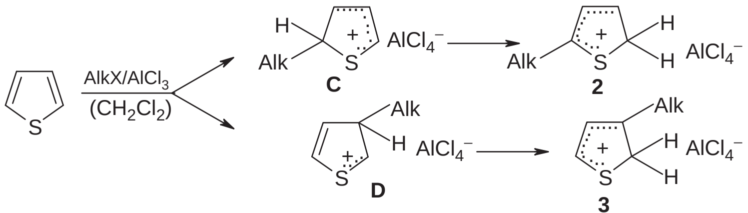
1a-c **2a-c**

a R = R' = H; b R = Me, R' = H; c R = R' = Me

Scheme 3

which allows the positive charge to be delocalized with participation of the sulfur atom as well as by the effect of substituents. The high stability of thiophenium ions was demonstrated by an MS-CI study of thiophenes with electrophiles in the gas phase where both counterions and solvation effects are excluded (82IZV85). The nature of substituents and their positions on a thiophene ring affect the stability of thiophenium ions to a great extent: 2,4-bis(alkylthio)thiophenes are transformed to the stable thiophenium ions **2d,e** in trifluoroacetic acid as proton donor and solvent (78ZOR641) or in an inert solvent under the action of HCl and $SnCl_4$ (79ZOR1289).

The high stability of thiophenium ions made it possible to create a new method of their generation: alkylation of thiophene with alkyl halides in the presence of an equimolar quantity of aluminum trichloride (77ZOR364) (Scheme 4). Owing to the known low selectivity of alkylation, products are mixtures of 5-alkyl-2*H*- (**2b,f–h**) and 3-alkyl-2*H*-thiophenium ions (**3b,f–h**) where deprotonation of the latter leads to mixtures of 2- and 3-alkylthiophenes. The reactions of thiophene with alkyl halides in the presence of $AlCl_3$ should give initially the ions **C** and **D** possessing an alkyl group and a hydrogen atom at the nodal center, that is "normal" σ-complexes corresponding to an alkylation. The latter evidently undergo isomerization including proton migration resulting in more stable ions with two hydrogen atoms in the nodal center. Note that the stability of thiophenium ions allows alkylation to be stopped at the



Alk = Me (**b**), Et (**f**), *i*-Pr (**g**), *t*-Bu (**h**)

AlkX	T, °C	Yield, %	α:β-Ratio	Percentage of dialkylthiophenes
MeBr	–10	(6)[a]	73:27	–
EtBr	–20	(45)[a]	65:35	Traces
i-PrCl	–70	51[b] (65)[a]	60:40	Traces
t-BuCl	–70	73.5[b]	83:17	1

[a] GLC data after deprotonation.

[b] Isolated yield.

Scheme 4

stage of monosubstitution when an equimolar rather than a catalytic amount of $AlCl_3$ is commonly used even when the alkyl halide is also a solvent (77ZOR364).

Attempted *tert*-butylation of 2-(*tert*-butyl)-4-methylthiophene (*tert*-BuCl–$AlCl_3$ in CH_2Cl_2) failed. The starting dialkylthiophene was recovered but in the reaction mixture 5-(*tert*-butyl)-3-methyl-2*H*-thiophenium ion was observed (97KGS1477). Probably, owing to steric shielding, the alkylation is very slow, and protonation by HCl–$AlCl_3$ appears, hydrogen chloride being the product of *tert*-butyl chloride dehydrohalogenation promoted by $AlCl_3$ (*cf*. (53LA(583)93, 56JOC761)).

3. POSITIONAL SELECTIVITY AND SOME TRANSFORMATIONS OF HETARENIUM IONS

In "standard" cases of heteroaromatic electrophilic substitution, the main or even the only transformations of intermediate hetarenium ions are their deprotonation to give the corresponding substituted derivatives. The situation with stable hetarenium ions is not so clear. For example, on partial protonation, the formed σ-complexes react as electrophiles with nonprotonated heterocycles according to reaction 2 (Scheme 2) to give products of acid-initiated oligomerization. This is true not only for acidophobic furan, pyrrole and selenophene but also for thiophene which is less sensitive to Brønstedt and Lewis acids than other five-membered π-excessive heteroaromatics. Transformations of stable hetarenium ions can distort the estimation of the α/β-ratio of both σ-complexes and the final neutral products of electrophilic substitution. Thiophenium ions and their transformations are studied in more detail than those of pyrrole and furan analogues.

3.1 Typical transformations of stable hetarenium ions

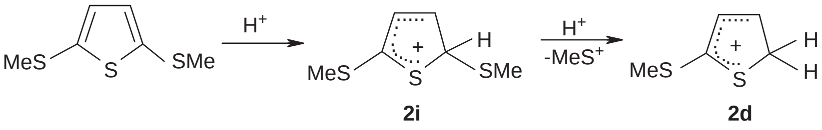
The **2**:**3** ratios obtained on alkylation (Scheme 4) might be regarded (77ZOR364) as a result of kinetic control owing to the mild conditions. Isomerizations of σ-complexes **C**→**2** and **D**→**3** do not change the carbon skeleton and the gain in energy probably is low. The higher selectivity of methylation and ethylation than isopropylation was due to (77ZOR364) the different nature of the reactive species: $Alk^+AlX_3^-$ for Alk = Pr^i or Bu^t and Alk_2X^+ for R = Me or Et (*cf*. (74JA884)). Such isomerizations are common to arenium ions and involve proton migrations (see, e.g. (83MI1)).

The formation of σ-complexes is reversible, not only for protons but also other electrophilic species able to eliminate from a nodal center, as was observed in the case of 2,5-bis(methylthio)-2*H*-thiophenium ion (**2i**)

(75ZOR424). The latter, in contrast to 2-methylthio- (**2d**) and 2-methyl-5-methylthio-2*H*-thiophenium (**2e**) ions, is only stable at low temperatures and eliminates an MeS group (probably, as cation) above −40 °C to give ion **2d** (Scheme 5).

With an HCl deficiency or when protonation is carried out in trifluoroacetic acid, the mixture contains some 2,5-bis(methylthio)-2*H*-thiophene which undergoes electrophilic sulfenylation. The reaction proceeds as an intermolecular disproportionation resulting in a complex mixture of products, mainly 2,4-bis-sulfide **4** (*ca*. 50%), and can be used for the preparative isomerization of 2,5-bis-sulfides to not easily accessible 2,4-isomers (78ZOR641). The driving force is the formation of 2,4-bis(alkylthio)thiophenium ions **4**, whose structure provides especially favorable conditions for positive charge delocalization (Scheme 6). The key role of thermodynamic stabilities of thiophenium ions in the transformations of the bis-sulfides under consideration has been corroborated by quantum chemical calculations (78ZOR1305). A similar mechanism governs the isomerization of 3-indolyl sulfides to their 2-isomers (89CC63, 92JOC2694). However, the mechanism of acid-catalyzed rearrangements of 2-pyrrolyl and 1-methyl-2-pyrrolyl sulfides to 3-isomers is regarded as an intramolecular 1,2-shift (82JOC3668).

Alkylthiophenium ions also undergo disproportionation. A *tert*-butyl group has one of the highest migration abilities allowing a transformation of the 83:17 mixture of 2- and 3-*tert*-butylthiophenes, formed on thiophene *tert*-butylation in the presence of an equimolar amount of $AlCl_3$ to 2-*tert*-butylthiophene containing only a minor admixture (3%) of the 3-isomer on simple storage of the mixture of σ-complexes at room temperature over 1–2 days (84T2471). 2,4-Di(*tert*-butyl)thiophene (in the form of corresponding σ-complex) is obtained as one of the disproportionation products; it can be prepared more conveniently from the mixture of 2,4- and 2,5-di(*tert*-butyl)thiophenes obtained, for example, by thiophene *tert*-butylation in the presence of tin tetrachloride (88KGS1034). Analogous transformation of σ-complexes corresponding to isopropylation and ethylation needs a higher temperature (up to 80 °C) or very long storage at room temperature (86T759). In the cases of unsymmetrically substituted 2-methyl- and 2-ethyl-5-(*tert*-butyl)thiophenes, a similar migration at room temperature happens only for the

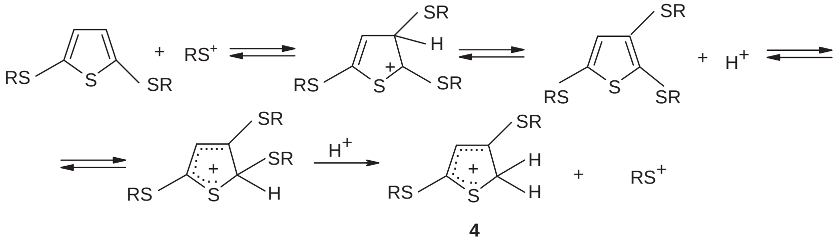


Scheme 5

tert-butyl group, and this behavior has been used for the synthesis of inaccessible 2-alkyl-4-(*tert*-butyl)thiophenes (93KGS1040).

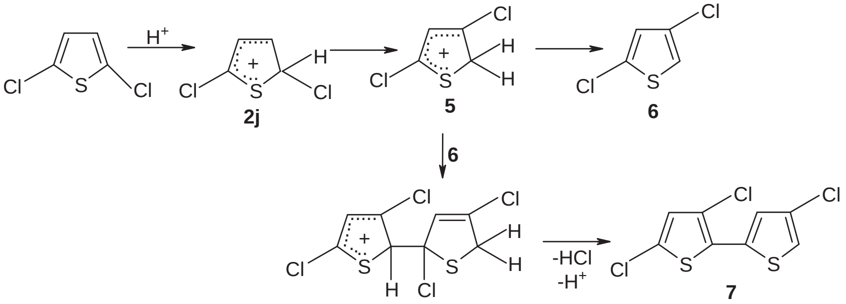
Halogen-substituted thiophenium ions have low stability and can be observed by ^{1}H NMR only at temperatures below –30 °C (86MRC699). Disproportionation of the 2,5-dibromo-2*H*-thiophenium ion with formation of 5-bromo- and 3,5-dibromo-2*H*-thiophenium ions was observed on increasing the temperature from −50 to −10 °C (86MRC699). For chlorothiophenium ions, the disproportionation could not be observed so distinctly. Note that 2,4-dichloro-2*H*-thiophenium ion (**5**) is stable at room temperature and is the main transformation product of the less stable 2,5-dichloro-2*H*-thiophenium ion (**2j**). The latter fact was used for the preparation of difficultly available 2,4-dichlorothiophene (**6**) from the 2,5-isomer; 3,5,4′-trichloro-2,2′-bithiophene (**7**) was isolated as a by-product resulted, probably, from the reaction of ion **5** with dichloride **6** (Scheme 7) (90G365).

Transfer of an acyl group from one molecule of acylthiophene to another (73ZOR1959) happens on heating of 2-acetylthiophene with chloroacetyl chloride in excess aluminum chloride without a solvent at 90–100 °C (30 min), the starting ketone (29%) is recovered, as well as the transacylation product of the latter, 2-chloroacetylthiophene (~0.5%). 2-Acetyl-4-chloroacetylthiophene is the major product (56.5%) with



4

Scheme 6

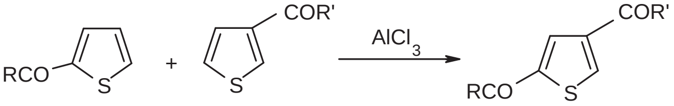


Scheme 7

traces of the 2,5-isomer. The yield of 2-chloroacetylthiophene increased to ~3% when the reaction was conducted at 110 °C, 1 h. 2-Acetylthiophene, when heated in excess aluminum chloride without a solvent at 110 °C, 36 h, was transformed to 2,4-diacetylthiophene (45% yield based on consumed monoketone). Under similar drastic conditions, reactions of 3-acylthiophenes with 2-acylthiophenes gave the corresponding 2,4-diacylthiophenes **8a–e** in 70–80% yields (Scheme 8) (73ZOR1959). In all cases, the diacylthiophenes were the 2,4-isomers, which is characteristic of acylation of 3-acylthiophenes (see also (01ARK(9)49)) while acetylation and chloroacetylation of 2-acetylthiophene under similar conditions resulted in diacylthiophenes contained 8–10% of the corresponding 2,5-isomer (69DOK(185)91).

The transformations of 2-acetylthiophene to 2,4-diacetylthiophene **8a**, Scheme 9 (73ZOR1959), occur with acylation of 3-acylthiophene as the final step along with resinification products. Taking into account the drastic conditions, this isomerization can be regarded as thermodynamically controlled.

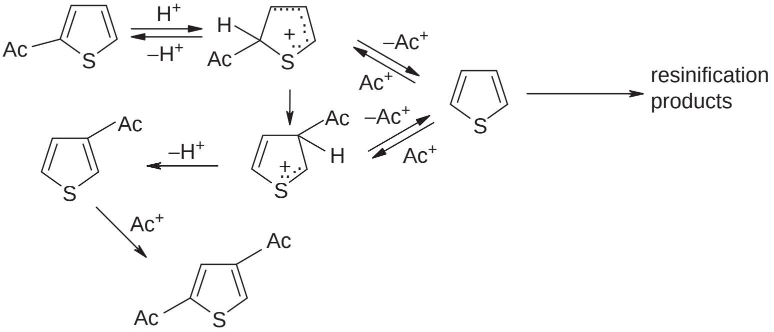
Sulfonation of *meso*-(2-thienyl)porphyrin with concentrated sulfuric acid showed a clear temperature dependence of the regioselectivity. At 0–20 °C (kinetic control) *meso*-(5-sulfonyl-2-thienyl)porphyrin is the main product, whereas at 130 °C the thermodynamically controlled (4-sulfonyl-2-thienyl)-substituted isomer is formed as the main product (Scheme 10) (08TL5810).



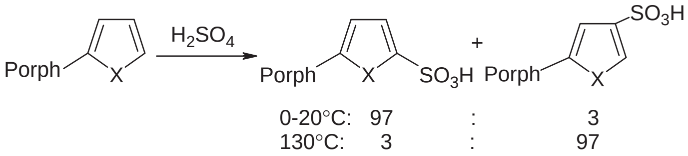
8a-e

8:**a** R = R' = Me; **b** R = Me, R' = Ph; **c** R = Ph, R' = Me; **d** R = R' = Ph; **e** R = Me, R' = CH_2Cl

Scheme 8

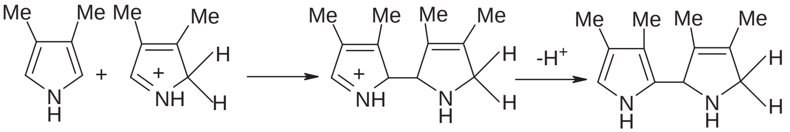


Scheme 9



Porph is porphyrin residue

Scheme 10



Scheme 11

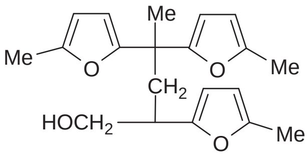
3.2 Hetarenium ions as reagents in electrophilic substitution and addition reactions

3.2.1 Electrophilic substitution reactions

The interaction of 2,4-dichlorothiophene (**6**) with 3,5-dichloro-2*H*-thiophenium ion (**5**) to give bithiophene **7** is an electrophilic substitution in which cation **5** is an electrophile. Similarly, the acid-induced oligomerization of five-membered heteroaromatics is a resinification. The structure of 3,4-dimethylpyrrole dimer formed in 6N HCl (68JCS(C) 2526) shows that the oligomerization may proceed (Scheme 11) through a 2*H*-pyrrolium ion, reaction 2 in Scheme 2.

β-Protonated species of pyrroles can be present in fairly high concentration and can act as reactive electrophiles. This is the case in the formation of pyrrole trimer ("red pyrrole") presented in Scheme 12 (57JCS4018).

Facile cleavage of a saturated heterocycle in an oligomerization process is peculiar to furan derivatives. Thus, the structure of the 2-methylfuran "tetramer" **9** has only three furan rings (74BCJ1467).

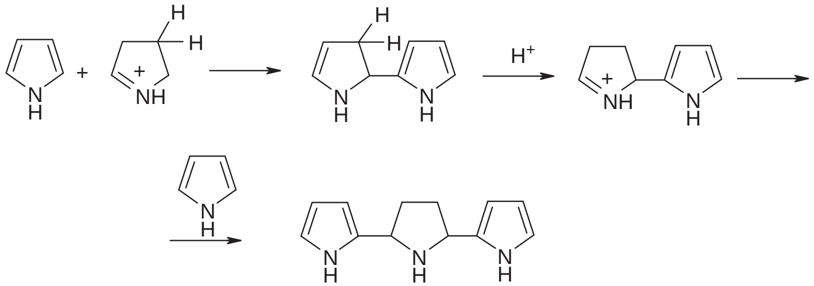


9

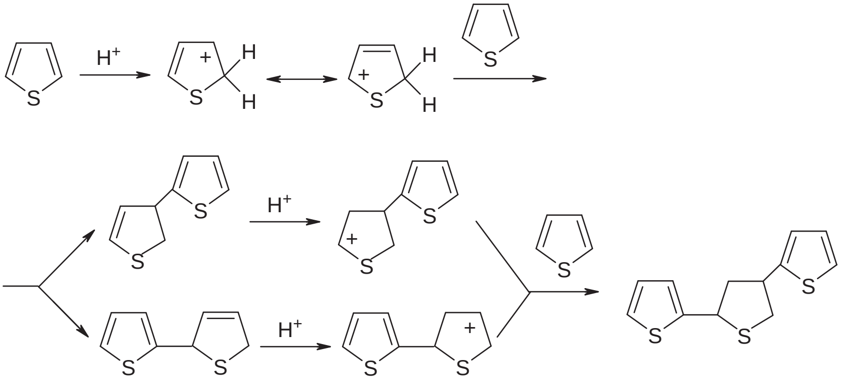
The key role of 2*H*-thiophenium ions as electrophilic species was indicated in 1950 by Hartough et al. (50JA1910), who isolated a so-called thiophene trimer and suggested a mechanism (Scheme 13) and proposed the structure of the trimer, later confirmed by X-ray diffraction method (69CC165).

Similar transformations were observed on coupling of 2-arylthiophenes using a cation-exchange resin (82CL1195) that resulted in 5,5′-diaryl-2,3′-bithiophenes. The role of substrate can also be played by another aromatic compound. For example, benzo[*b*]thiophene with various benzene derivatives in the presence of $AlCl_3$ or $TiCl_4$ proceeds (80JCS(P1)677) through C-protonation and gives aryl-substituted 2,3-dihydrobenzo[*b*]thiophenes, products of the formal addition of an aromatic molecule to the double bond of the thiophene ring.

Preparatively, most interesting results were obtained by Sone et al. (see review (99MI1)) who studied transformations of chlorosubstituted thiophenium ions, the latter playing a role as alkylating agents. Thus, with equimolar amounts of various aromatic compounds and aluminum chloride, 2-chlorothiophene is converted to the corresponding 2-arylthiophenes **10** (Scheme 14) (86BCJ83).



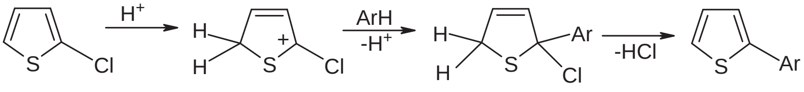
Scheme 12



Scheme 13

The results depend significantly on the reactivity of the aromatic compound under the electrophilic substitution conditions. Thus, with a mixture of 2-chlorothiophene and benzene, only traces of 2-phenylthiophene were detected in spite of a fivefold excess of the latter, and practically the only product was 5-chloro-2,2′-bithiophene isolated in 44% yield (86BCJ83). Here, 2-chlorothiophene is not only the source of the electrophilic agent but also plays the role of substrate. 4-Aryl-2-chlorothiophenes **11** result from 2,5-dichlorothiophene with aromatic compounds, 2-chloro-4-phenylthiophene being isolated in 62% yield (88BCJ3779). 2,4-Diarylthiophenes **12** are formed, in turn, on interaction of 4-aryl-2-chlorothiophenes **11** with aromatic compounds (88BCJ3779). 3-Aryl-2-chlorothiophenes are also converted to 2,4-diarylthiophenes **12** (97MI1) (Scheme 15).

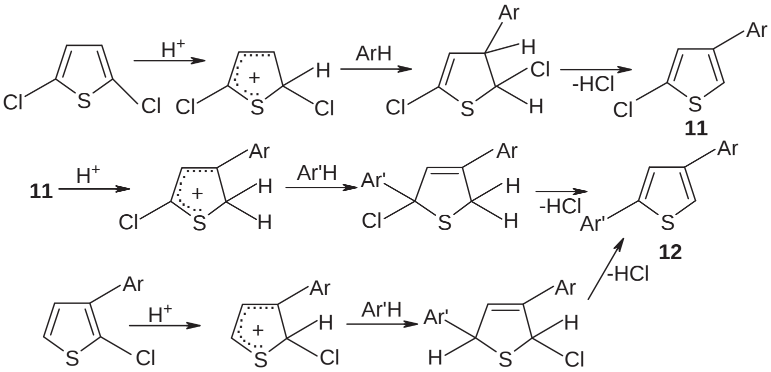
Stable 2*H*-thiophenium ions formed on acylation of thiophene and its homologs with aluminum chloride (due to hydrogen chloride originating during the reaction) essentially lower the yields of ketones. The formation of such σ-complexes, α-C-protonation products, does not take place on preparation of ketones under the usual conditions of acylation in thiophene series, namely, in the presence of tin tetrachloride with



10

Ar (yield of **10**, %): 4-MeOC$_6$H$_4$ (44), 2-Me-4-MeOC$_6$H$_3$ (51), 3-Me-4-MeOC$_6$H$_3$ (53), 2,4-(MeO)$_2$C$_6$H$_2$ (55), 4-methoxy-1-naphthyl (83), 2-ethoxy-1-naphthyl (59),

Scheme 14



Scheme 15

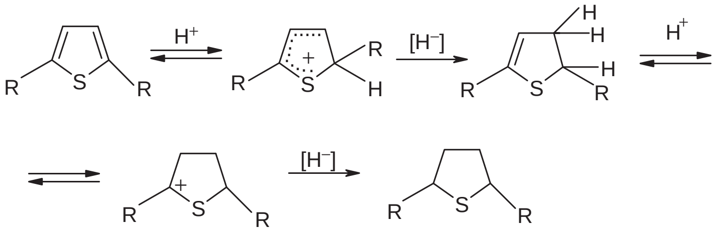
benzene solvent (43OSC(2)8) when stable σ-complexes do not form and yields of ketones reach 80–85%. Acyl chlorides with electron-withdrawing substituents practically do not enter into a Friedel–Crafts reaction when tin tetrachloride is used as a condensing agent (70ZOR2518). As shown for chloroacetyl chloride, oxalyl chloride and squaric acid dichloride, the undesirable formation of stable 2*H*-thiophenium ions can be suppressed by the addition of a base (e.g., pyridine), which destroys the ions (00CHE219, 01KGS81, 03KGS1785), or by lowering the medium polarity with dichloroethane−heptane mixtures (02IZV1392, 03KGS1785). The yields of target ketones increase up to 80–90%.

3.2.2 Ionic hydrogenation of thiophenes and some other heterocycles

Thiophenium ions not only play a key role in electrophilic substitution reactions but they also allow some addition reactions to be possible, such as the ionic hydrogenation of thiophene derivatives proceeding by repeated protonations and additions of hydride ion (Scheme 16) (73IZV1918, 75T311, 78T1703, 79MI1).

The reactions usually are carried out by the action of trifluoroacetic acid and triethylsilane. The first stage, protonation of a thiophene, depends, naturally, on the nucleophilicity of the particular thiophene, the latter determining the equilibrium concentration of 2*H*-thiophenium ion formed. An unsubstituted thiophene is hydrogenated very slowly but the introduction of one or two alkyl groups leads to a sharp acceleration (73IZV1918, 75T311). The second stage, addition of hydride anion to 2*H*-thiophenium cation, proceeds irreversibly and that shifts the equilibrium established in the first stage. As a result of successive protonation of the dihydrothiophene intermediate and addition of hydride ion to the originated cation, the latter is transformed to tetrahydrothiophene.

Acceleration of ionic hydrogenation can be attained by an increase in the acidity of the medium, by catalysis, for example, with boron trifluoride etherate, or as the result of carrying out the reaction in $HSiEt_3$−$HCl/AlCl_3$, that is, under conditions providing for the stability of the thiophenium ions (78T1703, 79MI1).



Scheme 16

Electron-withdrawing substituents stable under ionic hydrogenation conditions, for example, a carboxy group or a halogen atom deactivate thiophene ring. The presence of an acyl substituent, which is reduced on ionic hydrogenation, does not hinder the reaction but its products are the corresponding alkylthiophenes (from ketones) and thenyl ethers (from aldehydes). On ionic hydrogenation, sulfides of thiophene undergo reductive cleavage of C–S bonds in the side chain.

Ionic hydrogenation is also described for indole, carbazole and furan derivatives (79MI1). However, it is most important for thiophenes since the latter are well known as poisons for most hydrogenation catalysts.

4. POSITIONAL SELECTIVITY IN REACTIONS OF FURAN, THIOPHENE, SELENOPHENE, PYRROLE AND THEIR DERIVATIVES WITH ELECTROPHILES

The reactivity and positional selectivity of pyrrole, furan and thiophene in electrophilic substitution reactions were studied quantitatively about 40 years ago (71AHC(13)235). Quantitative data concerning the reactivity of selenophene also have been summarized (71AHC(13)235). However, the positional selectivity of electrophilic substitution in the selenophene series has been studied insufficiently. Numerous data are presented in well-known reviews of Magdesieva (70AHC(12)1) and Hörnfeldt (82AHC(30)127) but can be regarded only as qualitative. Therefore, the discussion is frequently limited to: pyrrole, furan and thiophene. Vast differences are observed in reactivity, which decreases by approximately 10 orders of magnitude in the series pyrrole $\gg$ furan $>$ thiophene, and may be explained by the different delocalization of electron density on the ring atoms where overlap takes place between the π-orbitals of the C atoms and the n-orbitals of the heteroatoms, the latter belonging to different Groups and Periods of the Periodic System. The differences in positional selectivity are not so large. For example, on acetylation the difference in α:β product ratio between the most selective furan and the least selective pyrrole is "only" three orders of magnitude. This ratio changes in the sequence furan $>$ thiophene $>$ pyrrole and does not correlate with the reactivity (substrate selectivity) series given above.

4.1 Positional selectivity and possible role of relative stabilities of onium states of ring heteroatoms

To explain the noncorrespondence in the series of substrate and positional selectivities in electrophilic substitution reactions of five-membered heterocycles with one heteroatom, a hypothesis was put forward (79MI2, 80KGS1587). Namely, the formation of β-substituted compounds proceeds through a σ-complex of type **B** (Scheme 1), in which only the heteroatom and one of the α-carbon atoms participate in charge delocalization and must depend more on the ability of heteroatom X to exist in the onium state. For the formation of α-substituted compounds all the ring atoms except for the geminal C atom participate in charge delocalization of cation **A**. A reduction in the stability of the onium states in the series $N^+ > S^+ > O^+$ correlates well with the experimental data on the ability of pyrrole, thiophene and furan to form β-substituted products.

Unsubstituted pyrrole, thiophene and furan are typical π-excessive heteroaromatics and readily react with electrophiles under mild conditions. The products of monosubstitution are mainly or solely 2-substituted derivatives.

Being the most reactive compound of the series, pyrrole often undergoes electrophilic substitution under nonconventional conditions. For example, it enters Friedel–Crafts acylation with acid anhydrides (77JOC3952) and chlorides without any addition of a Lewis or Brønstedt acid (72JOC3618, 80JCR(S)42, 88OSC(VI)618). In the absence of strong acid even at 300 °C the zeolite-catalyzed acylation of pyrrole with acetic anhydride gives 2-acetylpyrrole of 98% purity in 75% yield (08JP2008137964). At the same time, in ionic liquids [bmim][PF_6] or [bmim][BF_4], pyrrole reacts with alkyl halides, electrophilic olefins, arensulfonyl chlorides and benzoyl chloride to give the corresponding N-substituted pyrroles in excellent yield (04S1951).

The Vilsmeier–Haak procedure is very useful for the selective syntheses of pyrrole-2-carbaldehyde, 2-acylpyrroles (using complexes of dialkylamides of carboxylic acids other than DMF) and even of pyrrole-2-carbonitrile (on treatment of the complex formed with $NH_2OH \cdot HCl$ in DMF instead of hydrolysis) (80CJC409). Pyrrole reacts smoothly with aliphatic and aromatic acid chlorides in the presence of zinc metal in toluene at ambient temperature to afford corresponding 2-acylpyrroles in high (>80%) yields with high regioselectivity (02TL8133). *N*-Bromosuccinimide in THF converts pyrrole selectively to 2-bromopyrrole (81JOC2221).

Pyrrole, furan and indole undergo smooth alkylation with cyclic allylic acetates at 80 °C in the presence of 10 mol% of the mild and water-tolerant Lewis acid, indium trichloride, to afford 2-substituted furan and pyrrole and 3-substituted indoles in good yields (~75%) with high selectivity (06SL3447). The unexpectedly high activity of $Zn(OTf)_2 \cdot 6H_2O$ in a catalytic Friedel–Crafts acylation (10 mol% of zinc triflate, rt) is shown for different aromatic compounds including furan, thiophene and 2-chloro- and 2-bromothiophenes. The yields of α-acylsubstituted derivatives vary, 75–89% (08SC255).

Recently, H. Mayr et al. (08EJO2369) estimated the nucleophilicities of pyrrole and its alkyl-substituted derivatives. The second-order rate constants for the reactions of pyrroles with benzhydrylium ions were determined in acetonitrile. Since the formation of the σ-adducts is the rate-limiting step, the second-order rate constants correlate linearly with the electrophilicity parameters E of the benzhydrylium ions, nucleophilicity parameters N and the slope parameter s according to the linear free energy relation $\log k_2$ (20 °C) $= s(N+E)$. This latter made it possible to compare the nucleophilic reactivities of various pyrroles with other nucleophiles. The pyrroles were integrated into a comprehensive scale of nucleophilicity, covering a range of 8–9 orders of magnitude from *N*-(triisopropylsilyl)pyrrole ($N = 3.12$), the weakest nucleophile of this series, to 3-ethyl-2,4-dimethylpyrrole ($N = 11.63$). Highly reactive pyrroles show similar nucleophilic reactivities as enamines, whereas those of less-reactive pyrroles are comparable to allylsilanes or indoles.

Thus, a free α-position is kinetically favored for electrophilic attack in all cases, including the most reactive pyrrole. β-Substituted derivatives are usually the thermodynamically favored products of further transformation primarily formed on replacement of an α-hydrogen atom. These transformations are intermolecular disproportionation processes (see stable thiophenium ions) or intramolecular 1,2-shifts more familiar for unstable σ-complexes formed on acylation or sulfonation.

4.2 Electrophilic substitution of functionalyzed derivatives of five-membered heterocycles

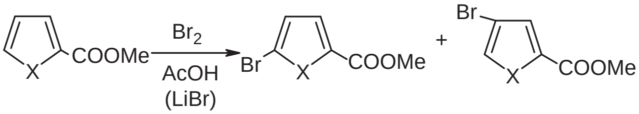
The existence of an electron-releasing substituent in any ring position should promote the formation of products of the electrophilic attack at a free α-position. However, for compounds bearing an electron-withdrawing substituent in position 2, there is a competition between an α-orienting effect of a heteroatom and a "*meta*"-orienting effect of the substituent. The results of this competition greatly differ for pyrrole, thiophene and furan derivatives. The character of these differences can be illustrated by the bromination of methyl 2-carboxylates (68JCS(B)392) (Scheme 17): thiophene and furan esters form only 5-bromosubstituted derivatives while pyrrole-2-carboxylic ester gives a mixture in which 4-bromosubstituted ester predominates.

For aldehydes, which have a stronger electron-withdrawing group, only furfural in the absence of a catalyst gives solely the 5-bromosubstituted derivative (54ZOK575). With 2-thiophenecarbaldehyde a small amount of the 4-isomer is detected together with 5-bromo-2-thiophenecarbaldehyde (64ZOK969), while from 2-pyrrolecarbaldehyde the 4-isomer is formed as almost the sole product and only a trace of the 5-bromosubstituted derivative was detected (65CJC409) (Scheme 18).

On electrophilic substitution of pyrrole, thiophene and furan derivatives carrying a carbonyl substituent at position 2, the orientation may be changed by strengthening its electron-withdrawing ability by the formation of complexes with proton and Lewis acids (see reviews (68AG547, 75IZV344, 86KGS749) and monograph (76MI1)).

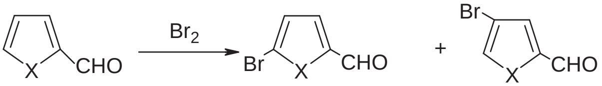
Allowing for the ability of pyrroles to form *β*-substituted products it is not surprising that the complexes with strong Lewis acids and practically any 2-RCO-substitutent in the pyrrole series leads exclusively to products of electrophilic substitution in position 4 (64CJC1279, 66CJC1831, 67CJC897, 69T3879, 71CJC2427, 71CR(273)276, 72BSF283, 78CJC654, 78JOC4849) (Scheme 19).

Modification of a substituent by complex formation with aluminum chloride (59DAN(128)538, 65IZV1539, 73IZV2733, 69DOK(185)91,



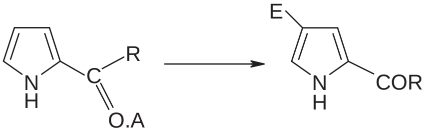
X	k_{OTH}.(for position 5)	α:β-ratio
NH	5.9×10^8	23:77
O	1.2×10^2	α-isomer only
S	1.0	α-isomer only

Scheme 17



X	Ratio	
	2,5-isomer	2,4-isomer
NH	traces	main product
O	2,5-isomer only	-
S	97	3

Scheme 18



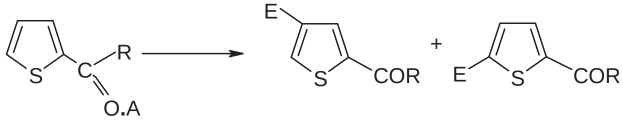
A = $AlCl_3$, $AlBr_3$, $GaCl_3$
R = Alk, AlkO, AlkS
E = Br, Ac, CHO, Alk

Scheme 19

71ZOR1743, 78KGS1474) or by protonation (71IZV1233, 71IZV2841, 71KGS1353) enables a high positional selectivity to be achieved with 2-acylthiophenes. In a mixture of 2,4- and 2,5-substituted products the content of the latter did not exceed a few percent (Scheme 20).

The synthesis of 4-substituted products from 2-acylfurans and 2-acylselenophenes is difficult. Their predominant formation was observed on bromination of aluminum chloride complexes of furfural and to a lesser extent of 2-acetylfuran (73IZV2733). Bromination of complexes of selenophene-2-carbaldehyde and 2-acetylselenophene with $AlCl_3$ leads mainly to 4-substituted derivative (exceeded 70%) (95JHC53). In all cases a significant amount of 4,5-dibromo-substituted products was obtained (Scheme 21). Competing reactions show that the complex of selenophene-2-carbaldehyde with aluminum chloride is brominated more rapidly than its thiophene analogue (95JHC53).

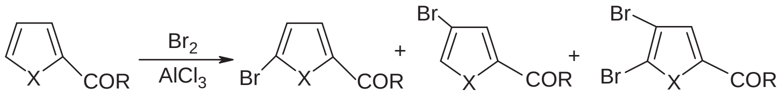
The data considered confirm the reactivity sequence pyrrole ≫ furan > selenophene > thiophene for substrate selectivity on electrophilic substitution (71AHC(13)235) and show that the positional selectivity is reduced in the series furan > selenophene ≥ thiophene > pyrrole, which correlate with that for the relative stability of the onium states of the elements ($O^+ < Se^+ \leq S^+ < N^+$) in agreement with the hypothesis proposed previously (79MI2, 80KGS1587), not including selenophene and its derivatives.



R = H, Me

A	E	Ratio of 2,4- : 2,5-isomer
$AlCl_3$	Br, CH_2Cl, Ac, $ClCH_2CO$	99.5 : 0.5 – 94 : 6
HCl–$SbCl_5$	Br, CH_2Cl, NO_2	98 : 2 – 89 : 11
H_2SO_4	Br, CH_2Cl, NO_2	90 : 10 – 67 : 33

Scheme 20



X	R	Ratio of 5-Br- : 4-Br- : 4,5-Br_2-substituted derivatives
O	Me	30 : 30 : 40
O	H	20 : 65 : 15
Se	Me	8 : 73 : 19
Se	H	4 : 86 : 10

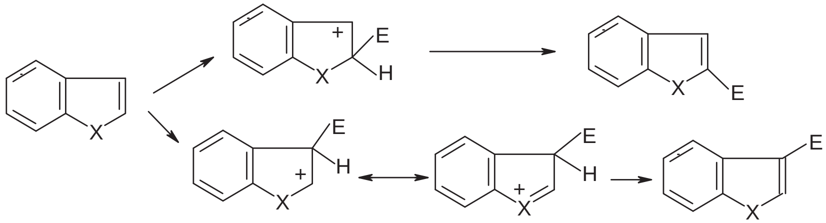
Scheme 21

4.3 Positional selectivities in reactions of indole, benzofuran, benzothiophene and benzoselenophene with electrophiles

Although the quantitative data obtained with the aid of kinetic measurements or by competing reactions are known only for benzothiophene and benzofuran (71AHC(13)235) it may be assumed that for benzannulated five-membered heterocycles with one heteroatom a sequence of relative reactivity analogous to that given above is retained on electrophilic substitution (indole ≫ benzo[*b*]furan > benzo[*b*]thiophene), though the position of benzo[*b*]selenophene relative to benzofuran and benzothiophene is difficult to judge. The *α*:*β* ratios fall along the series benzo[*b*]furan ≥ benzo[*b*]selenophene > benzo[*b*]thiophene > indole, as indicated by the data on acetylation (61JCS4267, 71JCS(B)79, 72BSF3955). These are in agreement with the concept that for delocalization of the positive charge in the nascent *σ*-complexes (without the participation of the benzene ring and consequently its loss of aromaticity) the attack at a *β*-position is more preferred the more stable is the onium state of the ring heteroatom (Scheme 22).

4.4 Quantum chemical study of positional selectivities in reactions of furan, thiophene, selenophene, N-unsubstituted pyrrole and related benzannulated systems with electrophiles

Since there are no quantitative data on the stability of the onium states (see, e.g., (98MI2)), the sequence given above $O^+ < Se^+ \leq S^+ < N^+$ is based on purely qualitative estimations (65HOU(VI/3)327, 55HOU(IX)174, 55HOU(IX)917) arising from the pioneer work of Meerwein (39JPR98).



E = Ac

X	α:β-Ratio	Ref.
NH	0 : 100	61JCS4267
S	1 : 6	71JCS(B)79
Se	7.0 : 1	72BSF3955
O	7.2 : 1	71JCS(B)79

Scheme 22

We undertook a quantum chemical study of the protonation of monocyclic and benzannulated five-membered heterocyclic systems with one heteroatom (03KGS38). The initial calculations, carried out by the semi-empirical CNDO/2 method (81ZOR1129), gave values for the differences in energy of the cations formed on protonation of the α- and β-positions ($\Delta E_{\alpha-\beta}$) that corresponded with the available experimental data on the sequence of change in positional selectivity furan > thiophene > pyrrole. However, the place of selenophene between thiophene and pyrrole in this series predicted by these calculations was contradicted by the experimental results obtained later (95JHC53). The results of calculations by the MNDO and PM3 methods also did not fit the experimental data, possibly linked with poor parametrization for selenium atom (97MI2).

In recent work (03KGS38), the assessment of values of $\Delta E_{\alpha-\beta}$ was carried out using *ab initio* quantum chemical methods RHF/6-31G(d) and MP2/6-31G (including correlation of electrons according to second-order perturbation theory) with the geometry preliminarily calculated by the RHF/6-31D(d) method as well as by B3LYP/6-31G based on density functional theory with complete optimization of the geometry. The main results are given in Table 1. The values of $\Delta E_{\alpha-\beta}$ obtained by all three methods qualitatively correctly reflect the dependencies of α:β ratios, experimentally observed on electrophilic substitution, on the structure of the heteroaromatic compound: furan > selenophene > thiophene > pyrrole and benzo[*b*]furan > benzo[*b*]selenophene > benzo[*b*]thiophene > indole. Special

Table 1 Differences in total energies (E_{tot}) of five-membered heterocycles with one heteroatom and cationic σ-complexes formed on their protonation for α- (ΔE_α) and β-positions (ΔE_β), as well as values of $\Delta E_{\alpha-\beta} = \Delta E_\alpha - \Delta E_\beta$ (all in kcal/mol)[a]

Molecule (cation)	RHF/6-31G(d)			MP2/6-31G(d)			DFT B3LYP/6-31G(d)		
	ΔE_α	ΔE_β	$\Delta E_{\alpha-\beta}$	ΔE_α	ΔE_β	$\Delta E_{\alpha-\beta}$	ΔE_α	ΔE_β	$\Delta E_{\alpha-\beta}$
Pyrrole	−222.0	−214.5	−7.6	−209.0	−204.0	−5.0	−214.7	−209.1	−5.6
Furan	−207.0	−193.8	−13.2	−193.2	−181.4	−11.8	−200.7	−188.5	−12.2
Thiophene	−202.6	−191.1	−11.5	−194.0	−185.5	−8.5	−201.1	−190.8	−10.3
Selenophene	−205.3	−192.6	−12.7	−196.7	−187.0	−9.7	−205.1	−193.5	−11.6
Indole	−218.3	−222.7	4.4	−202.9	−213.0	10.1	−213.3	−218.0	4.7
Benzo[*b*]furan	−218.1	−201.2	−16.9	−202.4	−190.7	−11.7	−204.9	−197.6	−7.3
Benzo[*b*] thiophene	−206.3	−198.9	−7.4	−192.8	−192.1	−0.7	−205.3	−199.8	−5.5
Benzo[*b*] selenophene	−208.7	−198.9	−9.8	−196.8	−186.3	−10.5	−208.5	−202.4	−6.1

[a] The calculated values of total energies used in Tables 1–3 were corrected on molecular vibrations at 0 K using the formula $E_0 = E_{\text{calc}} + k \cdot \text{ZPE}$, where ZPE is zero-point energy correction and k is normalization factor equal to 0.8929 (RHF/6-31G(d), MP2/6-31G(d)) and 0.9613 (B3LYP/6-31G(d)).

attention should be paid to the change in sign of the value of $\Delta E_{\alpha-\beta}$ in the case of indole, which reflects the higher reactivity of its β-position compared with the α-position (α-substituted products are practically not detected from indole with electrophiles).

The geometric characteristics of the systems calculated by the RHF/6-31G method are in good agreement with the experimental data for neutral molecules, which are summarized, for example, in the monograph (00MI1). On going from the neutral molecule to the cation in the case of 2*H*-hetarenium ions the bonds $X_{(1)}$–$C_{(2)}$, $C_{(2)}$–$C_{(3)}$ and $C_{(4)}$–$C_{(5)}$ in the monocyclic and $X_{(1)}$–$C_{(2)}$, $C_{(2)}$–$C_{(3)}$, $C_{(3a)}$–$C_{(4)}$, $C_{(5)}$–$C_{(6)}$ and $C_{(3a)}$–$C_{(7a)}$ in the bicyclic ions are lengthened. On the other hand, the bonds $X_{(1)}$–$C_{(5)}$ and $C_{(3)}$–$C_{(4)}$ in the mono- and $X_{(1)}$–$C_{(7a)}$ and $C_{(3)}$–$C_{(3a)}$ in the bicyclic ions are shortened. In the case of the 3*H*-hetarenium ions the bonds $X_{(1)}$–$C_{(2)}$, and $C_{(4)}$–$C_{(5)}$ in the monocyclic and $X_{(1)}$–$C_{(2)}$ in the bicyclic ions were shortened but the bonds $X_{(1)}$–$C_{(5)}$, $C_{(2)}$–$C_{(3)}$ and $C_{(3)}$–$C_{(4)}$ in the monocyclic and $X_{(1)}$–$C_{(7a)}$, $C_{(2)}$–$C_{(3)}$ and $C_{(3)}$–$C_{(3a)}$ in the bicyclic ions were lengthened. This clearly reflects the changes in bond orders on going from a neutral molecule to a σ-complex. In contrast to the bicyclic 2*H*-hetarenium ions the C–C bond lengths in the benzene rings in their 3*H*-isomers were changed far less than the corresponding values in the neutral molecules and differed less between themselves. All the values were within the range 1.37–1.39 Å characteristic of compounds in the benzene series. This feature, in our opinion, indicates that in the case of bicyclic 3*H*-hetarenium ions the benzene ring does not participate much in the delocalization of the positive charge, which is efficient in the five-membered ring along with the participation of the heteroatom and the $C_{(2)}$ atom (see Scheme 22).

The values of the charges on the atoms do not give a clear reflection of the changes in electron density on going from the neutral molecule to the cation, which affect the π-system most. In particular, the charges on the heteroatoms depend mainly on the electronegativity of the corresponding elements.

The DFT-derived Fukui indexes as reactivity descriptors make it possible to predict the preferential sites of electrophilic attack on pyrrole, furan and thiophene molecules. Their relative reactivities depend on the local softness of the most reactive site in each system. The results obtained by this approach are in total agreement with experiment (05MI1).

This approach allows one to evaluate the preferred sites of protonation and hydrogen bonding (05JPC(A)5509). Based on *ab initio* MO calculations the interactions of furan with H^+ and HF as well as with acids of varying strength (AH^+) have been investigated. The preferred protonation site of the substrate is determined first by the ability of the protonated species (BH^+) to delocalize the acquired positive charge, whereas in determining the preferred site for hydrogen bonding with HF the localization of a pair of electrons at a proton-acceptor site tends to be more important. The behavior of acids stronger than HF lies between these extremes. On interaction of a substrate (B) with a range of acids (AH^+), proton transfer generally takes place when the proton affinity of A is significantly less than that of B. When the proton affinity of A is greater than that of B, a hydrogen-bonded complex is generally formed without proton transfer. Specific interactions in the resulting complexes that allow proton transfer from AH^+ to take place are not predicted on the basis of protonation energies alone.

5. POSITIONAL SELECTIVITY IN REACTIONS OF N-SUBSTITUTED PYRROLES WITH ELECTROPHILES

5.1 Experimental data

Structural changes affect seriously an electrophilic substitution orientation in pyrroles owing to their low positional selectivity in reactions with electrophiles. Thus, in contrast to thiophene, selenophene, and, especially, furan analogues, even a relatively weak type II substituent in position 2 of the pyrrole ring is capable of overcoming the α-orienting effect of the heteroatom and directs an electrophile preferably to the position 4 (68JCS(B)392). *N*-(*p*-Nitrophenyl)pyrrole-2-carbaldehyde undergoes bromination exclusively in position 5 and only in the form of complex with aluminum chloride does it give 4-bromo-1-(*p*-nitrophenyl)pyrrole-2-carbaldehyde (82KGS662). Such behavior is like that of thiophene-2-carbaldehyde. Below we discuss the orientation of electrophilic substitution reactions of N-substituted pyrroles where a considerable effect of a substituent at the nitrogen atom on the ratio of α:β-isomers is expected. According to numerous data from quantum chemical calculations by semi-empirical methods (79MI3) (see also the references cited in the review (95ZOR801)), σ-complexes modeling the substitution at the α-position of pyrroles are thermodynamically prefered over their β-isomers, while kinetic factors (higher negative charge) favor β-substitution.

The α:β ratio is influenced by such factors as the character and steric requirement of a substituent at the nitrogen atom as well as its electrophile nature that may be dependent on the solvent used. Difficulty in interpretation of existing data is caused by simultaneous action of different factors.

5.1.1 Predominant steric effect of an N-substituent

The preparation of β-substituted *N*-(triisopropylsilyl)pyrroles is influenced by steric shielding of α-positions by the triisopropylsilyl protecting group (90JOC6317, 06AX(E)o3282, 07SM(157)924). Among electrophiles directed by a 1-(*i*-Pr)$_3$Si group into position 3 are Br^+, I^+, NO_2^+ and RCO^+ cations. Vilsmeier formylation of 1-(triisopropylsilyl)pyrrole is also directed into position 3. The protecting group is removed from the nitrogen atom quantitatively by fluoride anion (90JOC6317).

The fact that the percentage of *β*-aldehydes from Vilsmeier formylation of *N*-alkylpyrroles increases from *N*-methyl- to *N*-(*t*-butyl)pyrrole can be explained by the increasing steric shielding of the *α*-positions by an *N*-alkyl group in the same sequence (70JCS(C)2563) (Scheme 23).

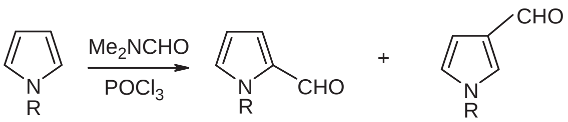
The positional selectivity on alkylation of *N*-(phenylsulfonyl)pyrrole in the presence of $AlCl_3$ changes from preferential *α*-substitution (with EtBr), through the formation of 1:1 mixture of *α*- and *β*-substituted derivatives (with *i*-PrCl), to preferential (80%) formation of the *β*-substituted derivative in the case of *t*-BuCl (85CJC896).

Regioselectivity of phosphorylation of 1-alkylpyrroles depends on the steric requirement of the substituent: 1-(*t*-butyl)pyrrole was regioselectively phosphorylated in 3-position by PBr_3 or PCl_3 (05HC599, 05KGS1102), while phosphorylation of 1-isopropylpyrrole with same phosphorus trihalides proceeds nonselectively at positions 2 and 3. Thermal 1,2-migration of the dihalophosphino group is observed, which quantitatively yields the 3-isomer (05HC599).

Reactions of pyrrole or 1-methylpyrrole with *N*-aroylbenzotriazoles (ArCO = 4-MeC_6H_4CO, 4-$O_2NC_6H_4CO$, 4-$Et_2NC_6H_4CO$, 2-furoyl, 2-pyridoyl, 2-indolcarbonyl, 2-pyrroloyl) in the presence of $TiCl_4$ afford 2-acylpyrroles in yields from 21% to 94%. In contrast, 1-(triisopropylsilyl) pyrrole under the same conditions gives the corresponding 3-acyl-substituted pyrroles (03JOC5720).

5.1.2 Predominant polar effect of N-substituent

In the case of *N*-(phenylsulfonyl)pyrrole, which also contains a substituent with high steric requirement at N atom, only *α*-aldehyde is formed (81TL4899). We have proposed that such a variation of orientation can also be caused by stabilization of the onium state of the



R	α:β-ratio	
Me	α-isomer only	-
Et	11.5	1
i-Pr	1.9	1
t-Bu	1	14

Scheme 23

heteroatom by electron-releasing and its destabilization by electron-withdrawing substituents (82KGS662, 94H(37)2029, 97MI2, 03KGS38). The same is true for substituents like *p*-nitrophenyl.

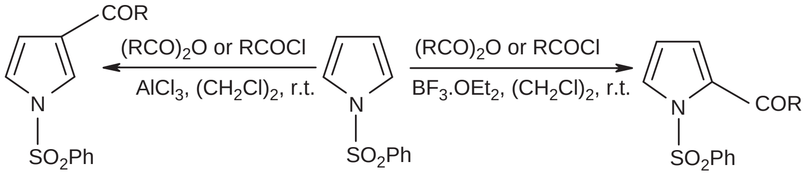
N-Tosylpyrroles are smoothly converted into the corresponding 2-acylpyrroles by reaction with carboxylic acids and trifluoroacetic anhydride; little or none of the isomeric 3-acyl derivatives being formed (04TL9573). The reactions of *N*-phenylsulfonylpyrrole were studied in detail. This substituent was simultaneously offered by two research groups (81TL4899, 81TL4901, 83JOC3214, 85CJC896) as an original protecting group that owing to its electron-withdrawing effect can preferably deactivate the α-position to give β-substituted derivatives, the $PhSO_2$ group being readily removed on alkaline hydrolysis (83JOC3214). The effect of the $PhSO_2$ group was studied in most detail for Friedel–Crafts acylation (81TL4899, 81TL4901, 83JOC3214, 84F277, 84YZ238, 85CJC896, 95TL1401, 98JHC1345). 1-(Phenylsulfonyl)pyrrole gives only 2-substituted derivatives on both Rieche formylation with alkyl dichloromethyl ethers (81TL4899, 81TL4901) and Vilsmeier formylation in the DMF–$POCl_3$ system (81TL4899), as well as on cyanation with cyanogen bromide in the presence of $AlCl_3$ or with chlorosulfonyl isocyanate (81TL4899, 81TL4901).

However, the real effects of substituents at ring nitrogen atom can be masked by further transformations of the initially formed products under reaction conditions.

5.1.3 Predominant effect of the electrophile nature and/or isomerization of preliminary formed α-substituted product

Orientation of electrophilic substitution in pyrrole series strongly depends on the nature of electrophile. This is evident from results of reactions carried out under the action of both the same electrophile on compounds with varied substituent at nitrogen atom and for different electrophiles with the same N-substituted pyrrole. Electrophilic hydrogen–deuterium exchange was investigated (86JHC1475) for pyrroles carrying a deactivating group X (X = Ac, PhCO, $MeSO_2$, CF_3SO_2, $PhSO_2$, Me_3N^+, Me_2NH^+) on the N atom. In all cases, the rate of the isotope exchange in α-positions exceeds that in β-positions by more than one order of magnitude. Allylation of *N*-methylpyrrole is directed preferably to the α-position (the α:β-ratio is 4:1) (86CC688), while silylation proceeds exclusively in the β-position (86T1299).

The role of the nature of the reagent (depended on reaction conditions) reveals itself most distinctly in the fact that acylation of *N*-(phenylsulfonyl)pyrrole in the presence of aluminum chloride results in the 3-acyl-substituted derivatives, while the reaction in the presence of boron trifluoride etherate gives the 2-isomers (83JOC3214) (Scheme 24).



Scheme 24

Nitration (HNO_3–Ac_2O) of 1-(phenylsulfonyl)pyrrole results almost exclusively in the 3-substituted product (83JOC3214). As was established recently, the same orientation displays the sulfonation of unsubstituted pyrrole and *N*-methylpyrrole with pyridine sulfotrioxide (00TL6605). The chlorosulfonation of 1-(*p*-R-phenylsulfonyl-1*H*-pyrroles (R = H, CH_3, NO_2, CF_3) and 1-arylsulfonyl-1*H*-indoles using chlorosulfonic acid in acetonitrile has been shown to give corresponding 3-sulfonyl chlorides (06T1699).

5.2 Transformations of initially formed α-substituted derivatives

The differences in orientation given above are usually interpreted within the framework of the HSAB principle: the orientation for a "hard" electrophile is determined mainly by negative charge in position 3, while the substitution in position 2 in the case of "softer" electrophile is the result of orbital control (81TL4901). However, these facts are resulted probably from rearrangements of initially formed 2-substituted derivatives to 3-isomers. In particular, formylation and acylations of 1-pentafluorophenyl-1*H*-pyrrole proceed mainly at the position 2. The 2-substituted products formed in these reactions selectively and in high yield are converted into 3-substituted isomers by treatment with trifluoromethanesulfonic acid. The latter transformation has been proposed as a general synthesis of 3-acylpyrroles (03MI2).

Hetarenium ions, originated on reactions of π-excessive hetarenes with cationic reagents used in reactions such as nitration, acylation, formylation, sulfonation, sulfonylation, are unstable and on deprotonation give mainly or exclusively expected α-substituted derivatives. However, the latter can undergo rearrangements to β-isomers under the action of acids. For carbonyl (81JOC839, 84KGS562) and sulfonyl (82JOC3668) compounds of pyrrole series, such isomerizations are well documented as intramolecular transformations of *ipso*-protonated pyrrole derivatives proceeding *via* 1,2-shift. The same mechanism is described (80KGS1235) for acid-catalyzed rearrangement of 3-acylindoles to 2-isomers (72KGS68, 78KGS921). Taking into account the nature of counterions in σ-complexes formed on acylation of *N*-(phenylsulfonyl) pyrrole, it is possible to explain the above-mentioned differences in final products obtained with different Lewis acids (83JOC3214). In both cases, electrophiles attack the α-position of pyrrole ring to form a normal cationic intermediate but with $AlCl_3$ it has the structure of the product of *ipso*-protonation of position 2 with super acid $HAlCl_4$ and undergoes rapid isomerization to 3-isomer even at room temperature, while in the second case, the strength of the acid is much lower owing to the nature of BF_3 bound in complex with diethyl ether.

5.3 Quantum chemical study of positional selectivity in reactions of N-substituted pyrroles with electrophiles

Using RHF/6-31G(d), MP2/6-31G(d)//RHF/6-31G(d) and B3LYP/6-31G(d) methods, a quantum chemical investigation of model *N*-R-pyrroles (R = Me, Et, *i*-Pr, *t*-Bu, $CH{=}CH_2$, $C{\equiv}CH$, Ph, $PhSO_2$, 4-$O_2NC_6H_4$) and their α- and β- protonated σ-complexes was carried out (03ARK59). The values of the differences in the energies of α- and β-protonated cations ($\Delta E_{\alpha-\beta}$) that can characterize the positional selectivity of electrophilic substitution are presented in Table 2. The $\Delta E_{\alpha-\beta}$ values obtained by all three methods do not indicate preferential β-substitution in any of the molecules studied. At the same time, a comparison of $\Delta E_{\alpha-\beta}$ values shows that the presence of an alkyl substituent at the N atom of the cycle makes β-substitution relatively more probable than in the case of N-unsubstituted pyrrole, while other substituents should promote the formation of α-substituted derivatives to approximately the same or greater extent as in the case of pyrrole.

Thus, the calculated values of total energies of cationic σ-complexes formed by α- and β-protonation of model molecules of *N*-phenylsulfonyl- and *N*-(4-nitrophenyl)pyrroles are consistent with experimental data concerning preferable reactivity of their α-positions, while the role of steric factors and charges on atoms should be considered for interpretation of the increase in percentage of β-substituted derivatives on formylation of *N*-alkylpyrroles in the sequence: Me < Et < *i*-Pr < *t*-Bu.

The main geometric characteristics and atomic charges calculated in Ref. 03ARK59 are not presented here. It should be only mentioned that the geometries of neutral molecules of *N*-isopropylpyrrole and *N*-(*tert*-butyl)pyrrole are evidence of steric strain. The bonds $N_{(1)}$–$C_{(2)}$ and $N_{(1)}$–$C_{(5)}$ in the former differ markedly from one another in length, while in the latter the distances between the centers of the hydrogen atom in position 2 and the nearest H atoms of two methyl groups (2.39 Å) are lower or equal to the sum of van der Waals radii. Also, the distance from the center of H atom in the position 5 to the center of the nearest H atom of the methyl group (2.33 Å) is lower than the sum of van der Waals atoms that is equal to 2.4 Å.

Table 2 Differences in total energies (E_{tot}) of N-substituted pyrroles and cationic σ-complexes formed on their protonation for the α- (ΔE_{α}) and β-positions (ΔE_{β}), and also values of $\Delta E_{\alpha-\beta} = \Delta E_{\alpha} - \Delta E_{\beta}$ (all in kcal/mole)

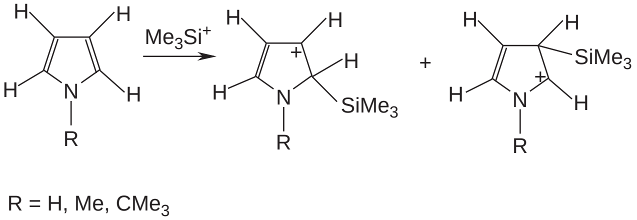
Molecule	RHF/6-31G(D)//RHF/6-31G(D)			MP2/6-31G(D)//RHF/6-31G(D)			B3LYP/6-31G(D)//B3LYP/6-31G(D)		
	ΔE_{α}	ΔE_{β}	$\Delta E_{\alpha-\beta}$	ΔE_{α}	ΔE_{β}	$\Delta E_{\alpha-\beta}$	ΔE_{α}	ΔE_{β}	$\Delta E_{\alpha-\beta}$
N-Methylpyrrole	−226.0	−221.6	−4.4	−214.1	−210.5	−3.6	−221.2	−216.0	−5.2
N-Ethylpyrrole	−228.0	−223.0	−5.0	−215.2	−211.8	−3.4	−221.6	−217.6	−4.0
N-Isopropylpyrrole	−128.7	−124.4	−4.3	−115.8	−113.2	−2.6	−222.9	−219.6	−3.3
N-(*t*-Butyl)pyrrole	−231.6	−227.1	−4.5	−218.7	−215.8	−2.9	−225.4	−221.9	−3.5
N-Vinylpyrrole	−218.7	−212.5	−6.2	−206.6	−202.2	−4.4	−216.9	−212.5	−4.4
N-Ethinylpyrrole	−215.8	−207.7	−8.1	−204.5	−198.5	−6.0	−211.4	−204.3	−7.1
N-Phenylpyrrole	−226.4	−221.8	−4.6	−217.1	−213.4	−3.7	−221.5	−217.1	−4.4
N-Phenylsulfonyl-pyrrole	−217.1	−209.1	−8.0	−207.4	−202.1	−5.3	−215.8	−210.4	−5.4
N-(4-Nitrophenyl)-pyrrole	−216.5	−210.5	−6.0	−205.8	−201.9	−3.9	−211.5	−206.7	−4.8

The charges on the atoms, in the molecules of *N*-isopropylpyrrole and *N*-(*tert*-butyl)pyrrole, are distributed unsymmetrically, which can be regarded as the result of disturbance of their geometrical symmetry. A similar distribution in the case of *N*-vinylpyrrole is caused by the arrangement of the vinyl group that is nearly coplanar with the ring, which provides for conjugation of both fragments. As a whole, the C atoms in the β-positions of pyrrole cycle carry marked negative charges while the charges on the C atoms in the α-positions are nearly zero. The charge values can be used to explain the β-substitution products, but these values have no predictive ability.

Thus, in general case, the results of calculation of 2*H*- and 3*H*-pyrrolium ions do not allow one to foresee orientation of electrophilic attack of N-substituted pyrroles. The only exception is the reaction of hydrogen isotopic exchange. For this reaction, the σ-complexes studied can be regarded as adequate models, and the results of calculations are in complete consistence with experimental data for a series of N-substituted pyrroles (86JHC1475).

A previous study (81ZOR1134) performed by the semi-empirical CNDO/2 method using formalism of so-called pseudo-atoms revealed a dependence of orientation of electrophilic substitution in the series of five-membered heterocycles upon the characteristics of electrophiles, such as electronegativity, ionic and covalent radii. A probability of preferential β-substitution was predicted for reactions of pyrrole with electrophiles having characteristics near to that of silicon atom. It could be proposed that modern quantum chemical calculations for real rather than model electrophiles, and accounting for the solvent effects, will allow orientation of electrophilic substitution in N-substituted pyrrole derivatives to be predicted. First results of such a kind show that the consistency with experiment can be achieved even without accounting solvent effect (04MI1, 05ZOR1362).

Positional selectivity (α:β ratio) of electrophilic substitution in pyrrole, *N*-methylpyrrole and *N*-(*tert*-butyl)pyrrole was analyzed by *ab initio* [RHF/6-31G(d), MP2/6-31G(d)//RHF/6-31G(d)] and DFT [B3LYP/6-31G(d)] calculations of σ-complexes derived from the substrates with trimethylsilyl cation (Scheme 25). All three methods predict



Scheme 25

preferential α-orientation for pyrrole and β-orientation for *N*-(*tert*-butyl) pyrrole (Table 3). In the case of *N*-methylpyrrole only MP2/6-31G(d) and B3LYP/6-31G(d) methods give results adequate to the experimental data (86T1299), according to which trimethylsilylation of *N*-alkylpyrroles with trimethylsilyl triflate gives the corresponding β-substituted products.

The calculated values of total energies of protonation and trimethylsilylation used in Tables 1–3 were corrected on molecular vibrations at 0 K. To simplify quantum chemical calculations, the latter for sulfonation intermediates (05ZOR1362, 06KGS1647, 07KGS34) were mainly carried out by DFT B3LYP/6-31G(d) method taking into account that it gives results closely related to those obtained by *ab initio* MP2/6-31G(d)//RHF/6-31G(d) method. The zero-point energy correction also was not taken into consideration since the use of this correction for a series of N-substituted pyrroles (03ARK59) as well as for their sulfonation intermediates (07IZV1425) has a little effect ($\sim 0.5\,\mathrm{kcal\,mol^{-1}}$) on $\Delta E_{\alpha-\beta}$ values. Remarkable features of sulfonation mechanism are the reversibility of the process and the possibility of participation of both usual σ-complex appearing as the result of addition of HO_3S^+ cation to an aromatic molecule ($\mathbf{A}_{\mathrm{sulf}}$ and $\mathbf{B}_{\mathrm{sulf}}$, Scheme 26) and a bipolar σ-complex deprotonating with the formation of an anion of sulfonic acid ($\mathbf{A}_{\mathrm{sulf/bipolar}}$ and $\mathbf{B}_{\mathrm{sulf/bipolar}}$, Scheme 27) (68MI1, 69RTC860, 98MI3). The formation of bipolar σ-complex on action of pyridine sulfotrioxide $Py \cdot SO_3$, the reagent used for sulfonation of pyrrole and *N*-methylpyrrole (00TL6605) seems to be more probable.

The results of calculations (05ZOR1362, 06KGS1647, 07KGS34) testify to the preferability of σ-complexes $\mathbf{A}_{\mathrm{sulf/bipolar}}$, formed on the attack of α-position and at the same time make evident the thermodynamic preferability of β-sulfonic acids, which increases from pyrrole to *N*-methylpyrrole and further to *N*-(*tert*-butyl)pyrrole. The imaginary contradiction of these results was interpreted taking into account two groups of arguments.

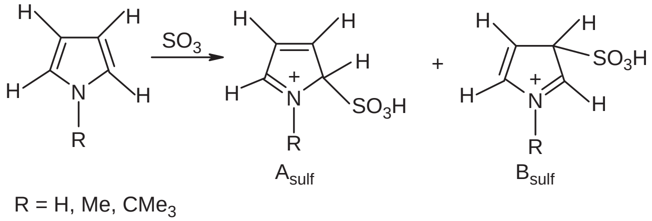
The first group (05ZOR1362) is based on above-mentioned reversibility of the first stage of sulfonation and high stability of σ-complexes of the type $\mathbf{A}_{\mathrm{sulf/bipolar}}$, formed by the attack of α-position. Indeed, the values of differences $E_{\mathrm{HetSO3H}-\alpha}$-$E_{\alpha}$ and $E_{\mathrm{HetSO3H}-\beta}$-$E_{\beta}$, characterizing the gain in energy for transformation of σ-complex to sulfonic acid in the series pyrrole – *N*-methylpyrrole – *N*-(*tert*-butyl)pyrrole considerably differ for α- (9.7, 7.5, $3.3\,\mathrm{kcal\,mol^{-1}}$) and β-positions (18.0, 18.9, 19.4 $\mathrm{kcal\,mol^{-1}}$), respectively. Heat effects ($\mathrm{kcal\,mol^{-1}}$) of sulfonation with SO_3 in α- and β-positions have been estimated as 120.5 and 121.4 for pyrrole, 137.7 and 139.5 for *N*-methylpyrrole and 186.5 and 193.6 for *N*-(*tert*-butyl)pyrrole, correspondingly.

Table 3 Total energies of cationic σ-complexes formed from pyrrole, *N*-methylpyrrole, and *N*-(*tert*-butyl)pyrrole on addition of trimethylsilyl cation at α- (E_α) and β-positions (E_β) as well as $E_{\alpha-\beta}$ values characterizing preferable site of electrophilic attack

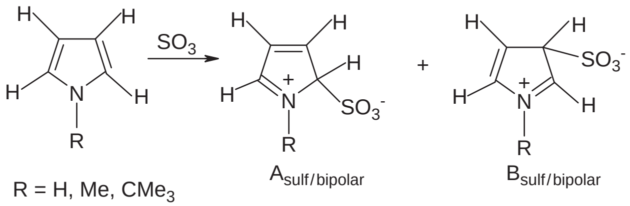
Molecule	RHF/6-31G(d)//RHF/6-31G(d)			MP2/6-31G(d)//RHF/6-31G(d)			B3LYP/6-31+G(d)//B3LYP/6-31+G(d)		
	E_α, a.u.	E_β, a.u.	$\Delta E_{\alpha-\beta}$, kcal/mole	E_α, a.u.	E_β, a.u.	$\Delta E_{\alpha-\beta}$, kcal/mole	E_α, a.u.	E_β, a.u.	$\Delta E_{\alpha-\beta}$, kcal/mole
Pyrrole	−616.2200	−616.2144	−3.5	−617.3561	−617.3557	−0.3	−619.0334	−619.0301	−2.1
N-Methylpyrrole	−655.2279	−655.2267	−0.8	−656.4982	−656.4997	0.9	−658.3212	−658.3216	0.2
N-(*tert*-Butyl) pyrrole	−772.2489	−772.2577	5.6	−773.9269	−773.93400	4.4	−776.1832	−776.1912	5.0

The other arguments (06KGS1647, 07KGS34) are based on the assumption that the presence of at least a small amount of the less favorable intermediate **B** in the reaction mixture, which makes it possible for the reaction to proceed by the less hindered route to the formation of *β*-pyrrolesulfonic acid, can be ensured as the result of the α/*β*-migration of the SO_3 group in the *σ*-complex (Scheme 28).

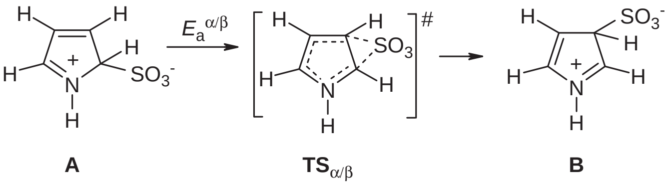
The quantum chemical calculations (07KGS34) of the energy parameters for the reaction of pyrrole and SO_3 with regard to the solvation effect were carried out by the B3LYP/6-31G(d) and HF/3-21+G methods using the model of overlapping spheres. In both methylene chloride ($\varepsilon = 8.93$) and dimethyl sulfoxide ($\varepsilon = 46.7$) as model solvents the calculated activation energy of the rearrangement to the more favorable *β*-pyrrolesulfonic acid for the less favorable *β*-isomer of the *σ*-complex was lower than on the path to the formation of the α-pyrrolesulfonic acid. It was shown that the significant increase in the polarity of the model



Scheme 26



Scheme 27



Scheme 28

medium in the transition to DMSO does not lead to substantial change in the energy parameters of the reaction. Thus, the activation energy $E_a^{\alpha/\beta}$ for the isomerization of σ-complexes $\mathbf{A} \rightarrow \mathbf{B}$ calculated for a solution in methylene chloride amounts to only 11.0 kcal mol^{-1}, whereas the dissociation of **A** into the initial pyrrole and SO_3 requires 20.9 kcal mol^{-1}. In the case of DMSO, the activation energy $E_a^{\alpha/\beta}$ increases only by 1.6 kcal mol^{-1} compared with the value calculated for methylene chloride and as before the ratio of the energy expenditures on the isomerization and dissociation routes of complex **A** (12.6 against 23.2 kcal mol^{-1}, respectively) suggests α/β-migration. The explanation for the positional selectivity during the sulfonation of pyrrole using $Py \cdot SO_3$ involves the participation of the pyridine in the transformation of the σ-complexes into the products.

Quantum chemical calculations have been made of the energy characteristics of the molecules of pyrrole, furan, thiophene and selenophene, the simplest derivatives of N, O, S and Se with sp^3- and sp^2-hybridized C atoms and heteroatoms, and also of the products of addition of proton or of certain other electrophiles such as Me^+, SiH_3^+ and BH_3 to these molecules (08KGS1645). The calculations were carried out by HF, B3LYP and MP2 methods with the 6-31+G(d) basis set with corrections to the energy of zero-point vibrations. The same methods have been used for calculations of model molecules containing two heteroatoms in the sp^3- and sp^2-hybridization states with different combinations of N, O, S and Se atoms (08KGS1801). The latter models allow one to compare the total energies of isomers of some particular cation with more than one heteroatom where only one of the heteroatoms exists in a cationic state. It was shown that the values of the affinity of the nitrogen-containing systems toward the electrophile were significantly greater than for their analogues, derivatives of chalcogens, while the relative stability of the onium states of the latter depends both on the hybridization of the heteroatoms, and also on the nature of the electrophile. Analysis of the results obtained made it possible to build a stability series of the onium compounds and to interpret the special features of the positional selectivity in electrophilic substitution reactions of five-membered heteroaromatic compounds with one heteroatom. Particularly, the calculation of affinity of proton and other electrophiles to N-substituted pyrroles may turn out useful for estimation of relative stabilities of nitrogen atoms carrying different substituents.

REFERENCES

39JPR98	H. Meerwein, *J. Prakt. Chem. [2]*, **154**, 98 (1939).
43OSC(2)8	*"Organic Syntheses"*, Coll. Vol. 2, p. 8. Wiley, New York (1943).

50JA1910 S. L. Meisel, G. C. Johnson, and H. D. Hartough, *J. Am. Chem. Soc.*, **72**, 1910 (1950).

53LA(583)93 H. H. Schlubach and V. Franzen, *Liebich Ann.*, **583**, 93 (1953).

54ZOK575 Z. N. Nazarova, *Zh. Obshch. Khim.*, **24**, 575 (1954).

55HOU(IX)174 J. Goerdeler, in "*Houben-Weyl Methoden der organischen Chemie*", 4 Aufl., Bd. IX, S. 174–194, G. Thieme Verlag, Stuttgart (1955).

55HOU(IX)917 H. Reinboldt, in "*Houben-Weyl Methoden der organischen Chemie*", 4 Aufl., Bd. IX, S. 917–1209, G. Thieme Verlag, Stuttgart (1955).

56JOC761 F. E. Condon, *J. Org. Chem.*, **21**, 761 (1956).

57JCS4018 H. A. Potts and G. F. Smith, *J. Chem. Soc.*, 4018 (1957).

59CJC1859 R. J. Abraham, E. Bullock, and S. S. Mitra, *Can. J. Chem.*, **37**, 1859 (1959).

59DAN(128)538 Ya. L. Gol'dfarb and Yu. B. Vol'kenshtein, *Dokl. Akad. Nauk SSSR*, **128**, 536 (1959).

61JCS4267 G. Hart, L. D. R. Liljegren, and K. T. Pitts, *J. Chem. Soc.*, 4267 (1961).

61ZOK1958 A. Fabricy, *Zh. Obshch. Khim.*, **31**, 1958 (1961).

63JA26 E. B. Whipple, Y. Chiang, and R. L. Hinman, *J. Am. Chem. Soc.*, **85**, 26 (1963).

63JA2763 Y. Chiang and E. B. Whipple, *J. Am. Chem. Soc.*, **85**, 2763 (1963).

63ZOK3768 A. Fabricy and K. Kozlowski, *Zh. Obshch. Khim.*, **33**, 3768 (1963).

64CJC1279 H. J. Anderson and L. C. Hopkins, *Can. J. Chem.*, **42**, 1279 (1964).

64ZOK969 Ya. L. Gol'dfarb, Yu. B. Vol'kenshtein, and B. V. Lopatin, *Zh. Obshch. Khim.*, **34**, 969 (1964).

65CJC409 H. J. Anderson and S.-F. Lee, *Can. J. Chem.*, **43**, 409 (1965).

65IZV1539 S. G. Mairanovskii, N. V. Barashkova, and Yu. B. Vol'kenshtein, *Izv. Akad. Nauk SSSR. Ser. Khim.*, 1539 (1965).

65HOU(VI/3)327 H. Meerwein, in "*Houben-Weyl Methoden der organischen Chemie*", 4 Aufl., Bd. VI/3, S. 327–365, G. Thieme Verlag, Stuttgart (1965).

66CJC1831 H. J. Anderson and L. C. Hopkins, *Can. J. Chem.*, **44**, 1831 (1966).

66MC1088 A. Fabricy and K. Kozlowski, *Monatsh. Chem.*, **97**, 1088 (1966).

66RZC1657 A. Fabricy, *Roczn. Chem.*, **40**, 1657 (1966).

66RTC1072 H. Hogeveen, *Recl. Trav. Chim.*, **85**, 1072 (1966).

67CJC897 H. J. Anderson and C. W. Huang, *Can. J. Chem.*, **45**, 897 (1967).

67RZC251 A. Fabricy and K. Kozlowski, *Roczn. Chem.*, **41**, 251 (1967).

67TL2951 U. E. Wiersum and H. Winberg, *Tetrahedron Lett.*, 2951 (1967).

68AG547 Ya. L. Gol'dfarb, Yu. B. Vol'kenshtein, and L. I. Belen'kii, *Angew. Chem.*, **80**, 547 (1968). *Angew. Chem. Int. Ed.*, **7**, 519 (1968).

68JCS(B)392 P. Linda and G. Marino, *J. Chem. Soc. (B)*, 392 (1968).

68JCS(C)2526 C. O. Bender and R. Bonnett, *J. Chem. Soc. (C)*, 2526 (1968).

68MI1 H. Cerfontain, *Mechanistic Aspects in Aromatic Sulfonation and Desulfonation*, Intersc. Publ., New York (1968).

69CC165 R. F. Curtis, D. M. Jones, G. Ferguson, D. M. Hawley, J. G. Sime, K. K. Cheung, and G. Germain, *Chem. Commun.*, 165 (1969).

69DOK(185)91 Ya. L. Gol'dfarb, A. P. Yakubov, and L. I. Belen'kii, *Dokl. Akad. Hauk SSSR*, **185**, 91 (1969).

69RTC860 C. W. F. Kort and H. Cerfontain, *Recl. Trav. Chim.*, **88**, 860 (1969).

69T3879 C. E. Loader and H. J. Anderson, *Tetrahedron*, **25**, 3879 (1969).

70AHC(12)1 N. N. Magdesieva, *Adv. Heterocycl. Chem.*, **12**, 1 (1970).

70JCS(C)2563 C. F. Candy, R. A. Jones, and P. H. Wright, *J. Chem. Soc. (C)*, 2563 (1970).

70RTC553	D. M. Brower and J. A. van Doorn, *Recl. Trav. Chim.*, **89**, 553 (1970).
70ZOR2518	L. I. Belen'kii, A. P. Yakubov, and Ya. L. Gol'dfarb, *Zh. Org. Khim.*, **6**, 2518 (1970).
71AHC(13)235	G. Marino, *Adv. Heterocycl. Chem.*, **13**, 235 (1971).
71CJC2427	J. K. Groves, H. J. Anderson, and H. Nagy, *Can. J. Chem.*, **49**, 2427 (1971).
71CR(273)276	C. Jaureguiberry, M. C. Fournier-Zaluski, J. P. Chevallier, and B. Roques, *Compt. Rend.*, **273**, 276 (1971).
71IZV1233	Ya. L. Gol'dfarb, E. I. Novikova, and L. I. Belen'kii, *Izv. Akad. Nauk SSSR. Ser. Khim.*, 1233 (1971).
71IZV2841	Ya. L. Gol'dfarb, E. I. Novikova, and L. I. Belen'kii, *Izv. Akad. Nauk SSSR. Ser. Khim.*, 2841 (1971).
71JCS(B)79	S. Clementi, P. Linda, and G. Marino, *J. Chem. Soc. (B)*, 79 (1971).
71KGS1353	L. I. Belen'kii, E. I. Novikova, and Ya. L. Gol'dfarb, *Khim. Geterotsikl. Soed.*, 1353 (1971). [*Chem. Heterocycl. Compd.*, **7**, 1265 (1971) (Engl. Transl.)].
71ZOK179	T. A. Melent'eva, T. A. Filippova, L. V. Kaznskaya, I. M. Kustanovich, and V. M. Berezovskii, *Zh. Obshch. Khim.*, **41**, 179 (1971).
71ZOR1743	L. I. Belen'kii, I. B. Karmanova, and Ya. L. Gol'dfarb, *Zh. Org. Khim.*, **7**, 1743 (1971).
72BSF283	P. Fournari, M. Farnier, and C. Fournier, *Bull. Soc. Chim. Fr.*, 283 (1972).
72BSF3955	T. Quang Minh, F. Mantovani, P. Faller, L. Christiaens, and M. Renson, *Bull. Soc. Chim. Fr.*, 3955 (1972).
72JOC3618	J. B. Harbuck and H. Rapoport, *J. Org. Chem.*, **37**, 3618 (1972).
72KGS68	V. A. Budylin, A. N. Kost, E. D. Matveeva, and V. I. Minkin, *Khim. Geterotsikl. Soed.*, 68 (1972). [*Chem. Heterocycl. Compd.*, **8**, 63 (1972) (Engl. Transl.)].
72KGS336	M. I. Struchkova, G. G. Dvoryantseva, N. R. Kostyuchenko, Yu. N. Sheinker, Yu. E. Sklyar, and R. P. Evstigneeva, *Khim. Geterotsikl. Soed.*, 336 (1972). [*Chem. Heterocycl. Compd.*, **8**, 305 (1972) (Engl. Transl.).
72KGS1594	V. G. Kul'nevich and Yu. M. Shapiro, *Khim. Geterotsikl. Soed.*, 1594 (1972). [*Chem. Heterocycl. Compd.*, **8**, 1443 (1972) (Engl. Transl.)].
72RTC1359	D. M. Brower, J. A. van Doorn, and A. A. Kiffen, *Recl. Trav. Chim.*, **91**, 1359 (1972).
73IZV1918	Z. N. Parnes, G. I. Bolestova, L. I. Belen'kii, and D. N. Kursanov, *Izv. Akad. Nauk SSSR. Ser. Khim.*, 1918 (1973).
73IZV2733	L. I. Belen'kii, Ya. L. Gol'dfarb, and G. P. Gromova, *Izv. Akad. Nauk SSSR. Ser. Khim.*, 2733 (1973).
73TL3929	H. Hogeveen, R. M. Kellogg, and K. A. Kuindersma, *Tetrahedron Lett.*, 3929 (1973).
73ZOR1959	A. P. Yakubov, L. I. Belen'kii, and Ya. L. Gol'dfarb, *Zh. Org. Khim.*, **9**, 1959 (1973).
74BCJ1467	A. Ishigaki and T. Shono, *Bull. Chem. Soc. Jpn.*, **17**, 1467 (1974).
74JA884	G. A. Olah, J. R. De Member, Y. K. Mo, J. J. Svoboda, P. Schilling, and J. A. Olah, *J. Am. Chem. Soc.*, **96**, 884 (1974).
75IZV344	L. I. Belen'kii, *Izv. Akad. Nauk SSSR. Ser. Khim.*, 344 (1975).
75T311	D. N. Kursanov, Z. N. Parnes, G. I. Bolestova, and L. I. Belen'kii, *Tetrahedron*, **31**, 311 (1975).

75TL3619	H. Winberg and U. E. Wiersum, *Tetrahedron Lett.*, 3619 (1975).
75ZOR424	L. I. Belen'kii, A. P. Yakubov, and Ya. L. Gol'dfarb, *Zh. Org. Khim.*, **11**, 424 (1975).
76JCS(P2)323	P. B. Koster and M. J. Janssen, *J. Chem. Soc., Perkin Trans. 2*, 323 (1976).
76MI1	L. I. Belen'kii, in "*Novye Napravleniya Khimii Tiofena* (*New Trends in Thiophene Chemistry*)" (Ya. L. Gol'dfarb, ed.), Chapter 1, pp. 16–95, Nauka, Moscow (1976) (in Russian).
76T1767	M. P. Carmody, M. J. Cook, N. L. Dassanayake, A. R. Katritzky, P. Linda, and R. D. Tack, *Tetrahedron*, **32**, 1767 (1976).
77JOC3952	A. G. Anderson and M. M. Exner, *J. Org. Chem.*, **42**, 3952 (1977).
77ZOR364	L. I. Belen'kii, A. P. Yakubov, and I. A. Bessonova, *Zh. Org. Khim.*, **13**, 364 (1977).
78CJC654	H. J. Anderson, C. R. Ricke, T. G. Costello, C. T. Loader, and G. H. Barnett, *Can. J. Chem.*, **56**, 654 (1978).
78JA4326	H. Hart and M. Sasaoka, *J. Am. Chem. Soc.*, **100**, 4326 (1978).
78JOC4849	P. Barker, P. Gendler, and H. Rappoport, *J. Org. Chem.*, **43**, 4849 (1978).
78KGS921	V. A. Budylin, M. S. Ermolenko, and A. N. Kost, *Khim. Geterotsikl. Soed.*, 921 (1978). [*Chem. Heterocycl. Compd.*, **14**, 742 (1978) (Engl. Transl.)].
78KGS1474	Ya. L. Gol'dfarb, I. B. Karmanova, Yu. B. Vol'kenshtein, and L. I. Belen'kii, *Khim. Geterotsikl. Soed.*, 1474 (1978). [*Chem. Heterocycl. Compd.*, **14**, 1196 (1978) (Engl. Transl.).].
78T1703	Z. N. Parnes, Yu. I. Lyakhovetsky, M. I. Kalinkin, D. N. Kursanov, and L. I. Belen'kii, *Tetrahedron*, **34**, 1703 (1978).
78ZOR641	A. P. Yakubov, N. V. Grigor'eva, and L. I. Belen'kii, *Zh. Org. Khim.*, **14**, 641 (1978).
78ZOR1305	I. A. Abronin, L. I. Belen'kii, G. M. Zhidomirov, and Ya. L. Gol'dfarb, *Zh. Org. Khim.*, **14**, 1305 (1978).
79JOC3917	D. A. Forsyth and D. E. Vogel, *J. Org. Chem.*, **44**, 3917 (1979).
79MI1	D. N. Kursanov, Z. N. Parnes, M. I. Kalinkin, and N. M. Loim, "*Ionnoe gidrirovanie (Ionic Hydrogenation)*", pp. 60–78 (in Russian), Moscow, Khimiya (1979).
79MI2	L. I. Belen'kii, "*III International Symposium on Furan Chemistry, Coll. of Pap.*", p. 4, Smolenice, Czechoslovakia (1979).
79MI3	I. A. Abronin, L. I. Belen'kii, and Ya. L. Gol'dfarb, in "*New Trends in Heterocyclic Chemistry*" (R. B. Mitra, N. R. Ayyangar, V. N. Gogte, R. M. Acheson, and N. Cromwell, eds.), p. 154, Elsevier, Amsterdam (1979).
79ZOR1289	Ya. L. Gol'dfarb, M. A. Kalik, N. A. Shul'ts, and L. I. Belen'kii, *Zh. Org. Khim.*, **15**, 1289 (1979).
80CJC409	G. H. Barnett, H. J. Anderson, and C. E. Loader, *Can. J. Chem.*, **58**, 409 (1980).
80JCR(S)42	D. J. Chadwick, G. D. Meakins, and C. A. Rodes, *J. Chem. Res. (S)*, 42 (1980).
80JCS(P1)677	P. D. Clark, K. Clarke, D. F. Ewing, and R. M. Scrowston, *J. Chem. Soc., Perkin Trans. 1*, 677 (1980).
80KGS1235	V. A. Budylin, E. D. Matveeva, and A. N. Kost, *Khim. Geterotsikl. Soed.*, 1235 (1980). [*Chem. Heterocycl. Compd.*, **16**, 933 (1980) (Engl. Transl.)].

80KGS1587 L. I. Belen'kii, *Khim. Geterotsikl. Soed.*, 1587 (1980). [*Chem. Heterocycl. Compd.*, **16**, 1195 (1980) (Engl. Transl.).].

81CL813 Y. Yokoyama, Y. Yamashita, K. Takahashi, and T. Sone, *Chem. Lett.*, 813 (1981).

81JOC839 J. R. Carson and N. M. Davis, *J. Org. Chem.*, **46**, 839 (1981).

81JOC2221 H. M. Gilow and D. E. Burton, *J. Org. Chem.*, **46**, 2221 (1981).

81LA789 R. Gassner and E. Krumtholz, *Liebigs Ann. Chem.*, 789 (1981).

81NJC505 R. Houriet, H. Schwarz, W. Zummack, J. G. Andrade, and P. von Ragué Schleyer, *Nouv. J. Chim.*, **5**, 505 (1981).

81TL4899 R. X. Xu, H. J. Anderson, N. J. Gogan, C. A. Loader, and R. Mc Donald, *Tetrahedron Lett.*, **22**, 4899 (1981).

81TL4901 J. Rokach, P. Hamel, M. Kakushima, and G. M. Smith, *Tetrahedron Lett.*, **22**, 4901 (1981).

81ZOR1129 L. I. Belen'kii and I. A. Abronin, *Zh. Org. Khim.*, **17**, 1129 (1981).

81ZOR1134 I. A. Abronin, L. I. Belen'kii, G. M. Zhidomirov, and Ya. L. Gol'dfarb, *Zh. Org. Khim.*, **17**, 1134 (1981).

82AHC(30)127 A.-B. Hörnfeldt, *Adv. Heterocycl. Chem.*, **30**, 127 (1982).

82CL1195 T. Sone, M. Kubo, and T. Kanno, *Chem. Lett.*, 1195 (1982).

82IZV85 V. I. Kadentsev, L. I. Belen'kii, N. G. Kolotyrkina, and O. S. Chizhov, *Izv. Akad. Nauk SSSR. Ser. Khim.*, 85 (1982).

82JOC3668 J. DeSales, R. Greenhouse, and J. Muchowski, *J. Org. Chem.*, **47**, 3668 (1982).

82KGS662 E. Baum, L. I. Belen'kii, V. G. Kul'nevich, and T. E. Goldovskaya, *Khim. Geterotsikl. Soed.*, 662 (1982). [*Chem. Heterocycl. Compd.*, **18**, 499 (1982) (Engl. Transl.).].

83BCJ2208 Y. Yokoyama, Y. Yamashita, K. Takahashi, and T. Sone, *Bull. Chem. Soc. Jpn.*, **56**, 2208 (1983).

83JOC3214 M. Kakushima, P. Hamel, R. Frenette, and J. Rokach, *J. Org. Chem.*, **48**, 3214 (1983).

83MI1 V. A. Koptyug, *Arenonievye Iony. Stroenie i Reaktsionnaya Sposobnost' (Arenium Ions. Structure and Reactivity)*, p.161. Nauka, Siberian Division, Novosibirsk (1983) (in Russian).

84CHEC(4)40 C. W. Bird and G. W. H. Cheeseman, Reactivity of five-membered rings with one heteroatom, in "*Comprehensive Heterocyclic Chemistry*" (A. R. Katritzky and Ch. W. Rees, eds.), Vol. 4, Part 3, pp. 40–88, Elsevier, Oxford (1984).

84CHEC(4)201 R. A. Jones, Pyrroles and their benzo derivatives: (ii) reactivity, in "*Comprehensive Heterocyclic Chemistry*" (A. R. Katritzky and Ch. W. Rees, eds.), Vol. 4, Part 3, pp. 201–312, Elsevier, Oxford (1984).

84CHEC(4)599 M. V. Sargent and F. M. Dean, Furans and their benzo derivatives: (ii) reactivity, in "*Comprehensive Heterocyclic Chemistry*" (A. R. Katritzky and Ch. W. Rees, eds.), Vol. 4, Part 3, pp. 599–656, Elsevier, Oxford (1984).

84CHEC(4)742 S. Rajappa, Thiophenes and their benzo derivatives: (ii) reactivity, in "*Comprehensive Heterocyclic Chemistry*" (A. R. Katritzky and Ch. W. Rees, eds.), Vol. 4, Part 3, pp. 742–861, Elsevier, Oxford (1984).

84CHEC(4)936 C. W. Bird, G. W. H. Cheeseman, and A.-B. Hörnfeldt, Selenophenes, tellurophenes, and their benzo derivatives, in "*Comprehensive Heterocyclic Chemistry*" (A. R. Katritzky and

Ch. W. Rees, eds.), Vol. 4, Part 3, pp. 936–971, Elsevier, Oxford (1984).

84F277 C. De Micheli, M. De Amici, and S. Locati, *Farmaco, Ed. Sci.*, **39**, 277 (1984).

84KGS562 V. A. Budylin, M. del C. Pina, and Yu. G. Bundel’, *Khim. Geterotsikl. Soed.*, 562 (1984). [*Chem. Heterocycl. Compd.*, **20**, 460 (1984) (Engl. Transl.)].

84T2471 L. I. Belen’kii and A. P. Yakubov, *Tetrahedron*, **40**, 2471 (1984).

84YZ238 N. Ezaki and Sh Sakai, *Yakugaku Zasshi*, **104**, 238 (1984). *Chem. Abstr.*, **101**, 130471 (1984).

85CJC896 H. J. Anderson, C. A. Loader, R. X. Xu, N. Le, N. J. Gogan, R. McDonald, and L. G. Edwards, *Can. J. Chem.*, **63**, 896 (1985).

86BCJ83 T. Sone, R. Yokoyama, Y. Okuyama, and K. Sato, *Bull. Chem. Soc. Jpn.*, **59**, 83 (1986).

86CC688 M. Renard and L. Hevesi, *Chem. Commun.*, 688 (1986).

86JHC1475 H. M. Gilow, Y. H. Hong, P. L. Millins, R. C. Snyder, and W. J. Casteel, Jr., *J. Heterocycl. Chem.*, **23**, 1475 (1986).

86KGS749 L. I. Belen’kii, *Khim. Geterotsikl. Soed.*, 749 (1986). [*Chem. Heterocycl. Compd.*, **22**, 587 (1986) (Engl. Transl.)].

86MRC699 Y. Yamashita, O. Yoshino, K. Takahashi, and T. Sone, *Magn. Reson. Chem.*, **24**, 699 (1986).

86T759 L. I. Belen’kii and A. P. Yakubov, *Tetrahedron*, **42**, 759 (1986).

86T1299 M. W. Majchrzak and G. Simchen, *Tetrahedron*, **42**, 1299 (1986).

88BCJ3779 T. Sone, M. Inoue, and K. Sato, *Bull. Chem. Soc. Jpn.*, **61**, 3779 (1988).

88KGS1034 M. M. Krayushkin, A. A. Loktionov, and L. I. Belen’kii, *Khim. Geterotsikl. Soed.*, 1034 (1988). [*Chem. Heterocycl. Compd.*, **24**, 850 (1988) (Engl. Transl.)].

88OSC(VI)618 D. M. Bailey, R. E. Johnson, and N. F. Albertson, *Org. Synth., Coll.*, **VI**, 618 (1988).

89CC63 P. Hamel, Y. Girard, and J. A. Atkinson, *J. Chem. Soc., Chem. Commun.*, 63 (1989).

90G365 L. I. Belen’kii, G. P. Gromova, and M. M. Krayushkin, *Gazz. Chim. Ital.*, **120**, 365 (1990).

90JOC6317 B. L. Bray, P. H. Mathies, R. Naef, D. R. Solas, Th. T. Tidwell, D. R. Artis, and J. M. Muchowski, *J. Org. Chem.*, **55**, 6317 (1990).

92JOC2694 P. Hamel, Y. Girard, and J. A. Atkinson, *J. Org. Chem.*, **57**, 2694 (1992).

92KGS733 L. I. Belen’kii, *Khim. Geterotsikl. Soed.*, 733 (1992).

93KGS1040 L. I. Belen’kii, G. P. Gromova, and M. M. Krayushkin, *Khim. Geterotsikl. Soed.*, 1040 (1993). [*Chem. Heterocycl. Compd.*, **29**, 883 (1993) (Engl. Transl.)].

94BCJ1161 M. V. Sigalov, S. Toyota, M. Oki, and B. A. Trofimov, *Bull. Chem. Soc. Jpn.*, **31**, 1161 (1994).

94BCJ1872 M. V. Sigalov, S. Toyota, M. Oki, and B. A. Trofimov, *Bull. Chem. Soc. Jpn.*, **31**, 1872 (1994).

94H(37)2029 L. I. Belen’kii, *Heterocycles*, **37**, 2029 (1994).

95JHC53 D. M. Antonov, L. I. Belen’kii, and S. Gronowitz, *J. Heterocycl. Chem.*, **35**, 53 (1995).

95TL1401 J. A. H. Lainton, J. W. Huffman, B. R. Martin, and D. R. Compton, *Tetrahedron Lett.*, **36**, 1401 (1995).

95ZOR801 M. V. Sigalov and B. A. Trofimov, *Zh. Org. Khim.*, **31**, 801 (1995).

96CHEC-II(2)40 R. A. Jones, Pyrroles and their benzo derivatives: reactivity, in *"Comprehensive Heterocyclic Chemistry II"* (A. R. Katritzky, Ch. W. Rees, and E. F. V. Scriven, eds.), Vol. 2, pp. 40–117, Elsevier, Oxford (1996).

96CHEC-II(2)297 H. Heaney and J. S. Ahn, Furans and their benzo derivatives: reactivity, in *"Comprehensive Heterocyclic Chemistry II"* (A. R. Katritzky, Ch. W. Rees, and E. F. V. Scriven, eds.), Vol. 2, pp. 297–350, Elsevier, Oxford (1996).

96CHEC-II(2)492 S. Rajappa and M. V. Natekar, Thiophenes and their benzo derivatives: reactivity, in *"Comprehensive Heterocyclic Chemistry II"* (A. R. Katritzky, Ch. W. Rees, and E. F. V. Scriven, eds.), Vol. 2, pp. 492–605, Elsevier, Oxford (1996).

96CHEC-II(2)731 L. E. E. Christiaens, Selenophenes, in *"Comprehensive Heterocyclic Chemistry II"* (A. R. Katritzky, Ch. W. Rees, and E. F. V. Scriven, eds.), Vol. 2, pp. 731–748, Elsevier, Oxford (1996).

97KGS1477 L. I. Belen'kii, G. P. Gromova, B. V. Lichitskii, and M. M. Krayushkin, *Khim. Geterotsikl. Soed.*, 1477 (1997).

97MI1 T. Sone and K. Sato, *16th International Congress of Heterocyclic Chemistry, Abstracts*, POII-249, Bozman, Montana, USA (1997).

97MI2 L. I. Belen'kii, *16th International Congress of Heterocyclic Chemistry, Abstracts,* OP-V-20, Montana State University, Boseman, USA, (1997).

98JHC1345 J. Nicolaou and V. J. Demopoulos, *J. Heterocycl. Chem.*, **35**, 1345 (1998).

98MI1 B. A. Trofimov and M. V. Sigalov, *Main Group Chem. News*, **5**, 30 (1998).

98MI2 G. Olah, K. K. Laali, Q. Wang, and G. K. S. Prakash, *Onium Ions*, 509 pp. J. Wiley, New York (1998).

98MI3 B. V. Salov and A. I. Gershenovich, in *"Poluchenie i Svoistva Organicheskikh Soedinenii Sery (Preparation and Properties of Organosulfur Compounds)"* (L. I. Belen'kii, ed.), p. 260, Khimiya, Moscow (1998) (in Russian).

99MI1 T. Sone and K. Sato, *Bull. Yamagata Univ.*, **25**(2), 69 (1999).

00AHC(76)85 W. Friedrichsen, T. Traulsen, J. Elguero, and A. R. Katritzky, *Adv. Heterocycl. Chem.*, **76**, 85 (2000).

00CHE219 V. Z. Shirinian, N. V. Kosterina, A. V. Kolotaev, L. I. Belen'kii, and M. M. Krayushkin, *Chem. Heterocycl. Compd.*, **36**, 219 (2000). (Engl. Transl.) [*Khim. Geterotsikl. Soed.*, 261, 431 corr. (2000).

00MI1 A. R. Katritzky and A. F. Pozharskii, *"Handbook of Heterocyclic Chemistry"*, Second edition, Pergamon, Amsterdam (2000). p. 61.

00TL6605 A. Mizuno, Y. Kan, H. Fukami, T. Kamei, K. Miyazaki, S. Matsuki, and Y. Oyama, *Tetrahedron Lett.*, **41**, 6605 (2000).

01ARK(9)49 L. I. Belen'kii, G. P. Gromova, A. V. Kolotaev, and S. I. Luiksaar, *ARKIVOC*, **ix**, 49 (2001).

01KGS81 V. Z. Shirinian, M. M. Krayushkin, L. I. Belen'kii, L. G. Vorontsova, Z. A. Starikova, A. Y. Martynkin, V. L. Ivanov, and B. M. Uzhinov, *Khim. Geterotsikl. Soed.*, 81 (2001).

02IZV1392 M. M. Krayushkin, V. Z. Shirinian, L. I. Belen'kii, A. Yu. Shadronov, L. G. Vorontsova, and Z. A. Starikova, *Izv. Akad. Nauk, Ser. Khim.*, 1392 (2002).

02TL8133 J. S. Yadav, B. V. S. Reddy, G. Kondaji, R. Srinivasa Rao, and S. Praveen Kumar, *Tetrahedron Lett.*, **43**, 8133 (2002).

03ARK59 L. I. Belen'kii, T. G. Kim, I. A. Suslov, and N. D. Chuvylkin, *ARKIVOC*, **xiii**, 59 (2003).

03JOC5720 A. R. Katritzky, K. Suzuki, S. K. Singh, and H.-Y. He, *J. Org. Chem.*, **68**, 5720 (2003).

03KGS38 L. I. Belen'kii, I. A. Suslov, and N. D. Chuvylkin, *Khim. Geterotsikl. Soed.*, 38 (2003). [*Chem. Heterocycl. Compd.*, **39**, 36 (2003) (Engl. Transl.)].

03KGS1785 L. I. Belen'kii, V. Z. Shirinian, G. P. Gromova, A. V. Kolotaev, Yu. A. Strelenko, S. N. Tandura, A. N. Shumskii, and M. M. Krayushkin, *Khim. Geterotsikl. Soed.*, 1785 (2003). [*Chem. Heterocycl. Compd.*, **39**, 1570 (2003) (Engl. Transl.)].

03MI1 L. I. Belen'kii, in "*Izbrannye Metody Sinteza i Modifikatsii Geterotsiklov*" (V. G. Kartsev, ed.), Vol. 2, p. 25, IBS Press, Moscow (2003) (in Russian); "*Selected Methods of Synthesis and Modification of Heterocycles*" (V. G. Kartsev, ed.), Vol. 2, p. 24, IBS Press, Moscow (2003) (English Version).

03MI2 K. Hrncarikova and D. Vegh, *Molecules*, **8**, 536 (2003). *Chem. Abstr.*, **140**, 321185 (2004).

04MI1 L. I. Belen'kii, N. D. Chuvylkin, T. G. Kim, and I. A. Suslov, *Chemistry Biology Interface: Synergistic New Frontiers, Abstracts*, IL92, New Delhi, India (2004).

04S1951 Zh.-G. Le, Zh.-Ch. Chen, Y. Hu, and Q.-G. Zheng, *Synthesis*, 1951 (2004).

04TL9573 Ch. Song, D. W. Knight, and M. A. Whatton, *Tetrahedron Lett.*, **45**, 9573 (2004).

05HC599 A. A. Chaikovskaya, Yu. V. Dmitriv, S. P. Ivonin, A. M. Pinchuk, and A. A. Tolmachev, *Heteroatom Chem.*, **16**, 599 (2005).

05JPC(A)5509 B. Chan, J. E. Del Bene, J. Elguero, and L. Radom, *J. Phys. Chem. A*, **109**, 5509 (2005).

05KGS1102 A. A. Chaikovskaya, S. P. Ivonin, Yu. V. Dmitriv, and A. M. Pinchuk, *Khim. Geterotsikl. Soed.*, 1102 (2005). *Chem. Heterocycl. Compd.*, **41**, 934 (2005) (Engl. Transl.).

05MI1 S. M. Mekelleche, A. Ghomri, and C. Morell, *Phys. Chem. News*, **24**, 93 (2005). *Chem. Abstr.*, **144**, 330910 (2006).

05RKZ(6)59 L. I. Belen'kii, *Ross. Khim. Zh.*, **49**(6), 59 (2005).

05ZOR1362 L. I. Belen'kii, N. D. Chuvylkin, A. I. Serykh, and I. A. Suslov, *Zh. Org. Khim.*, **41**, 1362 (2005).

06AX(E)o3282 A. R. Kennedy, A. I. Khalaf, C. J. Suckling, and R. D. Waigh, *Acta Crystallogr., Sect. E*, **E62**(8), o3282 (2006). *Chem. Abstr.*, **146**, 263001 (2007).

06KGS1647 L. I. Belen'kii, I. D. Nesterov, and N. D. Chuvylkin, *Khim. Geterotsikl. Soed.*, 1647 (2006). [*Chem. Heterocycl. Compd.*, **42**, 1414 (2006) (Engl. Transl.)].

06SL3447 J. S. Yadav, B. V. Subba Reddy, K. Vishweshwar Rao, P. Purushothama Rao, K. Sarita Raj, A. R. Prasad, A. Prabhakar, and B. Jagadeesh, *Synlett*, 3447 (2006).

06T1699 T. Janosik, H. Shirani, N. Wahlstroem, I. Malky, B. Stensland, and J. Bergman, *Tetrahedron*, **62**, 1699 (2006).

07IZV1425 N. D. Chuvylkin, I. D. Nesterov, and L. I. Belen'kii, *Izv. Akad. Nauk, Ser. Khim.*, 1425 (2007).

07KGS34	L. I. Belen'kii, I. D. Nesterov, and N. D. Chuvylkin, *Khim. Geterotsikl. Soed.*, 34 (2007). [*Chem. Heterocycl. Compd.*, **43**, 28 (2007) (Engl. Transl.)].
07SM(157)924	R. C. Foitzik, E. K. Bowen, A. M. Taylor, F. M. Pfeffer, and A. Kaynak, *Synth. Met.*, **157**(22–23), 924 (2007). *Chem. Abstr.*, **148**, 285562 (2008).
08CHEC-III(3)45	B. A. Trofimov and N. A. Nedolya, Pyrroles and their benzo derivatives: reactivity, in "*Comprehensive Heterocyclic Chemistry III*" (A. R. Katritzky, C. A. Ramsden, E. F. V. Scriven, and R. J. K. Taylor, eds.), Vol. 3, pp. 45–268, Elsevier, Oxford (2008).
08CHEC-III(3)407	H. N. C. Wong, K.-S. Yeung, and Z. Yang, Furans and their benzo derivatives: reactivity, in "*Comprehensive Heterocyclic Chemistry III*" (A. R. Katritzky, C. A. Ramsden, E. F. V. Scriven, and R. J. K. Taylor, eds.), Vol. 3, pp. 407–496, Elsevier, Oxford (2008).
08CHEC-III(3)741	S. Rajappa and A. R. Deshmukh, Thiophenes and their benzo derivatives: reactivity, in "*Comprehensive Heterocyclic Chemistry III*" (A. R. Katritzky, C. A. Ramsden, E. F. V. Scriven, and R. J. K. Taylor, eds.), Vol. 3, pp. 741–841, Elsevier, Oxford (2008).
08CHEC-III(3)975	E. T. Pelkey, Selenophenes, in "*Comprehensive Heterocyclic Chemistry III*" (A. R. Katritzky, C. A. Ramsden, E. F. V. Scriven, and R. J. K. Taylor, eds.), Vol. 3, pp. 975–1006, Elsevier, Oxford (2008).
08EJO2369	T. A. Nigst, M. Westermaier, A. R. Ofial, and H. Mayr, *Eur. J. Org. Chem.*, 2369 (2008).
08JP2008137964	T. Kurahashi, K. Yamamoto (Koei Chemical Co., Ltd., Japan), Jpn. Kokai Tokkyo Koho JP 2008137964; *Chem. Abstr.*, **149**, 79470 (2008).
08KGS1645	L. I. Belen'kii, I. D. Nesterov, and N. D. Chuvylkin, *Khim. Geterotsikl. Soed.*, 1645 (2008). [*Chem. Heterocycl. Compd.*, **44**, 1339 (2008) (Engl. Transl.)].
08KGS1801	L. I. Belen'kii, I. D. Nesterov, and N. D. Chuvylkin, *Khim. Geterotsikl. Soed.*, 1801 (2008). [*Chem. Heterocycl. Compd.*, **44**, 1460 (2008) (Engl. Transl.)].
08MI1	L. I. Belen'kii, in "*Sintezy organicheskikh soedinenii*" (Syntheses of Organic Compounds), Sbornik 3 иОХ РАН (Book 3 of N. D. Zelinsky Institute of Organic Chemistry) (M. P. Egorov, ed.), p. 18, MAX Press, Moscow (2008).
08SC255	F. He, H. Wu, J. Chen, and W. Su, *Synth. Commun.*, **38**, 255 (2008).
08TL5810	Y. Arai, J. Nakazaki, and H. Segawa, *Tetrahedron Lett.*, **49**, 5810 (2008).

CHAPTER 6

Cyclic Azomethine Imines from Diazenes (Azo Compounds)

Joachim G. Schantl

Contents

Institut für Organische Chemie, Universität Innsbruck, Innrain 52a, A-6020 Innsbruck, Austria
Email address: joachim.schantl@uibk.ac.at

Advances in Heterocyclic Chemistry, Volume 99
ISSN 0065-2725, DOI 10.1016/S0065-2725(10)09906-X

1. INTRODUCTION

In developing the concept of [3+2] cycloaddition reactions R. Huisgen (60TL1, 63ACE565) has recognized the 1,3-dipolar functionality of azomethine imines. Like in other 1,3-dipolar species, four π-electrons are confined to three atoms. By obeying the octet rule, azomethine imines are represented by two closed-shell resonance structures **A**↔**B**, both with charge separation (Figure 1). The traditional name "azomethine imine" does not suitably resemble the composite functionality: Structure **A** (subsequently employed) represents an "iminium imide", while structure **B** is a "diazenium ylide", but both more systematic names are uncommon.

This report covers two topics: (1) The generation of 2-thioxo-2,4-dihydro-3*H*-imidazol-1-ium-1-imides as intermediates in the course of [3+2] cycloaddition reactions of azoalkenes and thiocyanic acid resulting in the formation of 1-aminoimidazole-2-thione derivatives; some further reactions of these heterocycles are presented as well. (2) The rhodium-catalyzed intramolecular interaction of ω-diazenyl α'-diazo ketones giving rise to the formation of mostly two cyclic azomethine imine isomers with an exocyclic terminal nitrogen atom and with all three

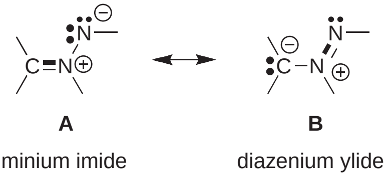


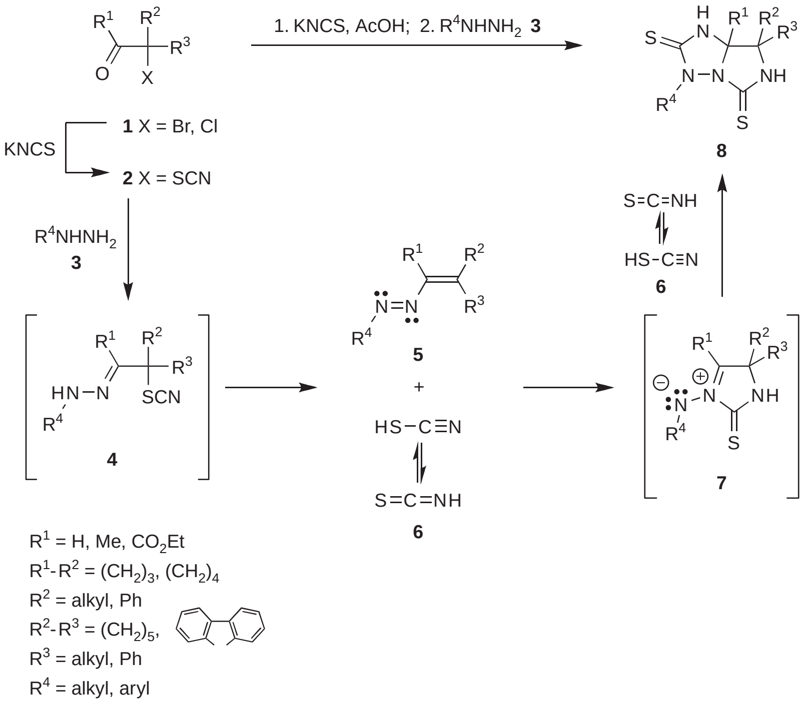
Figure 1 Resonance structures representing the azomethine imine functionality.

azomethine imine atoms embedded in the heterocyclic ring. The latter part also includes an outline of synthetic approaches to the starting materials, ω-diazenyl α′-diazo ketones, and provides some [3+2] cycloaddition reactions of the cyclic azomethine imines prepared.

2. [3+2] CYCLOADDITION REACTIONS OF *IN SITU* GENERATED AZOALKENES AND THIOCYANIC ACID. CYCLIC AZOMETHINE IMINE INTERMEDIATES

2.1 “Non-classical” criss-cross reaction: A parallel tandem cycloaddition. Formation of imidazo[1,5-*b*][1,2,4]triazoles

In a one-pot reaction, α,α-disubstituted α-halo carbonyl compounds **1** (R^2, $R^3 \neq H$), potassium thiocyanate, acetic acid, and monosubstituted hydrazines **3** are transformed into dihydro-1*H*-imidazo[1,5-*b*][1,2,4]triazole-2,5(3*H*,6*H*)dithiones **8** (Scheme 1) (93TH, 01TH). With R^3=H, the reaction takes a different course (*cf*. Section 2.3).

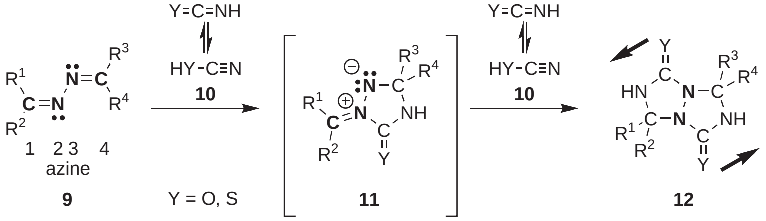


Scheme 1 One-pot synthesis of imidazo[1,5-*b*][1,2,4]triazoles **8** from of α,α-disubstituted α-halo carbonyl compounds **1** with potassium thiocyanate in acetic acid and monosubstituted hydrazines **3**.

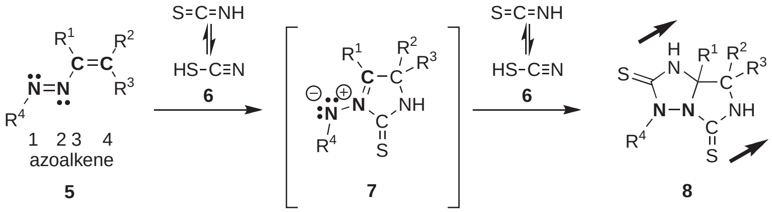
This multi-step reaction is conceived to proceed as follows: First, the halogen atom in the starting material **1** is displaced by the thiocyanate ion forming the α-thiocyanato carbonyl compound **2**. The same final product **8** is obtained when **2** is used as the starting material. However, the formation of **2** in the course of a one-pot procedure is more convenient and economical. In the following step, α-thiocyanato carbonyl compound **2** reacts with a monosubstituted hydrazine **3** to form the hydrazone intermediate **4**. Subsequent 1,4-elimination leads to the azoalkene **5** and thiocyanic acid **6**. It has been shown that an azoalkene **5** and *in situ* generated thiocyanic acid **6** (known to coexist with its tautomer, isothiocyanic acid (50JCP1437)) are indeed reaction intermediates: when reacting individually they furnish the same final product **8**. The intermediates, azoalkene **5** and thiocyanic ⇆ isothiocyanic acid **6**, in turn, react with each other in a [3+2] cycloaddition. The C,N multiple bond of thiocyanic ⇆ isothiocyanic acid **6** as a 2π-electron reactant adds across the C=C–N moiety of azoalkene **5**, the latter serving as an isoelectronic heteroatom equivalent of an allyl anion providing four π-electrons. The resulting heterocyclic adduct **7** featuring an azomethine imine functionality then undergoes a [3+2] cycloaddition with another molecule of thiocyanic acid **6** furnishing the final heterobicyclic product **8** (Scheme 1) (93TH, 01TH).

The formation of heterobicyclic adducts **8** is reminiscent of the criss-cross reaction (76S349, 97AA97). The "classical" criss-cross reaction (Scheme 2, upper equation) is a tandem cycloaddition of azines **9** with heterocumulenes **10** (HN=C=Y, Y = O, S) affording heterobicyclic products **12** (Scheme 2, upper equation) (17JA279, 17JA1322). The C=N bond of **10** (providing two π-electrons) adds across the N–N=C moiety of the azine (atoms 2 through 4 of the heterodiene **9** provide four π-electrons, thus resembling an isoelectronic heteroallyl anion equivalent). The primary cycloadduct **11** resembles an azomethine imine and adds another molecule **10** yielding the 1:2 cycloadduct **12**. In forming product **12** the two dipolarophilic reactants **10** have added in an antiparallel sense (*cf*. the heavy arrows along the C–NH moieties of **12**, Scheme 2).

Similarly, azoalkenes **5** (mostly generated *in situ*) undergo an analogous tandem cycloaddition with thiocyanic acid **6**; the heterodiene moiety of azoalkenes **5** differs from that of azines **9** by the formal exchange of atoms 1 and 3 (Scheme 2, lower equation). Thus, the first step of the cycloaddition of the C=N bond of reactant **6** across atoms 2 and 4 (N and C) of azoalkenes **5** is analogous to the reaction of **9** with **10**. However, the azomethine imine functionality of the 1:1 cycloadduct **7** differs from the adduct **11**. Both nitrogen atoms of azomethine imine **11** are embedded in the heterocyclic ring, and the carbon atom is exocyclic. A reverse situation is found in intermediate **7**. The carbon atom and the central nitrogen atom of the azomethine imine are part of the heterocyclic



"Classical" criss-cross reaction: antiparallel tandem cycloaddition



"Non-classical" criss-cross reaction: parallel tandem cycloaddition

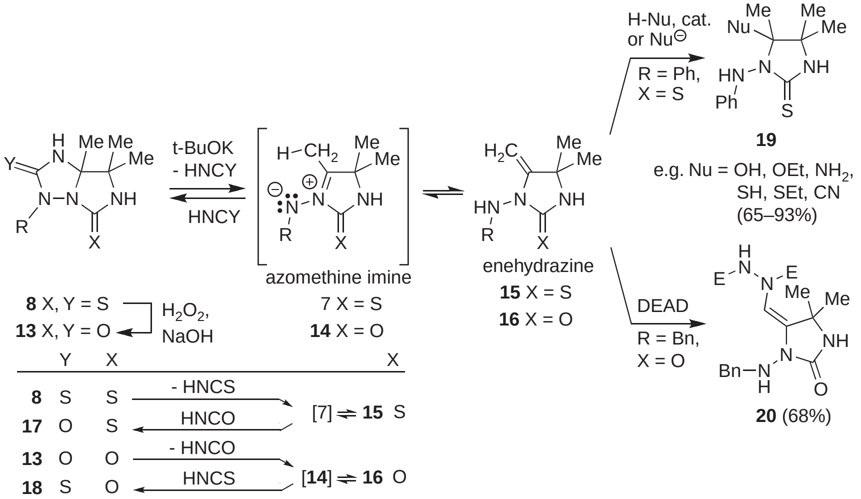
Scheme 2 Criss-cross reactions. The "*Classical*" criss-cross reaction, an *antiparallel* tandem cycloaddition of azines **9** and heterocumulenes **10** (upper equation). The "*Non-classical*" criss-cross reaction, a *parallel* tandem cycloaddition of azoalkenes **5** and thiocyanic acid **6** (lower equation).

ring, and the terminal nitrogen atom is exocyclic. This provides an opposite orientation of the dipolarophile **6** in the second cycloaddition step giving rise to the 1:2 cycloadduct **8** with a parallel orientation of both C–N bonds introduced by **6** (*cf.* the heavy arrows along the C–NH moieties of **8**, Scheme 2). This parallel tandem reaction of azoalkenes **5** adds a new facet to the long known criss-cross reaction.

The criss-cross reaction of azoalkenes is restricted to the addition of thiocyanic acid and could not be extended to cyanic acid, as this is the case in the classical reaction with azines. However, the cycloadduct expected to arise from the reaction of an azoalkene with cyanic acid, the heterobicyclic 2,5-dione **13**, can be obtained simply by reacting the 2,5-dithiones **8** with hydrogen peroxide in sodium hydroxide (Scheme 3) (93TH, 01TH).

2.2 Enehydrazines

Both heterobicyclic compounds **8** and **13** readily undergo a base-induced [3+2] cycloelimination (Scheme 3): Upon treatment with potassium *tert*-butoxide at room temperature, the HNCY fragment of the triazolidine moiety of **8** (Y = S) and **13** (Y = O) is eliminated, thus reversing the second step of the criss-cross cycloaddition (*cf.* Scheme 2).



Scheme 3 Conversion of 2,5-dithione **8** into 2,5-dione **13**. Base-induced elimination of HNCY from **8** and **13** yielding enehydrazines **15** and **16**, respectively. Reactions of enehydrazines **15** and **16**.

However, the structures of the isolated products formed upon elimination of one molecule of HNCY are not the expected azomethine imines **7** (X = S) and **14** (X = S), respectively; instead, the corresponding tautomers, enehydrazines **15** (X = S) and **16** (X = O) resulting from a 1,4-H shift are formed (Scheme 3) (93TH, 01TH). At higher temperature, the criss-cross reaction is completely reversed to give the parent azoalkene **5**.

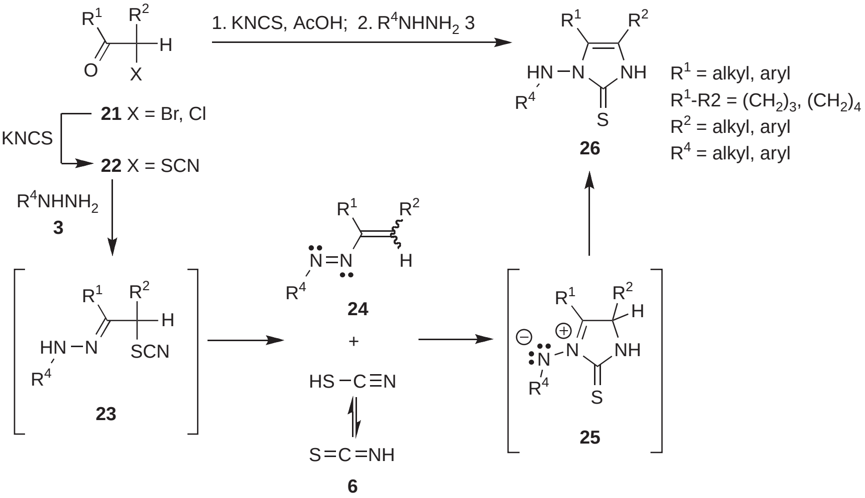
The isolated enehydrazines **15** and **16** exhibit an ambiguous reactivity resembling both the enehydrazine and azomethine imine functionalities (Scheme 3). Thus, enehydrazine **15** (X = S) upon reaction with suitable dipolarophiles undergoes [3+2] cycloaddition as expected for the azomethine imine form **7**. KNCS in acetic acid reverts enehydrazine **15** (X = S) to 2,5-dithione **8** (X, Y = S); reaction with KNCO in acetic acid gives the bicyclic 2-one-5-thione **17** (X = S, Y = O). Likewise, enehydrazine **16** (X = O) reacts with KNCO in acetic acid affording the bicyclic 2,5-dione **13** (X, Y = O), and with HNCS (*in situ* generated from KNCS and acetic acid) furnishing the bicyclic 5-one-2-thione **18** (X = O, Y = S) (93TH, 01TH).

On the other hand, protic (and anionic) nucleophiles (Nu = O–, N<, S–, CN) readily add across the exocyclic olefinic bond: Enehydrazine **15** (R = Ph, X = S) furnishes a number of 5-Nu-substituted 1-phenylaminoimidazolidine-2-thiones **19** (Scheme 3). Similarly, **16** (X = O) can be converted into 5-Nu-substituted 1-arylaminoimidazolidin-2-ones. Some electrophiles react with enehydrazine **16** (e.g., R = Bn, X = O) at the exocyclic methylene carbon atom providing substitution products like **20** (Scheme 3). Other nucleophilic sites of enehydrazines **15** and **16** are the exocyclic amino nitrogen atom, and the thione sulfur atom of **16**; acylation and alkylation occur at these functionalities (not shown in Scheme 3) (93TH, 01TH).

At ambient temperature, some enehydrazines **15** and **16** feature axial chirality (atropisomerism) about the N–N bond (*vide infra*, *cf*. Figure 2) (01TH).

2.3 N-substituted 1-amino-1,3-dihydro-2*H*-imidazole-2-thiones

α-Monosubstituted α-halo carbonyl compounds **21** (i.e., **1**, R^3=H), potassium thiocyanate, acetic acid and monosubstituted hydrazines **3** form *N*-substituted 1-amino-1,3-dihydro-2*H*-imidazole-2-thiones **26** (Scheme 4) (94H1873, 95FA379, 97H691, 98SL786, 01U). Except for the last step, the reaction appears to follow that of α,α-disubstituted α-halo carbonyl compounds **1** (R^2, R^3≠H; *cf*. Scheme 1) *via* the corresponding intermediates, α-thiocyanato carbonyl compound **22**, hydrazone **23**, and the 1,4-elimination products azoalkene **24** and thiocyanic acid **6**. The subsequent [3+2] cycloaddition of the latter intermediates **24** and **6** is considered to give rise to the heterocyclic azomethine imine **25**. Contrary to intermediate **7** (R^3 = H; *cf*. Scheme 1), azomethine imine **25** undergoes



Scheme 4 One-pot synthesis of 1-amino-1,3-dihydro-2*H*-imidazole-2-thiones **26** starting from α-substituted α-halo ketones **21**, potassium thiocyanate, and monosubstituted hydrazines **3**.

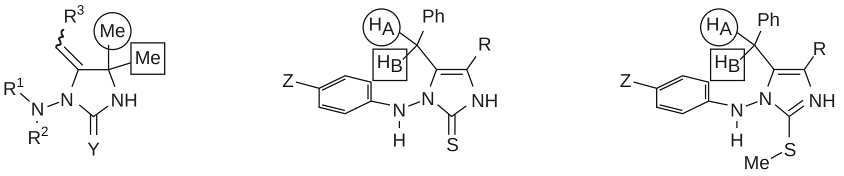
an apparently rapid H-shift, seemingly from ring position 4 to the exocyclic nitrogen atom, thus affording the monocyclic product **26**. Conceivably, the migration of the acidic thioamide proton (3-NH) to the exocyclic imide nitrogen atom is followed by a 1,2-H-shift from 4-CH to the neighboring thioamide nitrogen atom affording the N-substituted 1-amino-1,3-dihydro-2*H*-imidazole-2-thiones **26** (Scheme 4) (94H1873, 95FA379, 97H691, 98SL786, 01U).

2.4 Restricted rotation (atropisomerism) about N–N single bonds in 1-aminoimidazole derivatives

N-Aryl-substituted 1-amino-1,3-dihydro-2*H*-imidazole-2-thiones **26** display a dynamic feature in the ^{1}H NMR that becomes visible through suitable monitor groups. The rotation about the N–N single bond of the trisubstituted hydrazine moiety of **26** is restricted, and the resulting axial chirality (atropisomerism) can be monitored by means of diasterotopic groups, for example, the methylene protons of a benzyl group in various 4-substituted 1-anilino-5-benzyl-4-phenyl-1,3-dihydro-2*H*-imidazole-2-thiones **26** and the corresponding 2-(methylsulfanyl)-1*H*-imidazoles **27** (Figure 2) (02TH).

The same phenomenon is encountered in enehydrazines **15** and **16**, the geminal 4,4-dimethyl groups serving as ^{1}H NMR monitors (Figure 2) (01TH).

As an example, the temperature dependent ^{1}H NMR spectra of 5-benzyl-1-[(4-nitrophenyl)-amino]-4-phenyl-1,3-dihydro-2*H*-imidazole-2-thione **26** (R = Ph, Z = NO$_2$) are reproduced in Figure 3. With increasing temperature the signals of the AB quartet of the diastereotopic methylene



15 Y = S
16 Y = O

26

27

R^1 = aryl
R^2 = H, Me
R^3 = H, alkyl

R = alkyl, aryl
Z = OMe, Me, H, Br, Cl, CO$_2$H, CO$_2$Me, NO$_2$

Figure 2 Diastereotopic groups in imidazole derivatives **15**, **16** (Me), and **26**, **27** (CH$_A$H$_B$).

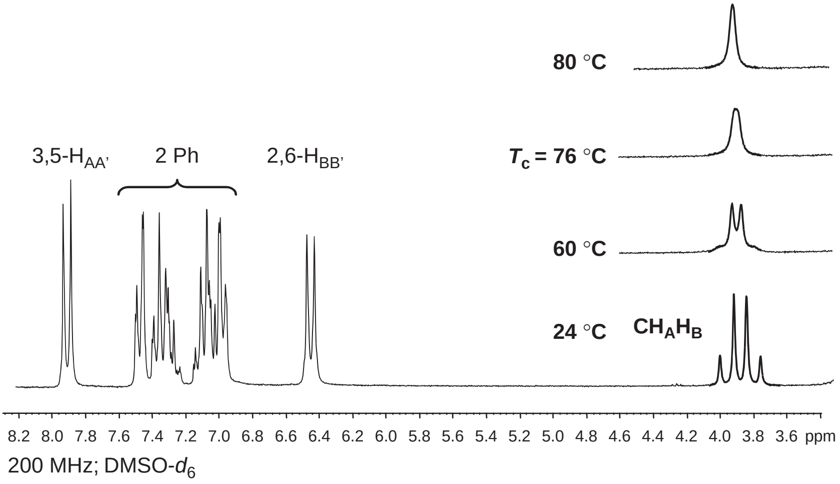


Figure 3 Temperature dependent ^{1}H NMR spectra of 5-benzyl-1-[(4-nitrophenyl) amino]-4-phenyl-1,3-dihydro-2*H*-imidazole-2-thione **26**.

protons broaden until they eventually collapse at the coalescence temperature T_c allowing the calculation of the rotational barrier (02TH).

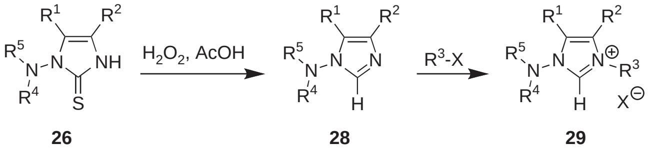
The nature of the 4-substituent Z of the 1-(*N*-anilino) substituent in **26** (as well as in **27**) markedly affects the coalescence temperature T_c and thus the rotational barrier $\Delta G^\ddagger$ (e.g., Z = NO_2: T_c 76 °C, $\Delta G^\ddagger$ 71.9 kJ mol^{-1}; Z = Me: T_c 1 °C, $\Delta G^\ddagger$ 57.6 kJ mol^{-1}). The increasing −M effect of the 4-substituent parallels the magnitude of the rotational barrier. The more pronounced resonance interaction of the 4-nitro *versus* the 4-methyl substituent entails (1) an increase in sp^2-hybridization of the 1-amino nitrogen thus "flattening" the pyramidal exocyclic amino nitrogen atom, and (2) a shortening of the bonds extended from it to the ligands including the N–N bond, thereby increasing the rotational barrier. This electronic effect exerted by remote substituents is a clear indication of the restricted rotation about the N–N bond causing the dynamic phenomenon; if this were caused by an inversion of the pyramidal nitrogen atom, the reverse effect is expected. In addition to the electronic effect, steric effects of neighboring groups also affect the rotational barrier as shown by the comparison of 1-(arylamino)-5-benzyl-4-phenyl-1,3-dihydro-2*H*-imidazole-2-thiones **26** and the corresponding 2-(methylsulfanyl)-1*H*-imidazoles **27**. The increased spatial demand of the bulkier 2-methylsulfanyl substituent in **27** *versus* the 2-thione group in **26** raises the coalescence temperature due to an increased rotational barrier (Z = NO_2: T_c>80 °C; Z = Me: T_c 5 °C, $\Delta G^\ddagger$ 59.2 kJ mol^{-1}) (02TH).

2.5 N-Substituted imidazolium salts, precursors for imidazolium ylide intermediates

Hydrogen peroxide in acetic acid converts 1-(arylamino)-1,3-dihydro-2*H*-imidazole-2-thiones **26** into 2-unsubstituted imidazoles **28** (an "oxidative reduction", Scheme 5) (98H929, 02TH). Alkylation at the unsubstituted ring nitrogen atom (3-N) of **28** furnishes imidazolium salts **29** (Scheme 5).

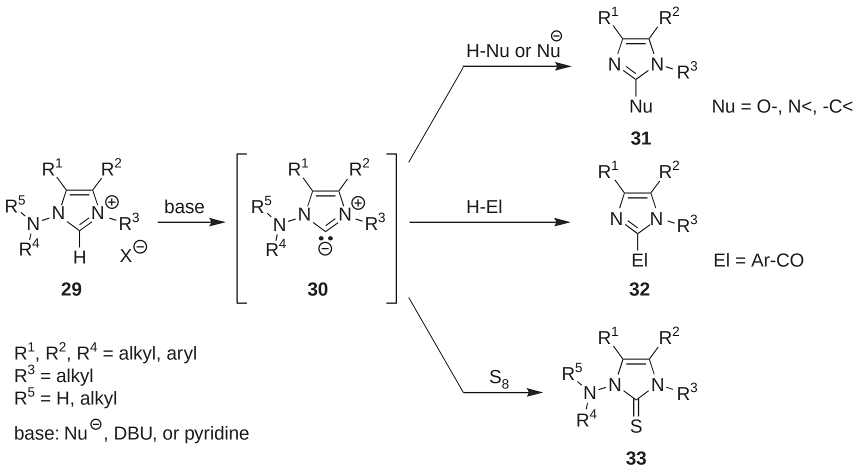
Upon deprotonation, imidazolium salts **29** react both with electrophiles and nucleophiles, thereby introducing a substituent derived from these reactants at position 2; concomitantly, the 1-arylamino substituent (R^4 = aryl, R^5 = alkyl) is eliminated (Scheme 6) (00TH).

These reactions are presumed to involve the "nucleophilic" carbene intermediate **30**. Addition of the nucleophile at the carbene atom 2-C (or across the iminium bond) of **30** is followed by the elimination of the 1-arylamino substituent yielding 2-Nu-substituted imidazoles **31** (00TH). Generation of intermediate **30** with a



R^1,R^2, R^4 = alkyl, aryl
R^3 = alkyl
R^5 = H, alkyl

Scheme 5 "Oxidative reduction" of thiones **26** and the conversion into imidazolium salts **29**.



Nu = O-, N<, -C<

El = Ar-CO

R^1, R^2, R^4 = alkyl, aryl
R^3 = alkyl
R^5 = H, alkyl
base: $Nu^\ominus$, DBU, or pyridine

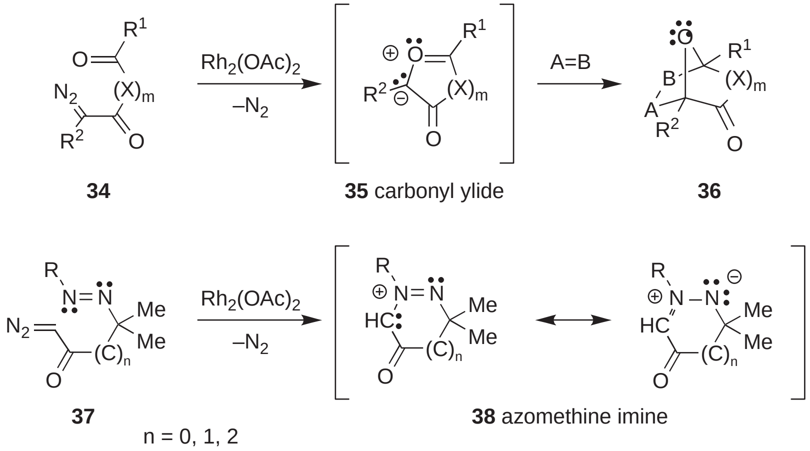
Scheme 6 Generation and reactions of imidazoline ylide **30** ("nucleophilic" carbene).

non-nucleophilic base followed by an electrophilic reagent like an aromatic aldehyde affords 2-aroyl-substituted imidazoles **32** (00TH). The reaction of imidazolium salts **29** with base and elemental sulfur gives 3-alkyl-substituted 1-(arylamino)-1,3-dihydro-2*H*-imidazole-2-thiones **33**.

3. INTRAMOLECULAR INTERACTION OF DIAZENE N-ATOMS WITH CARBENOID C-ATOMS. CYCLIC AZOMETHINE IMINES

The Rh-induced conversion of *ω*-carbonyl diazo ketones **34** generates carbonyl ylides **35**, and the interception of these transient 1,3-dipolar species with dipolarophiles gives rise to [3+2] cycloadducts **36** (Scheme 7, upper part) (96CRV223). The carbonyl group is isoelectronic with the diazene functionality of azo compounds. This prompted the investigation of *ω*-diazenyl *α*′-diazo ketones under similar conditions (Scheme 7, lower part).

In order to prevent tautomerization of the diazene group to a hydrazone, the carbon atom attached to either diazene nitrogen atom cannot carry a hydrogen atom; for instance, a tetragonal carbon atom has to be fully C-substituted or an aromatic carbon atom. This "hydrazone blocking" carbon is ignored in the definition of the tether between the diazene and diazo ketone functionalities; the tether is defined by counting the carbon atoms between this blocking center and the carbonyl group of the diazo ketone.



34

35 carbonyl ylide

36

37

n = 0, 1, 2

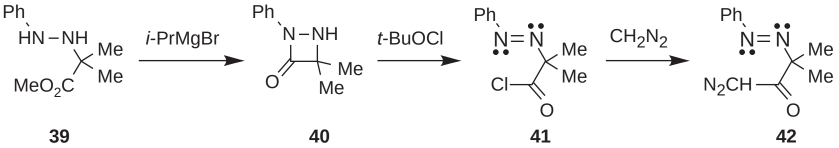
38 azomethine imine

Scheme 7 Rh-Induced interaction between diazo-C and carbonyl-O atoms forming carbonyl ylides **35** (above). Rh-induced interaction between diazo-C and diazene N-atom giving rise to azomethine imines **38** (below).

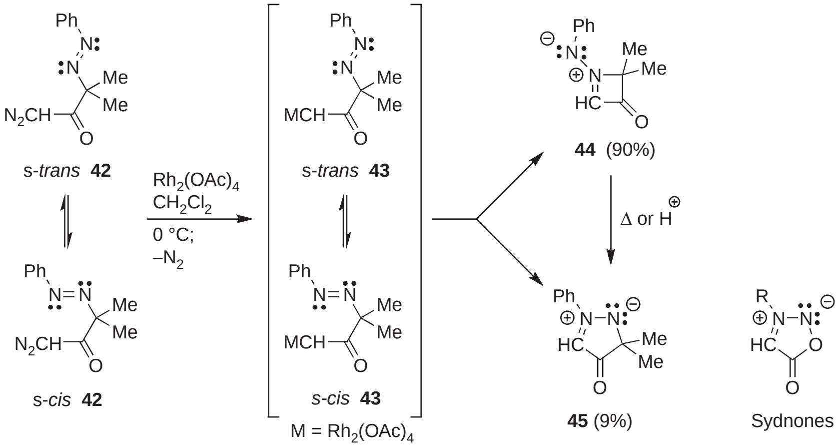
3.1 α-Diazenyl-α'-diazo ketone [carbon tether $(C)_n$, $n = 0$]. Cyclic azomethine imines: 2,3-dihydroazetium-1-anilinide (**44**) and 4,5-dihydro-1*H*-pyrazol-2-ium-1-ide (**45**)

To prove this hypothesis a suitable substrate, 1-diazo-3-methyl-3-[(*E*)-phenyldiazenyl]butan-2-one (**42**) was used. Methyl 2-(2-arylhydrazino)-2-methylpropanoate (**39**) reacting with a bulky Grignard reagent like isopropyl magnesium bromide gives 4,4-dimethyl-2-phenyl-1,2-diazetidin-3-one **40** (87TL6577). Oxidation with *tert*-butyl hypochlorite converts diazetidinone **40** into 2-methyl-2-(phenyldiazenyl)propanoyl chloride **41**, which upon treatment with diazomethane affords the desired diazo ketone **42** (Scheme 8) (98ACE2229).

α-Diazenyl-α'-diazo ketone **42** reacting with rhodium(II) acetate in dichloromethane at 0 °C affords a 9:1 mixture of two products: Separation by column chromatography provides yellow crystals of 2,2-dimethyl-3-oxo-2,3-dihydroazetium-1-anilide (**44**, with the terminal nitrogen atom of the azomethine imine functionality being exocyclic, 90%) and 5,5-dimethyl-4-oxo-2-phenyl-4,5-dihydro-1*H*-pyrazol-2-ium-1-ide (**45**, with all three azomethine imine atoms embedded in the heterocyclic ring, 9%) (Scheme 9) (98ACE2229).



Scheme 8 Preparation of 1-diazo-3-methyl-3-[(*E*)-phenyldiazenyl]butan-2-one (**42**).



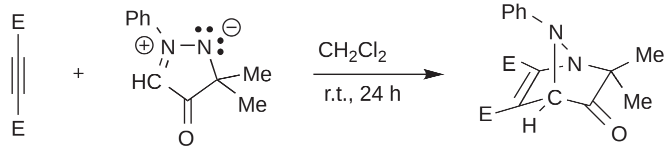
Scheme 9 Rhodium(II)-induced conversion of α-diazenyl-α'-diazo ketone **42** ($n = 0$) into cyclic azomethine imines **44** and **45**.

Treatment of azomethine imine **44** with acids or heating (at melting point temperature) causes a ring enlargement transforming the four-membered ring into the thermodynamically more stable five-membered azomethine **45** (Scheme 9) (98ACE2229). It may be assumed that in a kinetically controlled reaction the product ratio **44**:**45** (9:1) reflects the conformational isomer ratio (about the N–sp^3-C-bond) of the starting material *s-cis* **42**/*s-trans* **42** or the ratio of the transition metal stabilized carbene intermediates *s-cis* **43**/*s-trans* **43**. Thus, nucleophilic attack by the *proximal* diazene nitrogen atom of the *s-trans* conformer **43** at the carbenoid center gives rise to the four-membered heterocyclic product **44**, and reaction of the *distal* nitrogen atom of *s-cis* **43** affords the five-membered ring of **45**. While 2,2-dimethyl-3-oxo-2,3-dihydroazetium-1-anilide (**44**) constitutes a novel cyclic azomethine imine, 5,5-dimethyl-4-oxo-2-phenyl-4,5-dihydro-1*H*-pyrazol-2-ium-1-ide (**45**) is reminiscent of one of the earliest known azomethine imines, the sydnones (*cf.* Scheme 9). In a formal way, the ring oxygen atom of sydnones is replaced by the quarternary ring carbon atom in the cyclic azomethine imine **45**, which may be considered a "carba-sydnone". The pronounced stability of azomethine imine **45** is remarkable in view of the lack of aromaticity of the five-membered ring as compared to sydnones.

3.2 [3+2] Cycloadditions of cyclic azomethine imines **44** and **45** with dimethyl acetylene-dicarboxylate

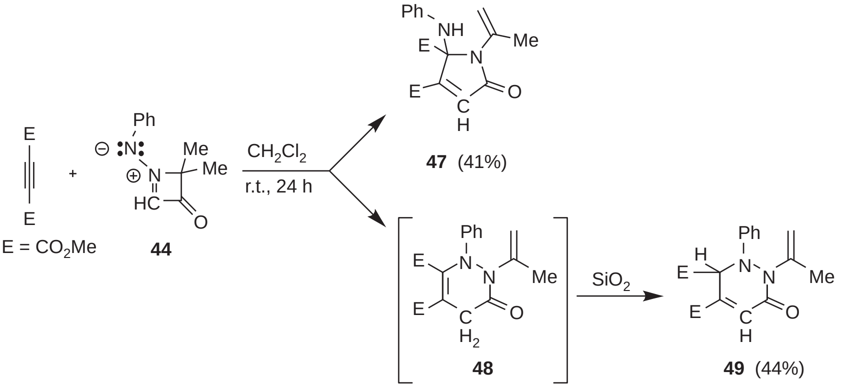
Both azomethine imines **44** and **45** react with dipolarophiles, e.g., dimethyl acetylene-dicarboxylate (DMAD). The 4,5-dihydro-1*H*-pyrazol-2-ium-1-ide **45** furnishes the expected bridged [3+2] cycloadduct, dimethyl 6,6-dimethyl-5-oxo-7-phenyl-1,7-diazabicyclo[2.2.1]-hept-2-ene-2,3-dicarboxylate (**46**, 66%) (Scheme 10) (97TH).

The reaction of the 2,3-dihydroazetium-1-anilide **44** with DMAD comes with an unexpected result. Instead of the anticipated fused bicyclic cycloadduct, two products are detected in the mixture by ^{1}H



E = CO$_2$Me **45** **46** (66%)

Scheme 10 [3+2] Cycloaddition reaction of the five-membered cyclic azomethine imine **45** with DMAD.



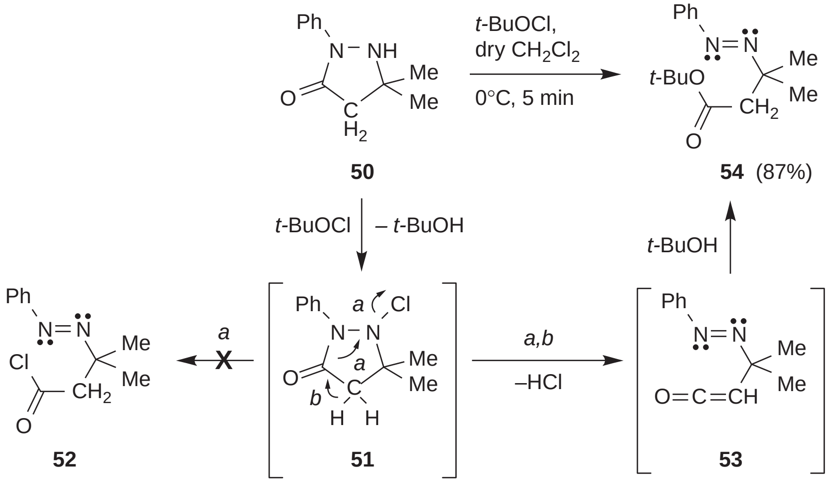
Scheme 11 Reaction of the four-membered cyclic azomethine imine **44** with DMAD.

NMR: dimethyl 2-anilino-1-isopropenyl-5-oxo-2,5-dihydro-1*H*-pyrrole-2,3-dicarboxylate (**47**) and dimethyl 1-isopropenyl-6-oxo-2-phenyl-1,2,5,6-tetrahydropyridazine-3,4-dicarboxylate (**48**) (Scheme 11) (97TH). Whereas product **47** can be isolated as such, the latter product **48** tautomerizes upon chromatographic separation on silica gel to give dimethyl 1-isopropenyl-6-oxo-2-phenyl-1,2,3,6-tetrahydro-pyridazine-3,4-dicarboxylate (**49**) (Scheme 11). Obviously, these products result from competing reactions along with skeletal rearrangements. The connectivity of CNN atoms constituting the azomethine imine functionality of the starting material **44** is completely or partly lost in products **47** and **48**/**49**, respectively (97TH).

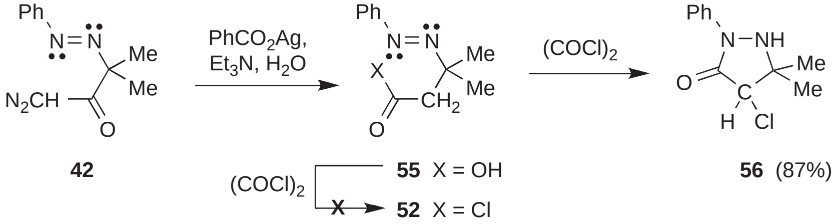
Exploration of the scope and limitations of the formation of both types of heterocyclic azomethine imines with an exocyclic terminal nitrogen atom and/or isomers with a ring larger by one nitrogen atom and with all azomethine imine atoms incorporated into the ring requires the extension of the carbon tether $(C)_n$ between the diazene and the diazo carbonyl functionalities of the ω-diazenyl α'-diazo ketone **37** (01TH).

3.3 Attempts to prepare a β-diazenyl-α'-diazo ketone [carbon tether $(C)_n$, $n = 1$]. Formation of 6,6-dimethyl-2-phenyl-1,2-diazabicyclo[3.1.0]hexan-3-one (59)

The efficient oxidative ring-opening of diazetidinone **40** with *tert*-butyl hypochlorite forming acid chloride **41** and its conversion into α-diazenyl diazo ketone **42** upon treatment with diazomethane (Scheme 8) was anticipated to be transferable to the five-membered homologue **50**. However, 5,5-dimethyl-2-phenylpyrazolidin-3-one (**50**) (96LA272, 85T575) and *tert*-butyl hypochlorite do not form the requisite 3-methyl-3-[(*E*)-phenyldiazenyl]butanoyl chloride (**52**) as expected but afford *tert*-butyl 3-methyl-3-[(*E*)-phenyldiazenyl]butanoate (**54**) (Scheme 12).



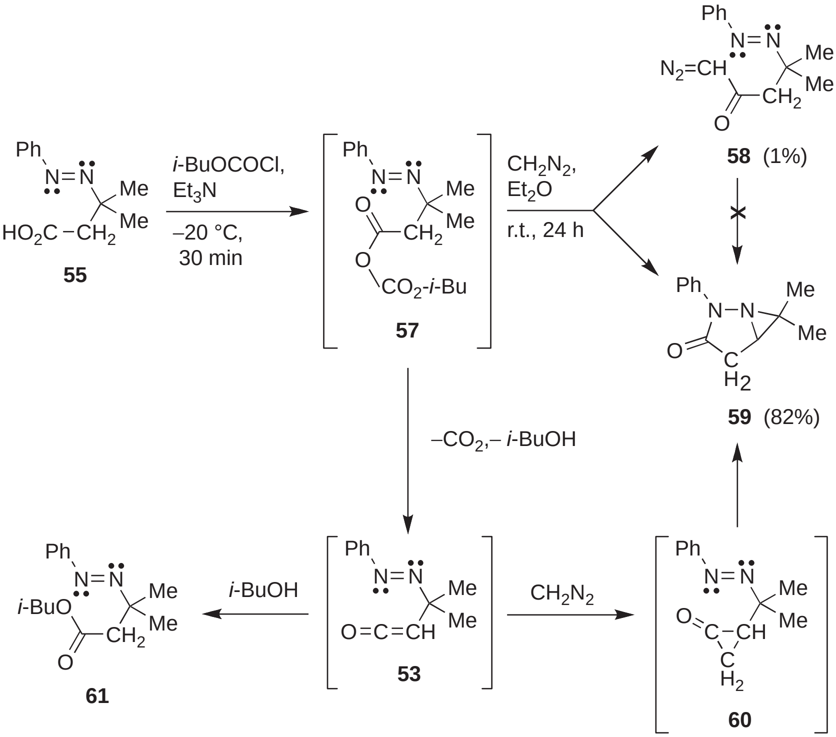
Scheme 12 Formation of *tert*-butyl 3-methyl-3-[(*E*)-phenyldiazenyl]butanoate (**54**).



Scheme 13 Formation of 4-chloro-5,5-dimethyl-2-phenylpyrazolidin-3-one (**56**).

The formation of *tert*-butyl ester **54** may be rationalized by N-chlorination of the pyrazolidinone **50** to give *N*-chloropyrazolidinone **51**. 1,4-Dehydrochlorination of intermediate **51** involving ring-opening by bond breaking steps *a* (steps *a* alone would lead to acid chloride **52**) and concomitant deprotonation *b* generates the ketene intermediate **53**. Addition of the previously formed *tert*-butyl alcohol to ketene **53** provides the otherwise not readily available *tert*-butyl ester **54** (87%).

As a general strategy for extending the C-tether, the Wolff rearrangement (50JA5163) converting diazo carbonyl compounds into homologous acids was considered next. Thus, diazo ketone **42** [$(C)_n$, $n = 0$] upon treatment with silver benzoate and triethylamine in water is transformed into 3-methyl-3-[(*E*)-phenyldiazenyl]butanoic acid (**55**) (Scheme 13). Attempts to convert acid **55** into acid chloride **52** by conventional methods with inorganic acid chlorides (PCl_5, $SOCl_2$, SO_2Cl_2, *etc.*) failed; only intractable materials were recovered. However, oxalyl chloride produces 4-chloro-5,5-dimethyl-2-phenylpyrazolidin-3-one (**56**) (87%; Scheme 13).



Scheme 14 Formation of 6,6-dimethyl-2-phenyl-1,2-diazabicyclo[3.1.0]hexan-3-one (**59**) *via* the postulated ω-diazenyl ketene intermediate **53**.

The next approach to prepare the desired β-diazenyl-α'-diazo ketone **58** utilized the mixed anhydride method (57JOC245). The reaction of 3-methyl-3-[(*E*)-phenyldiazenyl]butanoic acid (**55**) with isobutyl chloroformate and triethylamine followed by treatment of the resulting non-isolated mixed anhydride **57** with diazomethane yields only a minimal amount (1%) of diazo ketone **58** (Scheme 14). The main product is 6,6-dimethyl-2-phenyl-1,2-diazabicyclo[3.1.0]hexan-3-one (**59**) (82%), a light yellow oil that turns into a colorless solid at −15 °C; the structure of **59** was elucidated by 2D NMR.

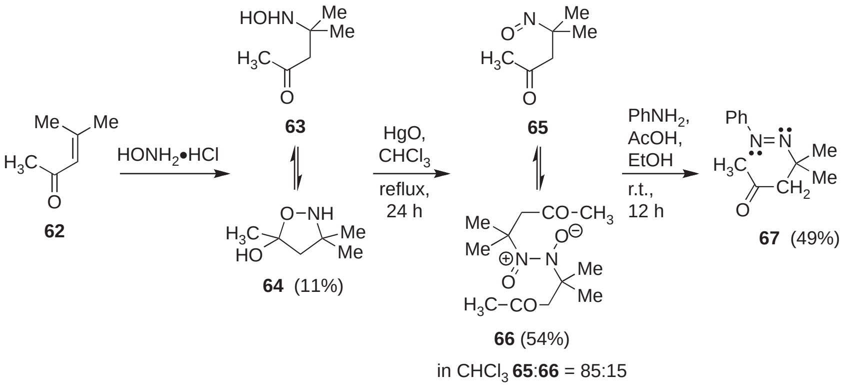
The bicyclic product **59** proved not to be derived from diazo ketone **58**. It may arise from the reaction of diazenyl ketene intermediate **53** with diazomethane *via* the postulated 2-[2-methyl-2-(phenyldiazenyl)propyl] cyclopropanone intermediate **60** and its subsequent isomerization to the bicyclic product **59** (Scheme 14). The formation of the diazenyl ketene intermediate **53** has been made plausible by carrying out the reaction in the presence of an excess of isobutyl alcohol to afford isobutyl 3-methyl-3-[(*E*)-phenyldiazenyl]butanoate (**61**) in a competing addition.

3.4 1-Diazo-4-methyl-4-[(*E*)-phenyldiazenyl]pentan-2-one (**58**) [carbon tether (C)$_n$, $n = 1$]

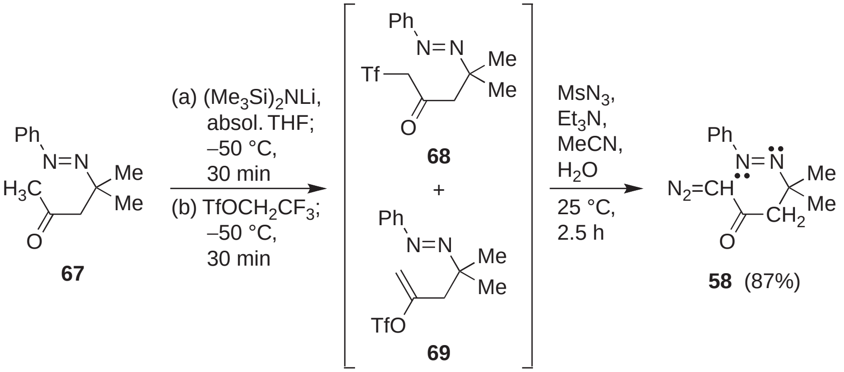
Finally, Danheiser's method (96JOC134) was applied to 4-methyl-4-[(*E*)-phenyldiazenyl]pentan-2-one (**67**) to prepare *β*-diazenyl-*α*′-diazo ketone **58** (*vide infra*).

The preparation of the requisite methyl ketone **67** starts from mesityl oxide (**62**) and hydroxylamine hydrochloride utilizing a known protocol (98BC1808) (Scheme 15). As correctly formulated in the original paper, hydroxylamine hydrochloride does not form the oxime but affords a low yield (11%) of the conjugate adduct, 4-(hydroxyamino)-4-methylpentan-2-one (**63**), which in solution is predominantly present as the hemiacetal cyclotautomer, 3,3,5-trimethylisoxazolidin-5-ol (**64**). Oxidation of **64** with mercuric oxide in chloroform furnishes a blue solution of 4-methyl-4-nitrosopentan-2-one (**65**) and its dimer **66** (ratio 85:15), which was isolated as colorless crystals **67** (54%). Condensation of nitroso ketone **65** with aniline in the presence of acetic acid provides *β*-phenyldiazenyl-*α*′-methyl ketone **67** as a yellow oil (49%) (Scheme 15).

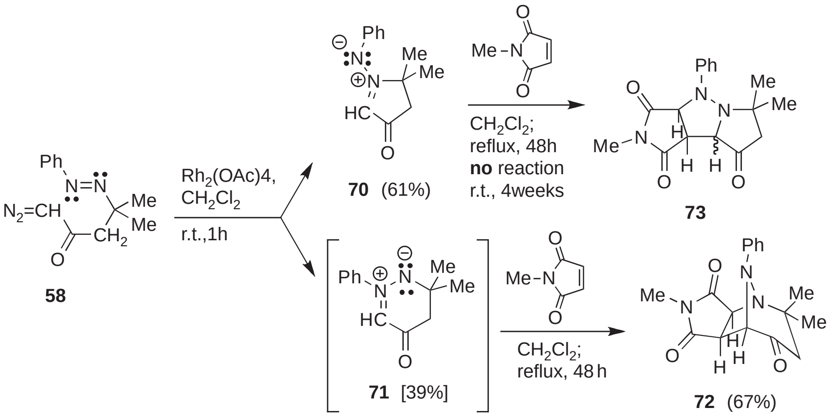
Applying Danheiser's method (96JOC134), phenyldiazenyl ketone **67** reacts with lithium bis(trimethylsilyl)amide in absolute tetrahydrofuran followed by 2,2,2-trifluoroethyl triflate forming a mixture of C- and O-triflate intermediates **68** and **69**, respectively. Upon treatment with mesyl azide, the mixture of **68** and **69** provides the desired 1-diazo-4-methyl-4-[(*E*)-phenyldiazenyl]pentan-2-one (**58**) as yellow crystals in very good yield (87%) (Scheme 16).



Scheme 15 Preparation of *β*-phenyldiazenyl-*α*′-methyl ketone **67** [carbon tether (C)$_n$, $n = 1$].



Scheme 16 Preparation of β-diazenyl-α'-diazo ketone **58** by Danheiser's method.



Scheme 17 Conversion of β-diazenyl-α'-diazo ketone **58** into azomethine imines **70** and **71**. Selective interception of the transient 6-ring isomer **71** with N-methyl-maleimide.

3.5 Cyclic azomethine imines: 2,2-dimethyl-4-oxo-3,4-dihydro-2*H*-pyrrolium-1-anilide (**70**) and 3,3-dimethyl-5-oxo-1-phenyl-2,3,4,5-tetrahydropyridazin-1-ium-2-ide (**71**). Generation and [3+2] cycloadditions

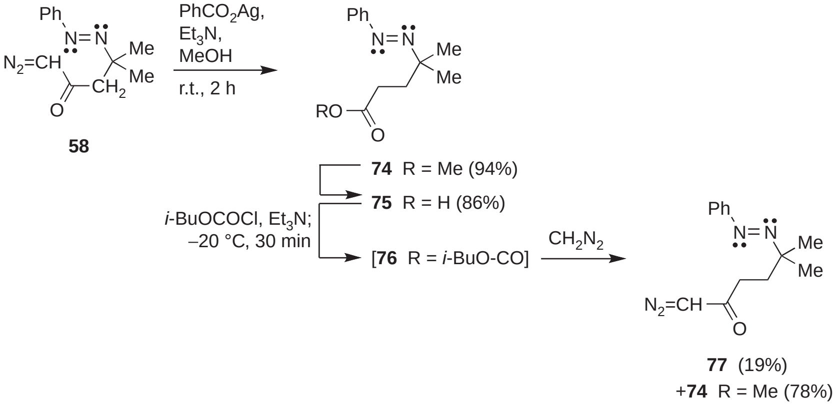
Addition of rhodium(II) acetate to a solution of β-diazenyl-α'-diazo ketone **58** in dichloromethane affords 2,2-dimethyl-4-oxo-3,4-dihydro-2*H*-pyrrolium-1-anilide (**70**) as orange crystals (61%) (Scheme 17).

The 6-ring azomethine imine isomer, 3,3-dimethyl-5-oxo-1-phenyl-2,3,4,5-tetrahydropyridazin-1-ium-2-ide (**71**) could not be isolated. However, when the reaction of the diazo ketone **58** and rhodium(II) acetate was repeated in the presence of *N*-methylmaleimide, the [3+2] cycloadduct **72** was isolated as colorless crystals (67%). Under these conditions, the five-membered azomethine imine **70** proved unreactive; it took four weeks at room temperature to partly convert **70** and *N*-methylmaleimide into the corresponding [3+2] cycloadduct **73**, which is labile and rapidly decomposed after isolation from the solution (Scheme 17).

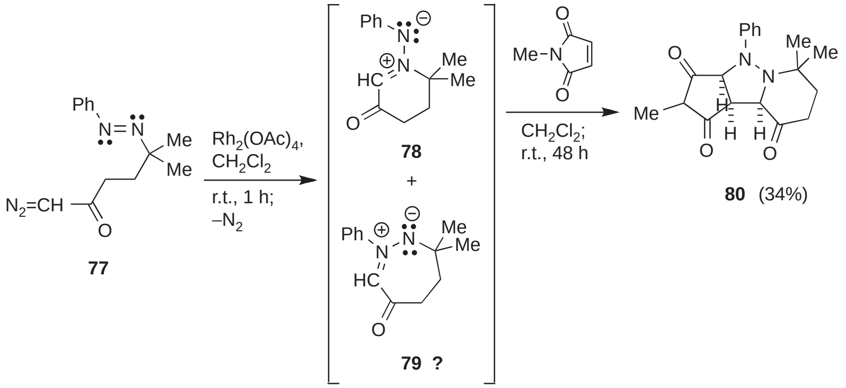
3.6 γ-Diazenyl-α'-diazo ketone 1-diazo-5-methyl-5-[(*E*)-phenyldiazenyl]hexan-2-one (**77**) [carbon tether (C)$_n$, $n = 2$]

Extension of the C-tether to $n = 2$ can be achieved by subjecting diazo ketone **58** to the Wolff rearrangement using silver benzoate, triethylamine and methanol. Hydrolysis of the resulting methyl 4-methyl-4-[(*E*)-phenyldiazenyl]pentanoate (**74**) (94%) yields the acid **75** (84%). Conversion of **75** into the mixed anhydride **76** followed by treatment with diazomethane gives 1-diazo-5-methyl-5-[(*E*)-phenyldiazenyl]hexan-2-one (**77**) in low yield (19%) and methyl ester **74** (78%) (Scheme 18).

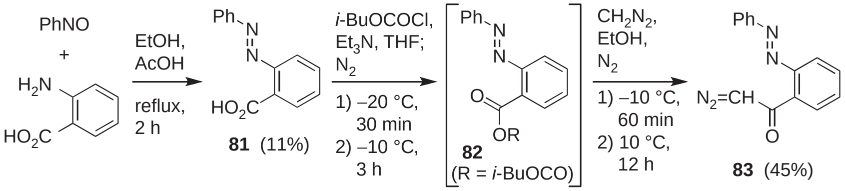
γ-Diazenyl diazo ketone **77** and rhodium(II) acetate gives none of the expected cyclic azomethine imine products **78** and **79** (Scheme 19). When the reaction is carried out in the presence of *N*-methylmaleimide the [3+2] cycloadduct derived from the anticipated six-membered azomethine imine **78** (3a*S*,9a*R*,9b*R*)-2,6,6-trimethyl-4-phenylhexahydro-1*H*-pyrrolo[3′,4′:3,4]pyrazolo[1,5-*a*]pyridine-1,3,9(2*H*,6*H*)-trione (**80**) (34%) is isolated (Scheme 19).



Scheme 18 Conversion of β-diazenyl-α'-diazo ketone **58** into γ-diazenyl-α'-diazo ketone **77**.



Scheme 19 Conversion of γ-diazenyl-α'-diazo ketone **77** into azomethine imine **78** and **79**. Interception of 6-ring azomethine imine **78** with *N*-methylmaleimide to yield cycloadduct **80**.

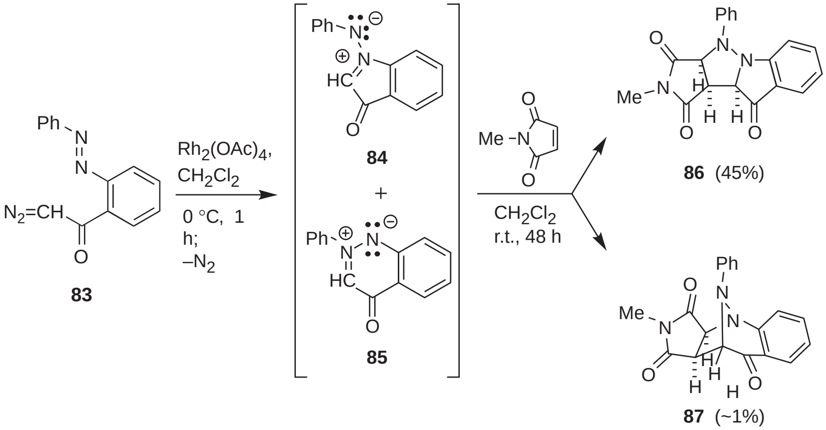


Scheme 20 Preparation of 2-diazo-1-[2-[(*E*)-phenyldiazenyl]phenyl]ethanone **83**.

3.7 2-Diazo-1-[2-[(*E*)-phenyldiazenyl]phenyl]ethanone (**83**). Aromatic ring as carbon tether [(C)$_n$, $n = 1$]

A diazene group attached to an aromatic ring is prevented from hydrazone formation; in addition to this "hydrazone blocking" feature, the neighboring *ortho*-carbon atom can be part of the tether as defined above. Accordingly, 2-diazo-1-[2-[(*E*)-phenyldiazenyl]phenyl]ethanone (**83**) was designed as the simplest azomethine imine precursor featuring two neighboring benzene carbon atoms as aromatic hydrazone blocking and as tether [(C)$_n$, $n = 1$] centers.

The requisite β-diazenyl-α'-diazo ketone **83** is readily available from the known condensation of nitrosobenzene with anthranilic acid (50JCS950). The resulting 2-[(*E*)-phenyldiazenyl]benzoic acid (**81**) when treated with isobutyl chloroformate forms the mixed anhydride **82** *in situ*, which in turn, reacts with diazomethane furnishing 2-diazo-1-[2-[(*E*)-phenyldiazenyl]phenyl]ethanone (**83**) in non-optimized yield (45%) (Scheme 20).



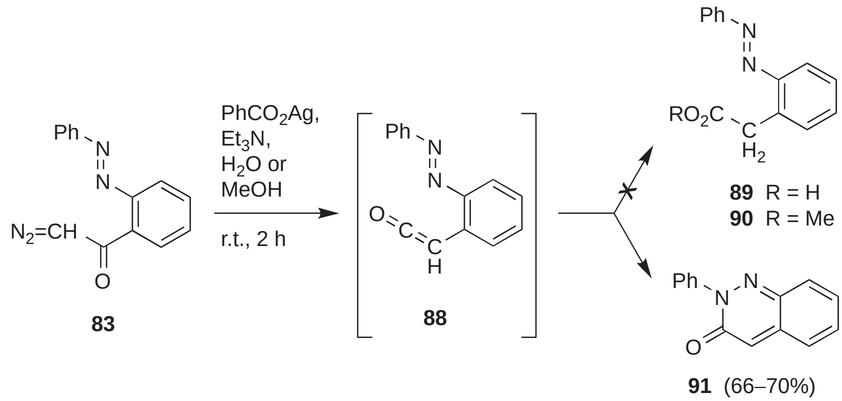
Scheme 21 Rh(II)-Induced conversion of 2-diazo-1-[2-[(*E*)-phenyldiazenyl]phenyl] ethanone (**83**) into transient azomethine imines **84** and **85** followed by interception with *N*-methylmaleimide.

β-Diazenyl-*α*′-diazo ketone **83** upon treatment with rhodium(II) acetate does not provides any isolable cyclic azomethine imines **84** and **85** because of their apparent instability. However, addition of *N*-methylmaleimide provides a mixture of two cycloadducts **86** and **87** (Scheme 21) after the nitrogen evolution has ceased; both products can be separated, the latter though in minimal yield, and their structures have been elucidated by 2D NMR.

3.8 Attempts toward an aromatic ring as carbon tether [(C)$_n$, $n = 2$]. Formation of 2-phenylcinnolin-3(2*H*)-one (**91**)

The incorporation of a phenyl ring as part of an extended carbon tether [(C)$_n$, $n = 2$] requires the preparation of the homologous [2-[(*E*)-phenyldiazenyl]phenyl]acetic acid **89** or its methyl ester **90** (Scheme 22), which in a subsequent step has to be transformed into 1-diazo-3-[2-[(*E*)-phenyldiazenyl]phenyl]acetone.

Wolff rearrangement of *β*-diazenyl-*α*′-diazo ketone **83** in the presence of water, methanol (or even with primary and secondary amines) under varied reaction conditions comes with surprise: Instead of the expected homologous acid **89**, methyl ester **90** (or the respective amide), 2-phenylcinnolin-3(2*H*)-one (**91**) is the only product indicative of the anticipated *in situ* formation of ketene intermediate **88** (Scheme 22). Obviously, the apparent 6*π*-electrocyclization reaction prevails forming the isolated heterocyclic product **91**, a so far unknown compound.



Scheme 22 Attempted conversion of 2-diazo-1-[2-[(*E*)-phenyldiazenyl]phenyl] ethanone (**83**) into [2-[(*E*)-phenyldiazenyl]phenyl]acetic acid (**89**) or methyl ester **90**. Formation of 2-phenylcinnolin-3(2*H*)-one (**91**).

REFERENCES

96LA272	B. Prentice, *Liebigs Ann. Chem.*, **292**, 272 (1896).
98BC1808	E. Harries and R. Gley, *Ber. Dtsch. Chem. Ges.*, **31**, 1808 (1898).
17JA279	J. R. Bailey and N. H. Moore, *J. Am. Chem. Soc.*, **39**, 279 (1917).
17JA1322	J. R. Bailey and A. T McPherson, *J. Am. Chem. Soc.*, **39**, 1322 (1917).
50JA5163	M. S. Newman and P. F. Beal, *J. Amer. Chem. Soc.*, **72**, 5163 (1950).
50JCP1437	C. I. Beard and B. P. Dailey, *J. Chem. Phys.*, **18**, 1437 (1950).
50JCS950	G. J. Bloink and K. H. Pausacker, *J. Chem. Soc.*, 950 (1950).
57JOC245	S. Tarbell and J. A. Price, *J. Org. Chem.*, **22**, 245 (1957).
60TL1	R. Huisgen, R. Fleischmann, and A. Eckell, *Tetrahedron Lett.*, **1**, 1 (1960).
63ACE565	R. Huisgen, *Angew. Chem.*, **75**, 604 (1963). *Angew. Chem. Int. Ed. Engl.*, **75**, 565 (1963).
76S349	T. Wagner-Jauregg, *Synthesis*, 349 (1976).
85T575	G. V. Shustov, N. B. Tavakalyan, and R. G. Kostyanovsky, *Tetrahedron*, **41**, 575 (1985).
87TL6577	J. G. Schantl, M. Decristoforo, and J. J. Daly, *Tetrahedron Lett.*, **52**, 6577 (1987).
93TH	P. Nadenik, "1,2,4,7-Tetraazabicyclo[3.3.0]octane-3,8-dithiones and 1-Amino-4,4-dimethyl-5-methyleneimidazolidin-2-one: Syntheses and Reactions", PhD Thesis, University of Innsbruck (1993).
94H1873	J. G. Schantl, H. Kählig, and M. Prean, *Heterocycles*, **37**, 1873 (1994).
95FA379	J. G. Schantl, *Farmaco*, **50**, 379 (1995).
96CRV223	A. Padwa and M. D. Weingarten, *Chem. Rev.*, **96**, 223 (1996).
96JOC134	R. L Danheiser, R. F. Miller, R. G. Brisbois, and S. Z. Park, *J. Org. Chem.*, **73**, 134 (1996).
97AA97	S. Rádl, *Aldrichimica Acta*, **30**, 97 (1997).
97H691	J. G. Schantl and I. M. Lagoja, *Heterocycles*, **45**, 691 (1997).

97TH	A. S. Rettenbacher, "Stable Cyclic Azomethine Imines. Synthesis, Structure Elucidation, Reactions", Diploma Thesis, University of Innsbruck (1997).
98ACE2229	J. G. Schantl, A. S. Rettenbacher, and K. Wurst, *Angew. Chem.*, **110**, 2346 (1998). *Angew. Chem. Int. Ed.*, **37**, 2229 (1998).
98H929	J. G. Schantl and I. M. Lagoja, *Heterocycles*, **48**, 929 (1998).
98SL786	J. G. Schantl and P. Nadenik, *Synlett*, 786 (1998).
00TH	Huang Ngoc Cuong, "2-Substituted Thiazoles and Imidazoles", PhD Thesis, University of Innsbruck (2000).
01TH	K. Libiseller, "Enehydrazine Heterocycles: Synthesis, Reactivity, and Rotational Barriers", PhD Thesis, University of Innsbruck (2001).
01TH	A. S. Rettenbacher, "Synthesis and Reactions of Cyclic Valence-Isomers of Azo-Ketocarbenes", PhD Thesis, University of Innsbruck (2001).
01U	J. G. Schantl, P. Nadenik, and K. Libiseller, unpublished results.
02TH	B. Herzog, "1-Aminoimidazoles: Syntheses, Reaktions, and Studies of the Restricted Rotation about the N–N-Bond", PhD Thesis, University of Innsbruck (2002).

CHAPTER 7

Pyrroles and *N*-Vinylpyrroles from Ketones and Acetylenes: Recent Strides

B.A. Trofimov, A.I. Mikhaleva,
E.Yu. Schmidt and **L.N. Sobenina**

Contents

A. E. Favorsky Irkutsk Institute of Chemistry, Siberian Branch of the Russian Academy of Sciences, 1 Favorsky Str., Irkutsk 664033, Russian Federation

Advances in Heterocyclic Chemistry, Volume 99
ISSN 0065-2725, DOI 10.1016/S0065-2725(10)09907-1

1. INTRODUCTION

Interest in the chemistry of pyrroles is far from fading and the isolation of relatively simple pyrroles, including antibiotics, pheromones, toxins, cell-fission inhibitors and immunomodulators from natural sources is being continued (02MI(1)334). The permanent attention given to pyrroles is mainly due to the fact that the pyrrole nucleus is the structural unit of many fundamental compounds, important from the biological point of view, such as chlorophyll, hemoglobin, vitamin B_{12}, alkaloids and others, which take part in the accumulation of solar energy, oxygen transfer processes and other life-supporting reactions (93MI2, 96OPP641, 98MI324). Diverse polycyclic secondary metabolites containing bromopyrrole structural elements (00JNP7) were found in marine organisms. A series was also found to contain alkyl and aryl substituted pyrrole moieties (96HCO9, 96JP(1)2103, 97JOC2894). From the microbe extract *Streptomyces rimosus*, a pyrrole, useful for the detection of bacterial histidinekinaze (99CC1039, 00JAN1) and possessing gram-positive antimicrobial activity against stable bacterial cultures (98ACS1040) was isolated. Polysubstituted pyrroles show activity against epidermotoidal human carcinoma (95JOC6637, 98T5075). 1,2-Diarylpyrroles are strong selective inhibitors of human cyclooxygenase-2 ferment, which plays an important role in the development of inflammatory processes (97JME1619). Some aroyl(aminoacyl)pyrroles possess anticonvulsive activity (97JME1578). Pyrroles are extensively used as pharmacophores (95TL1401, 97T7731, 00JME4582, 00JOC205). Research areas include electroconducting polypyrroles (87MM958, 07MI3), optoelectronic materials (92H(34)2003, 98JOC6715, 01TL1309) and sensors (00SM181), containing pyrrole structural elements. The above references are just illustrative. The number of monographs [(96CHEC(2)119, 96PHC103), reviews and papers (96AHC207, 98JOC10022, 98JP(1)615, 99JP(1)2849, 00JP(1)2845, 01TL3139, 01TL6027)] related to the diverse aspects of preparative, theoretical and applied pyrrole chemistry grows steadily. The synthesis of polysubstituted pyrroles were reviewed (01OPP411). The synthesis of simple pyrroles, especially alkyl substituted, still faces great difficulties (74MI4, 77MI5). Among the numerous methods of pyrrole ring construction (74MI4, 77MI5) only a few are of real preparative value, while most are multi-step, labor-consuming and require inaccessible initial or inconvenient compounds and dangerous organometallic reagents.

This situation has changed considerably with the discovery and systematic study of the synthesis of pyrroles from ketones (*via* ketoximes) and acetylenes in the superbase KOH–DMSO (the Trofimov reaction) [(81MI6, 84MI7, 90AHC177, 90MI(8)105, 92MI(9)27, 92MI(10)131, 94H(37)1193, 96ZOR1127, 98ZOR1767, 99CHE613, 99TL4519, 99UK506, 00H(53)2285, 00JOC2900, 01CHE141, 01JP(1)2491, 01MI125, 02CPB711, 02MI(1)334, 04CHE326, 06T7213, 06TL795, 07CRV4891, 09MI(11)336)]. The preparation of pyrroles and *N*-vinylpyrroles (the latter were almost unknown until the discovery of this reaction) with various substituents including alkyl groups, became possible not only in the laboratory, but also on a larger (bench) scale (84MI7).

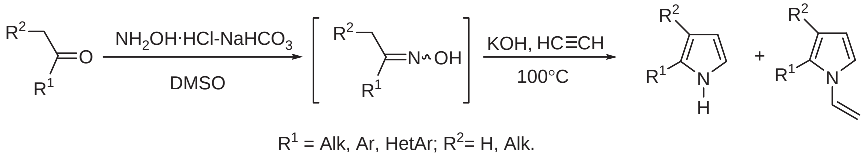
In principle, the synthesis can be realized as a one-pot process: treatment of ketones with hydroxylamine in KOH–DMSO following interaction of the formed ketoximes with acetylene. Various pyrroles with alkyl, cycloalkyl, aryl and hetaryl substituents, as well as pyrroles condensed with aliphatic macrocycles, terpenic and steroid structures, together with their vinyl derivatives now become available.

Since the publication of the latest review (02MI(1)334) summarizing the results of the Trofimov reaction, many new reports have appeared. These are the subject of the present review, which covers publications of the last decade only.

2. SYNTHESIS OF PYRROLES AND *N*-VINYLPYRROLES

2.1 One-pot synthesis of pyrroles and *N*-vinylpyrroles directly from ketones and acetylene

Alkyl, aryl and hetaryl ketones after one-pot oximation with $NH_2OH \cdot HCl$–$NaHCO_3$ (rt) and treatment with acetylene in the presence of KOH–DMSO superbase (100 °C, atmospheric pressure) were converted to 2-mono- and 2,3-disubstituted *NH*- and *N*-vinylpyrroles



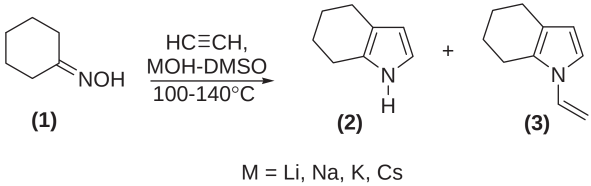
Scheme 1

(Scheme 1) with alkyl, aryl and hetaryl substituents in good yields (up to 72%) (05ARK(vii)11).

Consecutive treatment of ketones with $NH_2OH \cdot HCl–NaHCO_3$–DMSO and acetylene in excess in the presence of KOH (100–120 °C, initial acetylene pressure 12–15 atm) led to a selective formation of 2- and 2,3-disubstituted *N*-vinylpyrroles in 51–79% yields (07RJO228). Ketones of aliphatic, cycloaliphatic, aromatic, heteroaromatic and tetrahydronaphthalene series were involved into the reaction.

2.2 Pyrroles from cyclic ketones and acetylene

The kinetics of the reaction of cyclohexanone oxime (**1**) with acetylene (Equation (1)) in MOH–DMSO under atmospheric pressure was studied and quantitative data on the effect of alkaline cations on the yields of 4,5,6,7-tetrahydroindole (**2**) and its *N*-vinyl derivative **3** as well as on the reaction selectivity were obtained (08DOC(423)66).

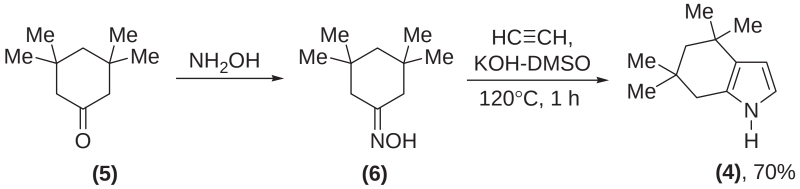


(1)

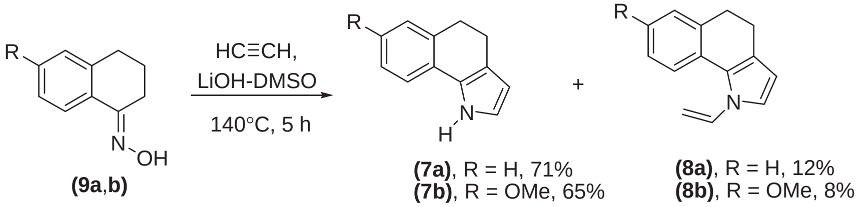
The rate of compound **2** formation increased dramatically on going from LiOH to NaOH and further to KOH and LiOH–CsF. However, vinylation in the presence of LiOH did not occur at all, but the reaction proceeded quite fast with NaOH, KOH and CsOH. The effect of NaOH–CsF turned out to be unexpected: the selectivity of pyrrole **2** formation increased and the vinylation was suppressed.

4,4,6,6-Tetramethyl-4,5,6,7-tetrahydroindole (**4**) was obtained from ketone **5** through oxime **6** in 70% yield (Scheme 2) (99TL4519).

4,5-Dihydro-1*H*-benz[*g*]indoles **7a**,**b** and their *N*-vinyl derivatives **8a**,**b** were prepared from oximes **9a**,**b** with acetylene and MOH–DMSO (M = Li, K) (Equation (2)) (00JOC2900).



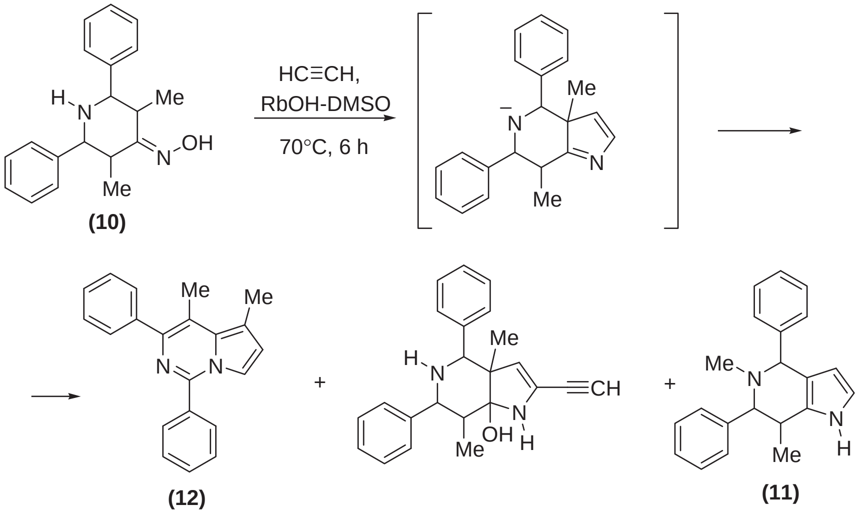
Scheme 2



(2)

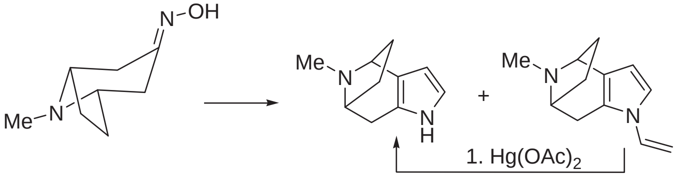
As reported (08DOC(423)66), the use of LiOH instead of KOH suppressed formation of *N*-vinyl derivatives **8a**,**b**.

In the reaction of 3,5-dimethyl-2,6-diphenylpiperid-4-one oxime (**10**) with acetylene and RbOH–DMSO, migration of the 3a-Me group to the anionic nitrogen atom occurred, leading to 5,7-dimethyl-4,6-diphenyl-4,5,6,7-tetrahydropyrrolo[3,2-*c*]pyridine (**11**) (04CHE326). The formation of the *N*-anion caused aromatization of the tetrahydropyridine ring. Tetrahydropyrrolo[1,2-*c*]pyrimidine **12** resulted from the decomposition of the intermediate 3*H*-pyrrole in a retro-Mannich reaction (Scheme 3).



Scheme 3

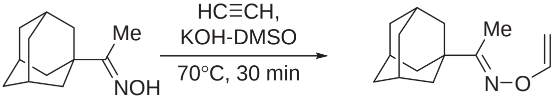
The synthesis of pyrroles **13** and **14** from tropinone oxime in 49% and 41% yields, respectively, was performed (Equation (3)) (99CHE613).



(13) **(14)**

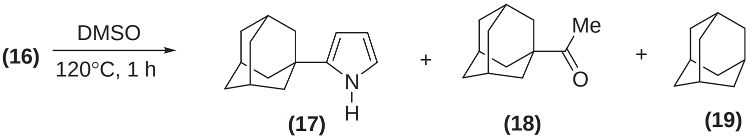
(3)

The oxime of 1-acetyl adamantane (**15**) was added to acetylene (initial acetylene pressure 13 atm) to afford the corresponding *O*-vinyl oxime **16** (Equation (4)) (08TL4362). The latter upon heating (DMSO, 120 °C, 1 h) rearranged to 2-(1-adamantyl)pyrrole (**17**), 1-acetyl adamantane (**18**) and adamantane (**19**) (6:3:1 mass ratio), the yield of the pyrrole **17** being 83% (based on 1-acetyl adamantane (**18**) consumed) (Equation (5)).



(15) **(16)**, 80%

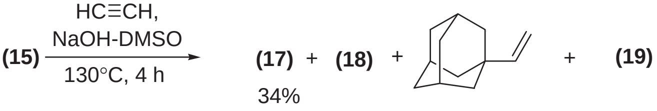
(4)



(17) **(18)** **(19)**

(5)

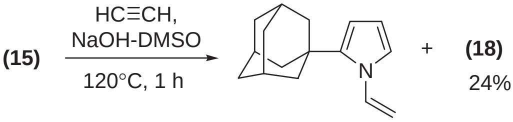
Under harsher conditions, oxime **15** reacted with acetylene to furnish pyrrole **17**, ketone **18**, 1-vinyl adamantane (**20**) and adamantane (**19**) (6:7:3:1 mass ratio), the isolated yield of pyrrole **17** reaching 34% (Equation (6)).



(20)

(6)

Under pressure, the same reaction led to 2-(1-adamantyl)-*N*-vinylpyrrole (**21**) and ketone **18** in 48% and 24% yields, respectively (Equation (7)).



(21), 48%

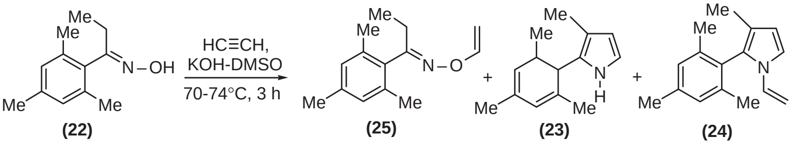
(7)

Pyrrole **21** was easily deprotected to the corresponding 1*H*-pyrrole **17** in 77% yield by subsequent treatment (aqueous MeCN) with $Hg(OAc)_2$ and $NaBH_4$ (08TL4362).

2.3 Synthesis of pyrroles from alkylarylketones

Recently, 2-phenylpyrrole needed for a fluorescent dye (BODIPY) assembly was successfully synthesized from acetophenone and acetylene (07CRV4891).

The reaction of *E*-ethylmesityl ketoxime **22** with acetylene (atmospheric pressure) afforded 2-mesityl-3-methylpyrrole (**23**) (23%), 2-mesityl-3-methyl-*N*-vinylpyrrole (**24**) (8%), *Z*- (5%) and *E*- (2%) isomers of *O*-vinylethylmesitylketoxime **25** (Equation (8)) (05T2683).

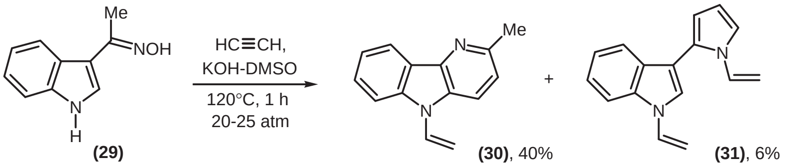


(8)

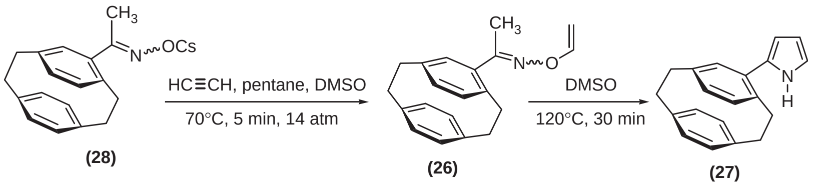
Rearrangement of the vinyl ether of acetylparacyclophane oxime **26**, the key intermediate in the Trofimov reaction, gave 2-([2,2]paracyclophan-5-yl)pyrrole (**27**) in 74% yield (Scheme 4) (04TL5489). The intermediate *O*-vinyl oxime **26** was synthesized (78%) by vinylation of a Cs-derivative of the oxime of 5-acetyl[2,2]paracyclophane (**28**) with acetylene (Scheme 4) under pressure in a DMSO-*n*-pentane two-phase system (04TL5489).

2.4 Indolylpyrroles and δ-carbolines from acylindoles

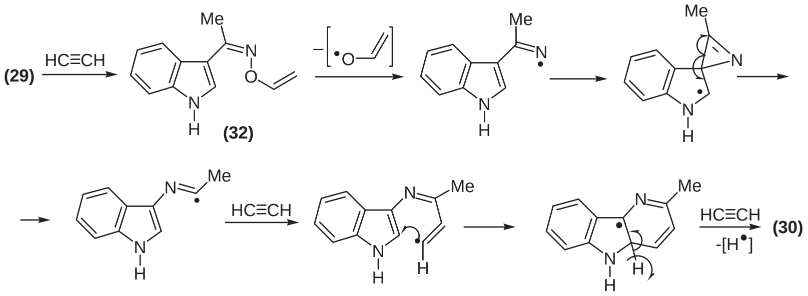
3-Acetylindole oxime (**29**) and acetylene unexpectedly gave 4-methyl-1-vinyl-δ-carboline (**30**) along with a minor product, pyrrolylindole **31** (Equation (9)) (07MC40).



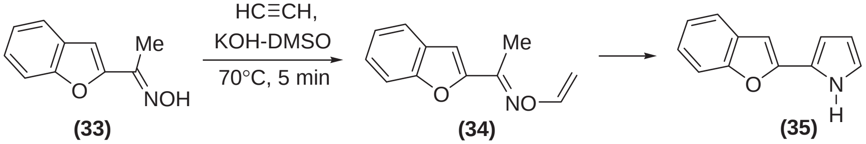
(9)



Scheme 4



Scheme 5



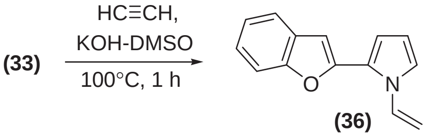
Scheme 6

The reaction was assumed to proceed via homolysis of the intermediate *O*-vinyl oxime **32** followed by an uptake of the rearranged iminyl radical by a second molecule of acetylene (Scheme 5).

2.5 Benzofuranyl- and benzothienylpyrroles from acetylcoumarone and acetylbenzothiophene

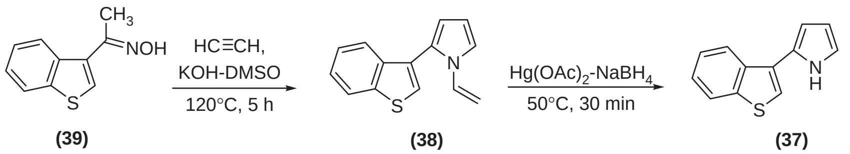
The oxime of 2-acetylcoumarone **33** poorly reacted with acetylene under pressure, *O*-vinyl oxime **34** and 2-(pyrrol-2-yl)coumarone (**35**) being obtained in 22% and 24% yields, respectively (Scheme 6) (05CHE444).

At higher temperature (100 °C) and longer time (1 h), *N*-vinylpyrrole **36** (yield 46%) was formed as the sole product (Equation (10)).



(10)

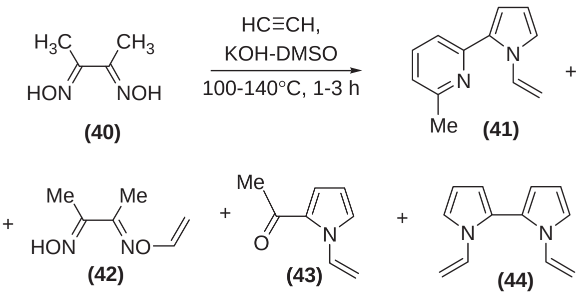
2-(Benzo[*b*]thiophen-3-yl)pyrrole (**37**) and 2-(benzo[*b*]thiophen-3-yl)-*N*-vinylpyrrole (**38**) were synthesized directly from 3-acetylbenzo[*b*] thiophene oxime (**39**) and acetylene in 68% yield (Scheme 7) (09CEJ5823). Devinylation of pyrrole **38** led to the corresponding 1*H*-pyrrole **37** in 63% yield.



Scheme 7

2.6 Methylpyridylpyrrole from dimethylglyoxime

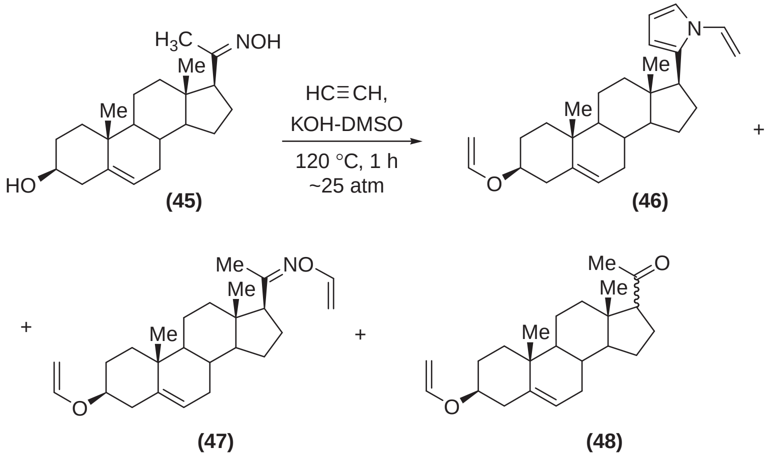
Dimethylglyoxime **40** with acetylene under pressure in KOH–DMSO gave 2-[2′-(6′-methylpyridyl)]-*N*-vinylpyrrole (**41**) (36%) along with the expected *O*-vinyl oxime **42** (10%), 2-acetylpyrrole **43** (18%) and dipyrrole **44** (15%) (Equation (11)) (01MC74).



(11)

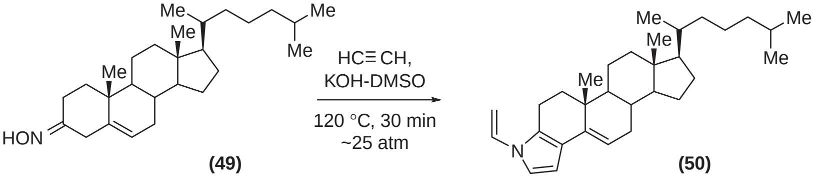
2.7 Pyrrole-steroid assemblies and pyrroles fused with a steroid skeleton from steroid ketones

The oxime of pregnenolone **45** reacted with acetylene in KOH–DMSO system to form *N*-vinylpyrrole **46** as the major product (63% yield) along with the *O*-vinyl oxime **47** (10%) and *O*-vinyl pregnenolone **48** (25%) (Equation (12)) (01CHE1488).



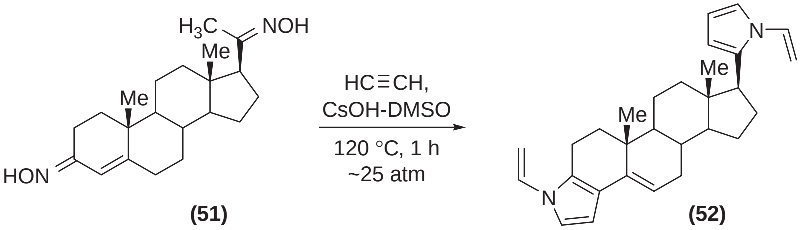
(12)

The annulation of the *N*-vinylpyrrole ring with a steroid skeleton of 5-cholestene was achieved in a single regiospecific step from 5-cholesten-3-one oxime **49** with acetylene in KOH–DMSO to furnish the fused pyrrole-steroid **50** in 25% yield (Equation (13)) (02CHE60).



(13)

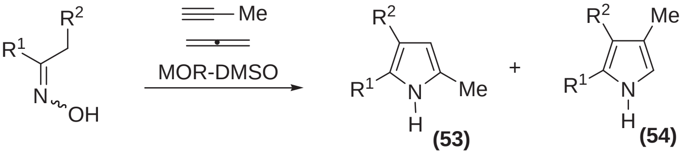
Progesterone dioxime **51** reacted with acetylene in a superbasic system to afford dipyrrole **52** in 7% yield. The reaction was accompanied by prototropic migration of the double bonds in the steroid fragment and vinylation of the *NH*-pyrrole groups (Equation (14)) (03RJO1406).



(14)

2.8 Synthesis of pyrroles from ketoximes using propyne (allene)

Heterocyclization of ketoximes with propyne or allene in superbase MOR–DMSO, leading to 2-alkyl(aryl, hetaryl)-5-methyl- **53** and 2,3-dialkyl-4-methylpyrroles **54** in yields of up to 63%, was accomplished (Equation (15)) (00S1585).



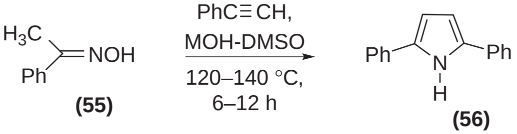
(15)

M = K, Cs; R = H, *t*-Bu; R^1 = Me, *i*-Pr, *t*-Bu, Ph, 2-furyl, 2-thienyl; R^2 = H, Me;
R^1-R^2 = $(CH_2)_4$

The reaction is mostly regioselective affording mainly or exclusively 2,5-di- and 2,3,5-trisubstituted pyrroles. The minor isomers in most cases were the corresponding 2,4-di- and 2,3,4-trisubstituted pyrroles, only in the case of acetoxime was the isomer ratio *ca*. 1:1. For oximes of methyl isopropyl ketone and pinacolone, the 4-methyl isomers were predominant (78% and 83%, respectively) (00S1585).

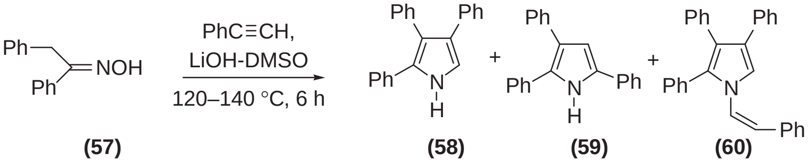
2.9 Synthesis of pyrroles using phenylacetylene

Acetophenone oxime **55** reacted with phenylacetylene to afford 2,5-diphenylpyrrole (**56**) in 14–18% yields (Equation (16) (09ARK(iv)14)).



(16)

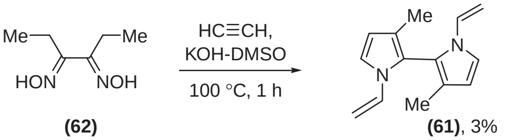
Benzylphenyl ketoxime **57** with phenylacetylene delivered a mixture of 2,3,4- (**58**), 2,3,5-triphenylpyrrole (**59**) (in 17% total yield) and 2,3,4-triphenyl-*N*-[(*Z*)-2-phenylethenyl]pyrrole (**60**) (7%) (Equation (17)) (09ARK(iv)14).



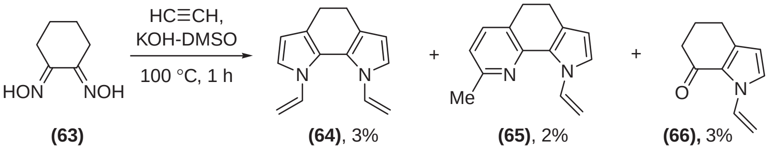
(17)

2.10 Dipyrroles from diketones

Divinyl-2,2′-dipyrrole **61** was obtained from 3,4-hexanedione dioxime (**62**) with acetylene under pressure (Equation (18)). In the case of 1,2-cyclohexanedione dioxime (**63**), 2,2′-dipyrrole **64**, 2-pyridyl- (**65**) and 2-acylpyrroles **66** were isolated (Equation (19)) (06CHE34). Dioximes **67** and **68** gave their mono- (**69** and **70**) and divinyl derivatives **71** and **72**, mostly 3,4-diphenyl- (**73**) and 3,4-di(furan-2-yl)-1,2,5-oxadiazoles **74** (Equation (20)).

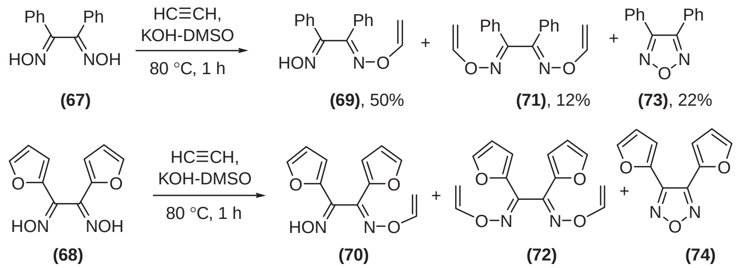


(18)



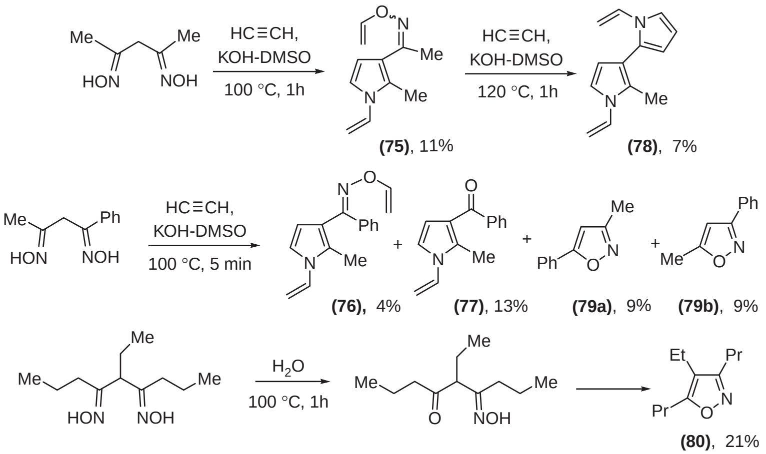
(19)

(19)



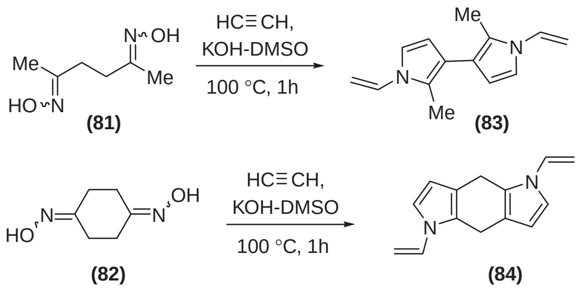
(20)

Dioximes of 1,3-diketones with acetylene gave pyrroles containing an *O*-vinyl oxime **75** and **76** or an acyl substituent **77** and dipyrrole **78**. With sterically hindered 1,3-dioximes, the main products were isoxazoles **79a, b** and **80**, formed due to hydrolysis of oxime function (Equation (21)) (05CHE722).



(21)

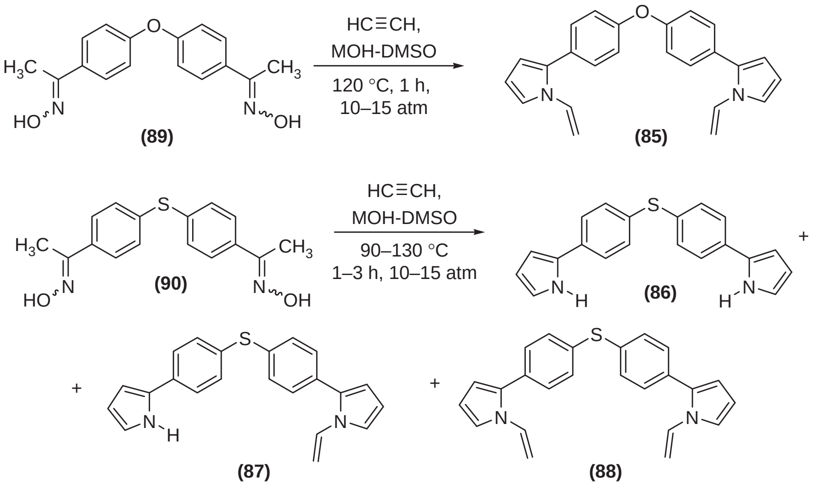
Dioximes of hexane-2,5-dione (**81**) and cyclohexane-1,4-dione (**82**) reacted with acetylene under pressure to give dipyrrole **83** and 1,5-divinyl-4,8-dihydropyrrolo[2,3-*f*]indole (**84**) in 12% and 6% yields, respectively, thus exemplifying a very simple, straightforward route to inaccessible or unknown pyrrolic assemblies (Equation (22)) (04TL3789).



(22)

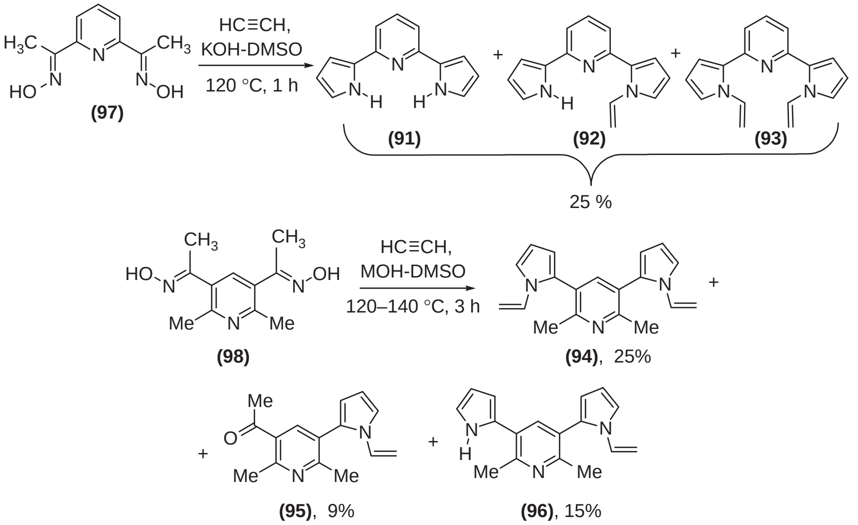
2.11 Dipyrroles separated by conjugated systems from diacylarenes and -hetarenes

4,4′-Bis[(*N*-vinylpyrrol-2-yl)]diphenyloxide (**85**), 4,4′-bis(pyrrol-2-yl) diphenylsulfide (**86**), 4-(pyrrol-2-yl)-4′-[(*N*-vinylpyrrol-2-yl)]diphenylsulfide (**87**) and 4,4′-bis[(*N*-vinylpyrrol-2-yl)]diphenylsulfide (**88**) were synthesized in a one-pot procedure from oximes of the corresponding diacetylphenylenoxide **89** and -sulfide **90** through reaction with acetylene (MOH–DMSO, M = Li, K), thus illustrating the applicability and general character of the synthesis of diverse dipyrrole–phenylene assemblies and their *N*-vinyl derivatives (Equation (23)) (05T7756).



(23)

2,6-Di(pyrrol-2-yl)pyridine (**91**), 2-(pyrrol-2-yl)-6-(*N*-vinylpyrrol-2-yl)pyridine (**92**), 2,6-bis(*N*-vinylpyrrol-2-yl)pyridine (**93**), 3,5-bis(*N*-vinylpyrrol-2-yl)-2,6-dimethylpyridine (**94**), 3-acetyl-2,6-dimethyl-5-(*N*-vinylpyrrol-2-yl)pyridine (**95**) and 2,6-dimethyl-3-(pyrrol-2-yl)-5-(*N*-vinylpyrrol-2-yl)pyridine (**96**) were prepared in a one-pot procedure from oximes of the corresponding diacetylpyridines **97** and **98** with acetylene in MOH–DMSO (M = Li, K) (Equation (24)) (05EJO4338).



(24)

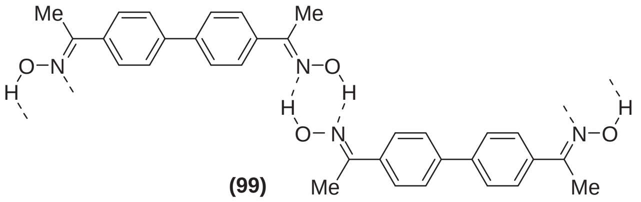


Figure 1

Amazingly, the dioxime of 4,4′-diacetyldiphenylene (**99**) with acetylene did not give the expected pyrroles under common conditions, apparently due to the formation of associates as shown by X-ray diffraction analysis (Figure 1) (08DOC(423)273).

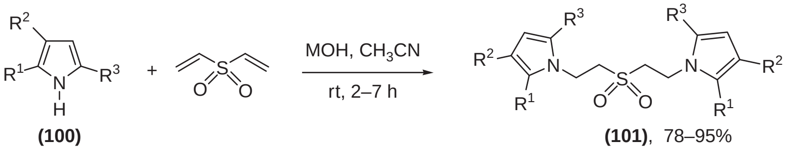
3. REACTIONS OF PYRROLES AND *N*-VINYLPYRROLES

A number of hitherto inaccessible or unknown *NH*- and *N*-vinylpyrroles, becoming available through the Trofimov reaction, has opened new horizons for further developing pyrrole chemistry. Here, the reactions of pyrroles and *N*-vinylpyrroles synthesized from ketones and acetylenes are briefly discussed.

3.1 Reactions on the pyrrole moiety of *NH*- and *N*-vinylpyrroles

3.1.1 Addition of *NH*- and *N*-vinylpyrroles to electrophilic alkenes

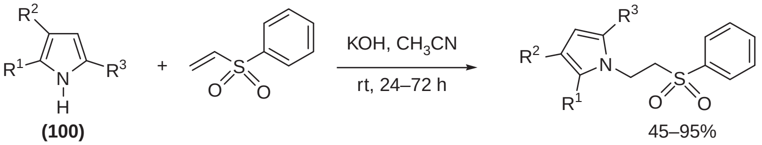
Pyrroles **100** readily added to divinylsulfone in the presence of catalytic amounts of MOH to afford selectively di[2-(pyrrol-1-yl)ethyl]sulfones (**101**) (Equation (25)) (99ZOR1226).



(25)

M = Na, K; R^1 = H, Ph; R^2 = H; $R^1 - R^2 = (CH_2)_4$; R^3 = H, C(S)SBu, $COCF_3$

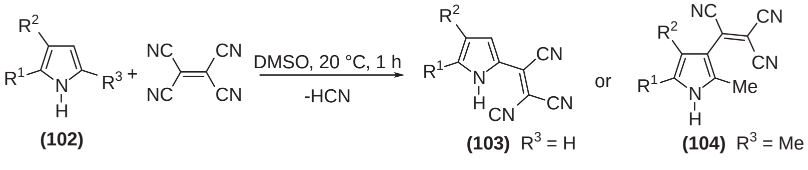
The addition of pyrroles **100** to the double bond of phenylvinylsulfone required a higher concentration of KOH (equimolar amount) and longer time (Equation (26)) (99ZOR1226).



(26)

R^1 = H, Ph; R^2 = H; R^3 = $COCF_3$

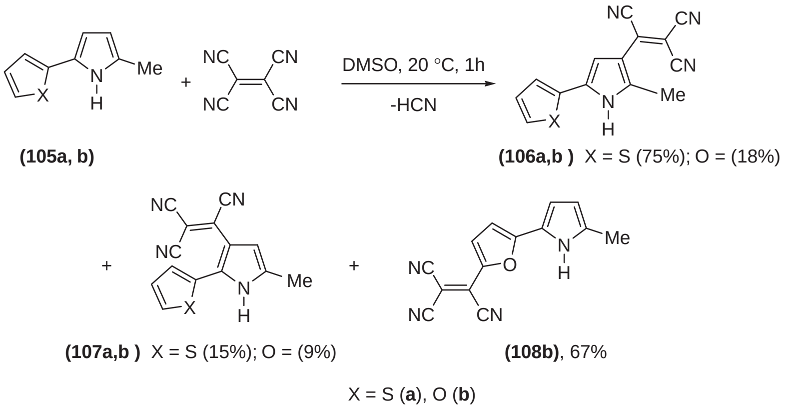
In the reactions of the pyrroles **102** with tetracyanoethene, one of the nitrile groups in the latter compound was replaced by a 2- or 3-pyrrole moiety to form tricyanoethenylpyrroles **103** (R^3 = H) or **104** (R^3 = Me) in quantitative yields. The reaction proceeded as an addition–elimination sequence (Equation (27)) (00RJO1504, 01ARK(ix)37).



R^1 = H, Ph; R^2 = H; $R^1 - R^2 = (CH_2)_4$; R^3 = H, Me

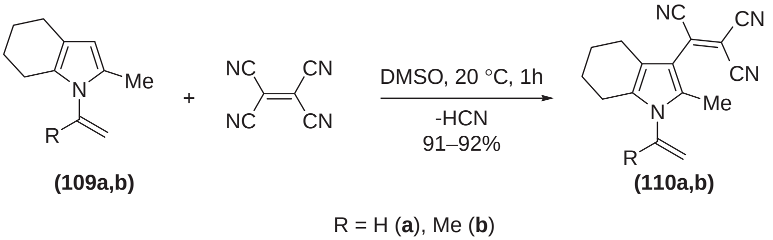
(27)

2-Methyl-5-(thiophen-2-yl)pyrrole (**105a**) with tetracyanoethene yielded 3-tricyanoethenyl isomer **106a** along with 4-tricyanoethenyl derivative **107a**. The reaction of 2-(furan-2-yl)-5-methylpyrrole (**105b**) with tetracyanoethene involved the α-position of the furan ring to deliver **108b** (Equation (28)) (01ARK(ix)37).



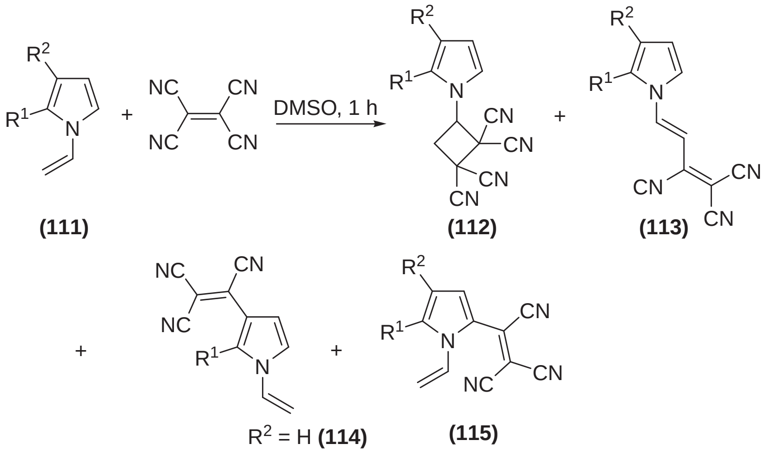
(28)

The reaction of *N*-vinyl- (**109a**) and *N*-isopropenyl-(**109b**) -4,5,6,7-tetrahydroindoles with tetracyanoethene afforded the 3-tricyanoethenyl derivatives **110a**,**b** as the only products (Equation (29)) (01ARK(ix) 37).



(29)

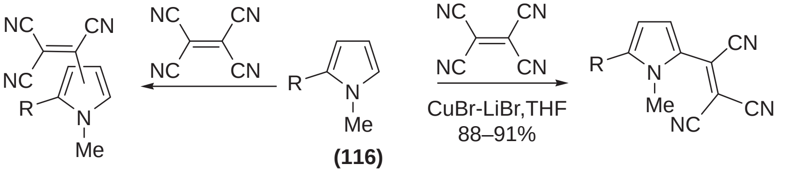
However, 2-aryl-*N*-vinylpyrroles **111** in acetone, THF and benzene reacted with tetracyanoethene chemo- and regiospecifically across the vinyl group to give 3-(2-arylpyrrol-1-yl)-1,1,2,2-cyclobutanetetracarbonitriles **112**. The latter, upon recrystallization from EtOH, eliminated HCN and entirely rearranged to afford stereospecifically *trans*-(3*E*)-4-(2-arylpyrrol-1-yl)-1,3-butadiene-1,1,2-tricarbonitriles **113**. In DMSO, along with the above [2+2]-cycloaddition giving pyrroles **112** and **113**, tricyanoethenylation of the pyrrole ring occurred to form 3-(**114**) and 5-(**115**)-tricyanoethenylpyrroles, the ratio being dependent on the substituents in the pyrrole ring and the conditions (Equation (30)) (09T4326).



(30)

R^1 = Ph, 4-BrC_6H_4, 4-$MeOC_6H_4$; R^2 = H, *n*-Pr, *n*-C_7H_{15}

The reaction of *N*-methylpyrroles **116** with tetracyanoethene in various solvents (DMSO, acetone, THF) proceeded nonselectively to deliver a mixture of 5-, 3- and 4-tricyanoethenylpyrroles (Equation (31)). In the presence of THF-soluble CuBr–LiBr, *N*-methylsubstituted pyrroles **116** reacted with tetracyanoethene regioselectively to afford exclusively the tricyanoethenylation products through the α-position of the pyrrole ring (08S2631).

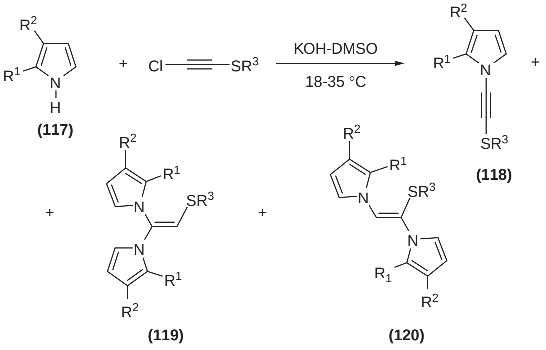


(31)

R = H, Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-ClC_6H_4

3.1.2 Addition of *NH*- and *N*-vinylpyrroles to electrophilic acetylenes

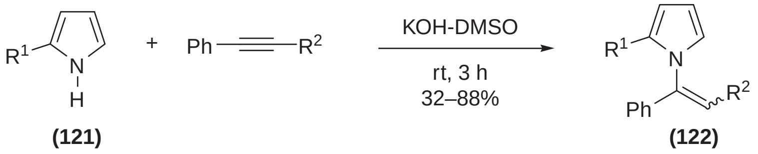
Pyrroles **117** reacted with alkylsulfanylchloroacetylenes in KOH–DMSO to give mainly *N*-(alkylsulfanylethynyl)pyrroles **118** as a formal substitution product along with 2-alkylsulfanyl-1,1-bis(pyrrol-1-yl)- (**119**) and 1-alkylsulfanyl-1,2-bis(pyrrol-1-yl)ethenes **120** from further nucleophilic addition of the pyrroles to the triple bond of the first product. With excess pyrrole ethene **119** was the major adduct (yield up to 56%) (Equation (32)) (99RJO916, 02COR1121).



(32)

R^1= H, Ph; R^2= H; R^1– R^2 = $(CH_2)_4$; R^3= Et, *n*-Pr

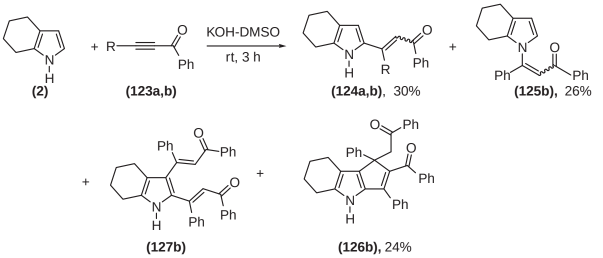
The reaction of pyrroles **121** with acyl- and cyanophenylacetylenes proceeded smoothly and selectively in KOH–DMSO to furnish functionalized *N*-ethenylpyrroles **122** (Equation (33)) (02COR1121, 03S1272).



(33)

R^1 = H, Ph; R^2 = CN, COPh, 2-furoyl

Under analogous conditions, 4,5,6,7-tetrahydroindole **2** added to benzoylacetylene **123a** (R = H) selectively to give *C*-adduct **124a** (*E*/*Z* = 5:1) (03RJO1195). The reaction of the above pyrrole with benzoylphenylacetylene **123b** (R = Ph) afforded *N*-(**125b**, *E*- and *Z*-isomers) and *C*-adducts **124b** (*Z*-isomer) in a yield of 56% together with cycloadduct **126b**, resulting from cyclization of the intermediate diadduct **127b** (Equation (34)) (03CHE1115, 03S1272).



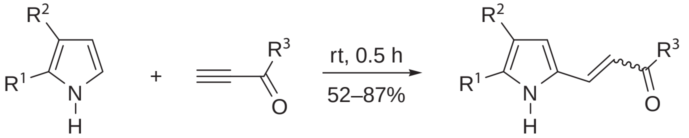
(34)

R = H (**a**), Ph (**b**)

Nucleophilic additions to acetylenes were commonly considered as typical anionic reactions, a possibility of the single electron transfer normally being not considered. The appearance of radicals upon vinylation of 4,5,6,7-tetrahydroindole (**2**) in KOH–DMSO was demonstrated by a spin trapping method, seemingly for the first time (02COR1121). In the nucleophilic addition of pyrrole to acyl- and cyanophenylacetylenes in KOH–DMSO, the formation of radicals was detected by ESR. One of the signals was assignable to the *N*-adducts of the pyrrolyl radical to acetylenes (03DOC(390)137).

In recent years, the addition of pyrroles as *C*-nucleophiles to an electron-deficient triple bond was extensively studied because it provided the most direct approach to functionally substituted *C*-ethenylpyrroles.

The noncatalytic reactions of pyrroles with terminal acylacetylenes **128** proceeded under mild conditions to give 2-(2-acylethenyl)pyrroles **129** (predominantly, the *Z*-isomers) (Equation (35)) (99RCB1542).

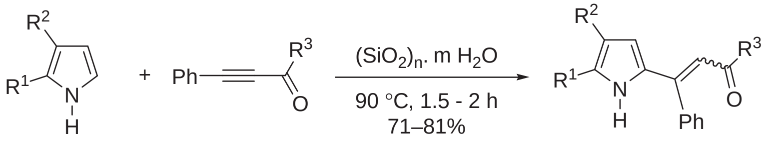


(128) **(129)**

(35)

R^1= H, *n*-Pr, Ph; R^2 = H, Me, *n*-C_7H_{15}; R^1– R^2 = $(CH_2)_4$; R^3= Ph, 2-thienyl

Unlike acetylene **128**, acylphenylacetylenes **130** did not react with pyrroles at room temperature. The latter reaction was performed upon heating equimolar amounts of the reagents in the presence of a 5–10-fold excess of silica gel. The *Z*-isomers of 2-(2-acyl-1-phenylethenyl)pyrroles **131** were obtained (Equation (36)) (99CHE1107, 00IZV1945, 02RCB111, 03ZOB471, 03ZOR1391, 03RJO1636).

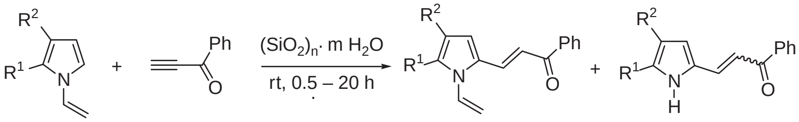


(130) **(131)**

(36)

R^1 = H, Ph; R^2 = H; R^1– R^2 = $(CH_2)_4$; R^3 = Ph, 2-furyl, 2-thienyl, CCl_3

Regio- and stereospecific *C*-ethenylation of *N*-vinylpyrroles with benzoylacetylene proceeded at room temperature on the surface of silica gel to form *E*-isomers of *C*-ethenylpyrroles **132** (Equation (37)) (01S1878, 02RJO1775).



(132), 50–83% **(133)**, 5–6%

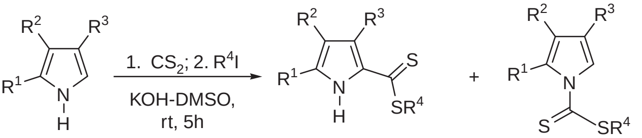
R^1 = H, Me, *n*-Bu, 2,5-$Me_2C_6H_3$, Ph; R^2 = H, Me, *n*-Pr

(37)

The reaction of the pyrroles (R^1 = Me, R^2 = *n*-Pr or R^1 = Ph, R^2 = Et) with benzoylacetylene afforded adducts **132** and **133**, the latter was free of the vinyl group due to hydrolysis on $(SiO_2)_n \cdot mH_2O$ (01S1878).

3.1.3 Addition of *NH*-pyrroles to carbon disulfide

Pyrrole anions generated in KOH–DMSO attacked carbon disulfide either exclusively or preferably at position 2 to afford pyrrole-2-carbodithioate anions, which after alkylation gave the corresponding esters of pyrrole-2-carbodithioic acids **134** (Equation (38)) (03MI127, 05MI97).



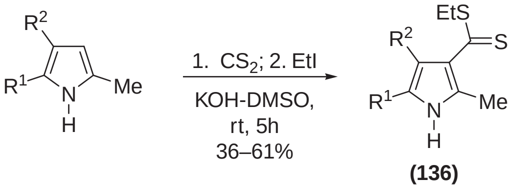
(134), 44–71% **(135)**, 24–33%

(38)

R^1 = H, Me, *n*-Pr, *n*-Bu, Ph, 4-ClC_6H_4, 2-naphthyl; R^2 = H, Me, *n*-Pr; R^1– R^2 = $(CH_2)_4$;
R^3 = H, Me; R^4 = Et, *n*-Bu, Allyl

Substituents in the pyrrole ring affected drastically the ratio of pyrrole-1- to pyrrole-2-carbodithioate isomers. With unsubstituted pyrrole, only the 1-isomer **135** ($R^1 = R^2 = R^3$ = H, R^4 = Et) was formed (63%) and practically no 2-isomer was detected. When just one methyl group was introduced into pyrrole's *a*-position, the pyrrole-2-carbodithioates **134** became the only product (46%) (Equation (38)). Any combinations of alkyl substituents on the pyrrole ring selectively gave pyrrole-2-carbodithioates **134** in a yield of up to 71%. With an aryl substituent at the *a*-position, along with the major pyrrole-2-carbodithioates **134** (44–59%), the 1-isomers **135** were also formed in 24–33% yields (Equation (38)).

When both α-positions were substituted, only pyrrole-3-carbodithioates **136** were isolated (Equation (39)) (00T7325, 03MI127, 05MI97).



(39)

R^1= Me, Ph, 2-furyl, 2-thienyl; R^2 = H, Me; R^1– R^2 = (CH$_2$)$_4$

From 2-aryl(hetaryl)-5-methylpyrroles, only the 4-isomers were formed (44–61%) (00T7325, 03MI127, 05MI97).

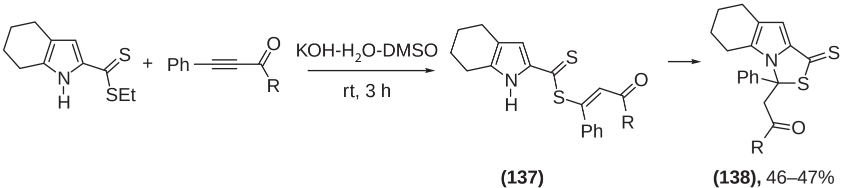
The regiochemistry of the addition of multident pyrrole anions to carbon disulfide was theoretically analyzed (01SUL181, 01ZSK645, 02JQC542, 04JQC360, 04ZSK990).

As highly nucleophilic species, pyrrole-2-carbodithioate anions added smoothly to elecrtophilic alkenes such as acrylonitrile, acrylamide or methyl acrylate to furnish the corresponding derivatives of propionic acid (99ZOR1534, 01S293, 03MI127, 05MI97).

The addition of 4,5,6,7-tetrahydroindole-2-carbodithioate to acylacetylenes occurred to deliver stereoselectively the *Z*-adducts. The sterically overcrowded double bond of adducts **137** still remained active and participated in further intramolecular ring-closure to give functionally substituted pyrrolothiazolidines **138** (Scheme 8) (01S293, 01RJO547, 03MI127, 05MI97).

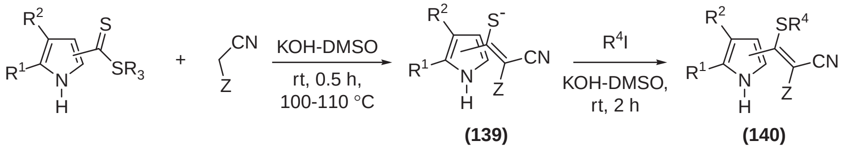
Carbanions generated from diverse CH-acids such as malononitrile and malononitrile amide in KOH–DMSO added to the thiocarbonyl group of pyrrole-2- and pyrrole-3-carbodithioates to afford ethenylthiolates **139**, which, after alkylation, gave the functionalized 2- and 3-ethenylpyrroles **140** (Scheme 9) (02ZOB848, 02ZOB1011, 02RCR563, 03SUL95, 03TL3501, 04CRV2481, 05MI97).

C-Ethenylpyrroles **140** proved to be rewarding starting materials for the synthesis of diverse functionalized heterocyclic assemblies with pyrrole moieties: pyrrolyl-pyrazoles (99RJO1214, 00SUL1, 01RJO1736),

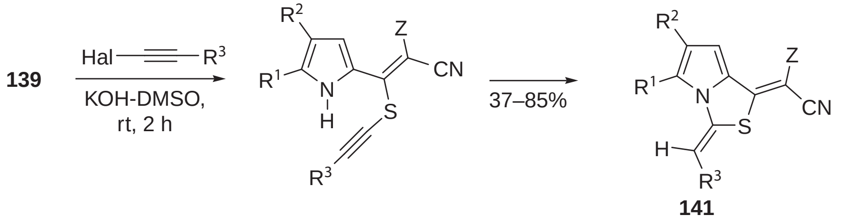


R = Ph, 2-thienyl

Scheme 8



Scheme 9



R^1 = Me, *n*-Pr, *n*-Bu; R^2 = Me, Et, *n*-Pr; R^1– R^2 = $(CH_2)_4$; R^3 = SEt, COPh;
Z = CN, $CONH_2$; Hal = Br, Cl

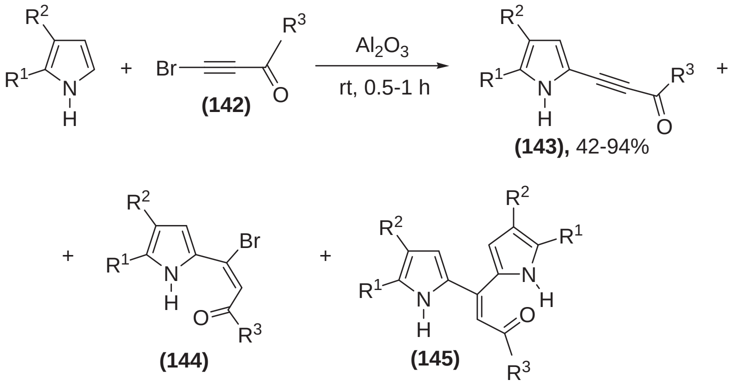
Scheme 10

pyrrolyl-pyrazolopyrimidines (03RJO1471), pyrrolyl-isoxazoles [(05T4841, 05ARK(vii)28), iminopyrrolizines (07JHC505, 08RJO1338), pyrrolizine-3-ones (07JHC505), *etc.*] and stable enols of pyrroles (06T4146, 06TL3645, 08RJO237).

Ethenylthiolates **139** with haloacetylenes such as benzoylbromoacetylene and chloroethylsulfanylacetylene led to functionally substituted pyrrolothiazolidines **141** (Scheme 10) (02CHE86, 02SUL87, 04CRV2481, 05MI97).

3.1.4 Direct ethynylation of pyrroles with haloacetylenes

Pyrroles were cross-coupled with acylbromoacetylenes **142** on the surface of Al_2O_3 to afford 2-(acylethynyl)pyrroles **143** with 100% regioselectivity and in good yields, thus representing the first example of a palladium-, copper-, base- and solvent-free ethynylation of pyrroles (Equation (40)) (04TL6513, 05MC229, 06RJO1348). Experimentally, the reactants were ground with a 10-fold mass excess of Al_2O_3 under solvent-free conditions. In the absence of Al_2O_3, the ethynylation did not take place.



(40)

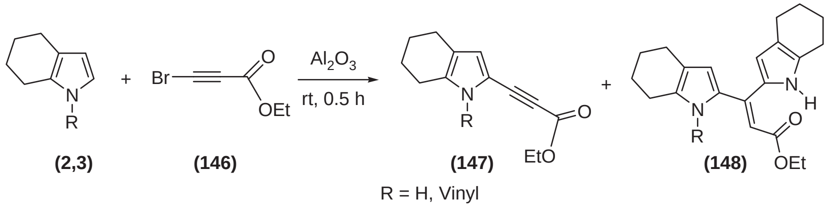
The mechanism of this new ethynylation apparently involves an addition–elimination sequence (04TL6513, 06RJO1348).

2-(2-Acyl-1-bromoethenyl)pyrroles **144** were converted with Al_2O_3 to 2-ethynylpyrroles **143** (Equation (40)) (06RJO1348).

Side products of the coupling were 1,1-di(pyrrol-2-yl)-2-acylethenes **145**, which likely resulted from the exchange of a bromine atom in pyrroles **144** for a second molecule of the pyrrole (Equation (40)) (04TL6513, 06RJO1348).

The yields of adducts **145** were normally up to 19%, expectedly increasing (up to 39%) when excess pyrrole, higher temperatures or longer times were employed.

Ethyl 3-bromo-2-propynoate **146** underwent a similar easy cross-coupling with 4,5,6,7-tetrahydroindole (**2**) on alumina to afford 4,5,6,7-tetrahydroindole-2-propynoate (**147**) (R = H) in 46% yield (Equation (41)) (07TL4661). The yield of the side product, ethyl 3,3-di(4,5,6,7-tetrahydroindol-2-yl)acrylate (**148**), under certain conditions can reach 79%.

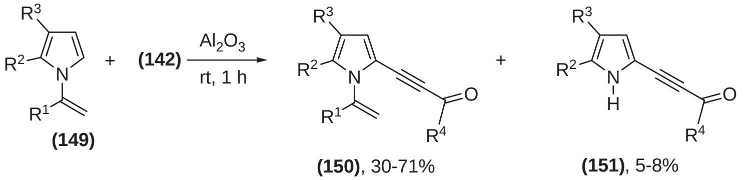


(41)

Noteworthy, *N*-vinyl-4,5,6,7-tetrahydroindole **3** also entered readily into the cross-coupling with acetylene **146** to give selectively propynoate **147** (R = Vinyl) in 71% yield (Equation (41)).

N-Vinyl- and *N*-isopropenylpyrroles **149** reacted with acylbromoacetylenes **142** on Al_2O_3 to furnish regioselectively the corresponding 2-acylethynylpyrroles **150** (Equation (42)) (07S447). The ethynylation of

N-isopropenylpyrroles was accompanied by deisopropenylation to give minor amounts of pyrroles **151**, obviously due to HBr-catalyzed hydrolysis of the *N*-isopropenyl group (Equation (42)).

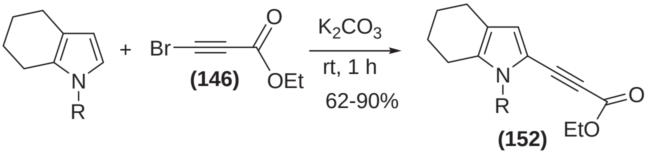


(42)

R^1 = H, Me; R^2= H, Ph; R^3 = H; R^2– R^3 = $(CH_2)_4$; R^4 = Ph, 2-thienyl

The solvent-free interaction of 2-phenylpyrrole with benzoylbromoacetylene **142** (R=Ph) upon grinding with solid metal oxides (MgO, CaO, ZnO, BaO, Al_2O_3, TiO_2, ZrO_2) and salts ($CaCO_3$, $ZrSiO_4$) was investigated (Equation (40)) (08T5541). This led to either the cross-coupling product **143** or the adduct of 2-phenylpyrrole to the triple bond of acetylene **142**, pyrrole **144**. The activity of the metal oxides in the ethynylation reaction fell in the order: ZnO (81%), BaO (73%), Al_2O_3 (71%), MgO (69%), CaO (50%), (in the brackets, the content of 2-benzoylethynyl-5-phenylpyrrole in the reaction mixture is given). The oxides, SiO_2 (04S2736), TiO_2, ZrO_2, and the salts, $CaCO_3$ and $ZrSiO_4$, were inactive in the ethynylation. Adduct **144** was isolated with the ZrO_2, yields reaching 60% (08T5541).

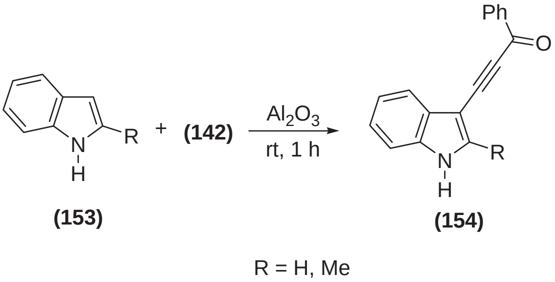
4,5,6,7-Tetrahydroindoles underwent a rapid, facile selective ethynylation with propynoate **146** on solid K_2CO_3 at position 2 to afford ethyl 3-(4,5,6,7-tetrahydroindol-2-yl)-2-propynoates **152** in good to excellent yields. The reaction did not take place in solvents (ether, $CHCl_3$) both with and without K_2CO_3 (Equation (43)) (08TL3946).



(43)

R = H, Et, Bn, Vinyl, *i*-Pr(CH)CH_3, *n*-Bu(CH)CH_3, $(CH_2)_2$SEt, $(CH_2)_2$SPr-*n*

Recently, indoles **153** were found to react smoothly with 1-benzoyl-2-bromoacetylene **142** to give 3-(2-benzoylethynyl)indoles **154** chemo- and regioselectively in good yields, thus representing the first example of direct ethynylation of the indole nucleus (Equation (44)) (06TL7139).



(153) **(154)**

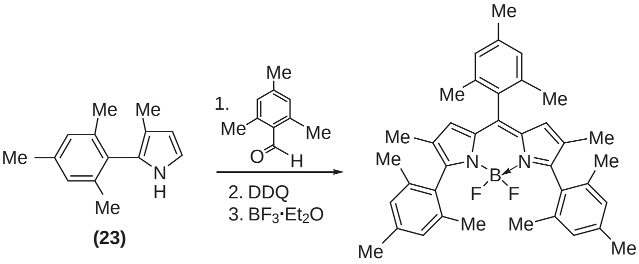
(44)

Ethyl bromopropyonate **146** with indoles **153** on alumina gave the corresponding 3-(indol-3-yl)propynoates in 17% and 12% yield and ethyl 3,3-di(indol-3-yl)acrylates in 41% and 57% yield (08RJO1512).

All these ethynylation reactions are particularly important since the common Sonagashira coupling does not allow ethynylpyrroles with strong electron-withdrawing substituents at the acetylenic fragments to be synthesized (99J(P1)2669).

3.1.5 BODIPY (4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacenes)

2-Mesityl-3-methylpyrrole (**23**) was used for the synthesis of 4,4-difluoro-2,6-dimethyl-3,5,8-trimesityl-4-bora-3a,4a-diaza-*s*-indacene (**155**) (Equation (45)) with mesityl substituents having hindered internal rotation and preventing *π*-stacking at high concentrations (05T2683, 06JPH238, 08RJC2247).

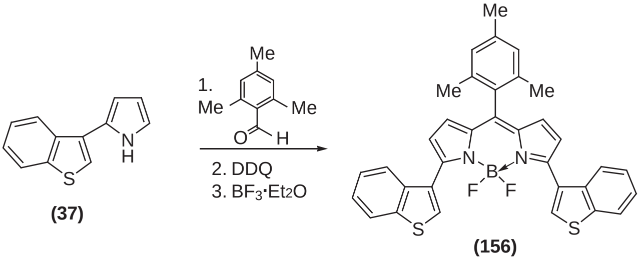


(23) **(155)**, 8%

(45)

The latter factor ensured the fluorescence of crystals of BODIPY, a feature that was not previously documented for such molecules.

2-(Benzo[*b*]thiophen-3-yl)pyrrole (**37**) was reacted sequentially with mesityl aldehyde, DDQ and $BF_3 \cdot OEt_2$ to afford 4,4-difluoro-3,5-di(benzo[*b*]thiophen-3-yl)-8-mesityl-4-bora-3a,4a-diaza-*s*-indacene (**156**) (Equation (46)), a representative of the novel BODIPY fluorophore family in 34% overall yield (09CEJ5823).

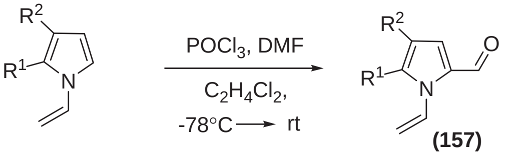


(46)

The BODIPY fluorophore displayed an intense red-shifted fluorescence emission in CH_2Cl_2 (625 nm, 0.84 fluorescence quantum yield), fully preserved in the solid state.

3.1.6 Formylation of *N*-vinylpyrroles and syntheses based on *N*-vinylpyrrole-2-carbaldehydes

N-Vinylpyrrole-2-carbaldehydes **157** were synthesized in 56–91% yields from *N*-vinyl derivatives by a modified Vilsmeier–Haack reaction (Equation (47)) (06TL3693).

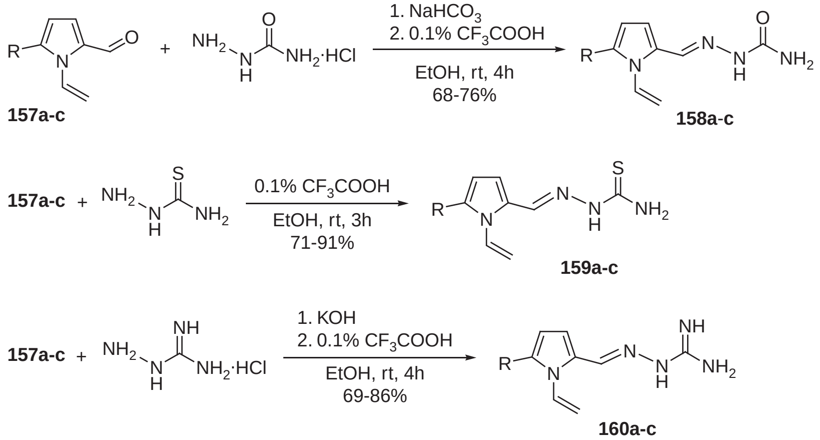


R^1 = Et, Ph, 4-EtC_6H_4, 4-$MeOC_6H_4$, 2-naphthyl, 2-thienyl; R^2 = H, *n*-Pr; R^1-R^2 = $(CH_2)_4$

(47)

N-Vinylpyrroles were also formylated by dimethylformamide-oxalyl chloride (CH_2Cl_2, rt, 40 min) to give the corresponding *N*-vinylpyrrole-2-carbaldehydes **157** in yields up to 97% (09S587).

N-Vinylpyrrole semicarbazones **158a–c**, thiosemicarbazones **159a–c** and guanylhydrazones **160a–c** were obtained in 68–91% yields from *N*-vinylpyrrole-2-carbaldehydes **157a–c** with semicarbazide, thiosemicarbazide and aminoguanidine (Equation (48)) (08CHE1117).

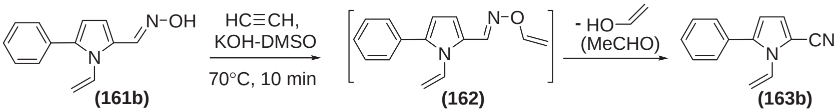


R = H (a); Ph (b); 2-naphthyl (c)

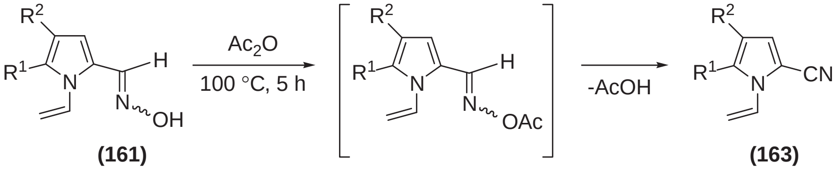
(48)

Attempted vinylation of oxime of 5-phenyl-*N*-vinylpyrrole-2-carbaldehyde **161b** gave instead of the expected *O*-vinyl oxime **162**, 5-phenyl-*N*-vinylpyrrole-2-carbonitrile **163b** (yield 65%) (Scheme 11), a product of the starting oxime dehydration (08RJO1395).

Recently, it was reported (09TL97) that *N*-vinylpyrrole-2-carbonitriles **163** were synthesized from *N*-vinylpyrrole-2-carbaldehyde oximes **161** by two methods: using the above reaction with acetylene (KOH–DMSO, 70 °C, 10 min, yields 58–67%) (Scheme 11) and with acetic anhydride (90–100 °C, 5 h, yields 83–93%) (Scheme 12).



Scheme 11

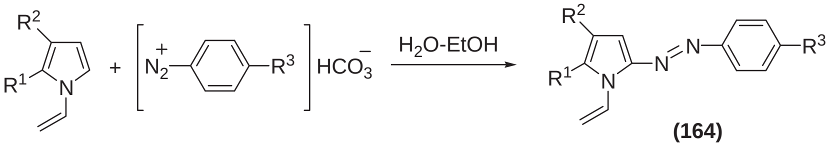


R^1 = H, Ph, 4-EtC_6H_4, 2-naphthyl; R^2 = H; R^1 - R^2 = $(CH_2)_4$

Scheme 12

3.1.7 Azo-coupling of *N*-vinylpyrroles

A large family of 2-arylazo-*N*-vinylpyrroles **164**, novel reactive dyes, was synthesized by the modified azo-coupling of *N*-vinylpyrroles with arenediazonium hydrocarbonates (0 °C, aqueous ethanol) in yields of 52–94% (Equation (49)) (06EJO4021).



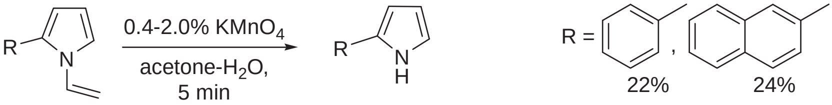
R^1 = H, Me, Ph, 4-$MeOC_6H_4$, 2-furyl, 2-thienyl; R^2 = H, R^1-R^2 = $(CH_2)_4$;
R^3 = H, EtO, NO_2, Br, PhN_2

(49)

3.2 Reactions of *N*-vinyl group of *N*-vinylpyrroles

3.2.1 Oxidative devinylation of *N*-vinylpyrroles

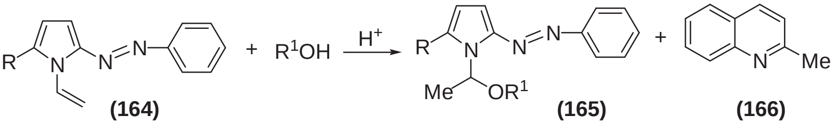
Certain *N*-vinylpyrroles were shown to be capable of devinylation within a few minutes when treated with diluted (0.4–2.0%) aqueous $KMnO_4$ to save the pyrrole moiety intact (−20 °C, rt, nonoptimized yields 22–24%) (Equation (50)) (08RJO1247).



(50)

3.2.2 Addition of alcohols to 2-phenylazo-*N*-vinylpyrroles

2-Phenylazo-*N*-vinylpyrroles **164** add alcohols to the *N*-vinyl group in the presence of acids or $PdCl_2$ to form 1-(2-alkoxyethyl)-2-phenylazopyrroles **165** in the yield up to 49% (Equation (51)) (07RJO1495).



R = H, Me, Ph; R^1 = Me, Et, *i*-Pr, *t*-Bu

(51)

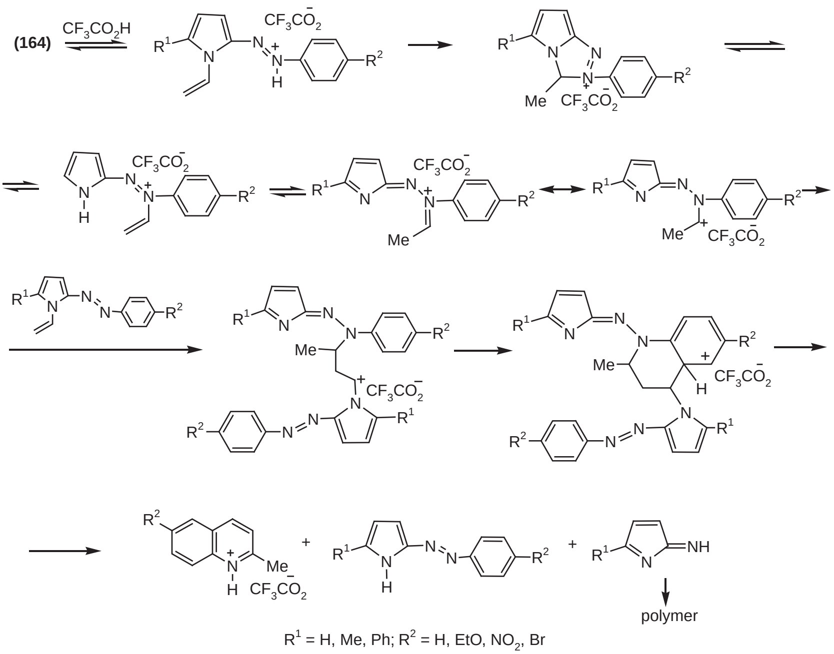
In the presence of trifluoroacetic acid (1%, 3.5 h, reflux), the unexpected formation (apparently with participation of phenylazo- and

N-vinyl groups) of 2-methylquinoline **166** (yield up to 26%) was observed (Equation (51)) (07RJO1495).

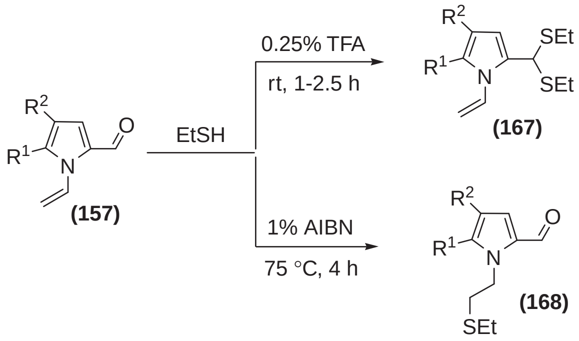
With an equimolar amount of CF_3CO_2H (benzene, reflux, 5 h), a series of 2-methylquinolines **166** was obtained in yields up to 56% (09T4855). The sequence was shown (^1H, ^{13}C, and ^{15}N NMR) to start with protonation of the azo group followed by inter- and intramolecular reactions involving two protonated *N*-vinyl groups to finally build up the quinoline ring instead of the aryl moiety (Scheme 13) (09T4855).

3.2.3 Thiylation of *N*-vinylpyrrole-2-carbaldehydes

N-Vinylpyrrole-2-carbaldehydes **157** were selectively thiylated with ethanethiol either at the aldehyde (acid catalysis) or vinyl group (free-radical initiation) to afford in high to excellent yields *N*-vinylpyrrole-2-carbaldehyde thioacetals **167** (88–99%) and 1-(2-ethylthioethyl) pyrrole-2-carbaldehydes **168** (68–89%), respectively (Equation (52)) (07S452).



Scheme 13

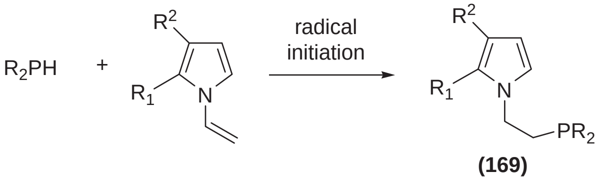


(52)

R^1 = H, Ph, 2-thienyl; R^2 = H; R^1-R^2 = $(CH_2)_4$

3.2.4 Phosphorylation of *N*-vinylpyrroles

Secondary phosphines reacted readily with *N*-vinylpyrroles under radical initiation to give regiospecifically anti-Markovnikov adducts, diorganylethyl-2-(pyrrol-1-yl)phosphines **169** in 88–91% yields (Equation (53)) (03TL2629).

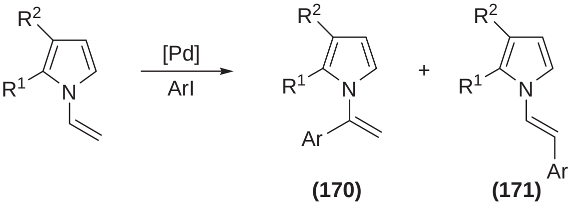


(53)

R = *n*-Bu, $Ph(CH_2)_2$, 2-$Py(CH_2)_2$; R^1 = *n*-Pr, R^1-R^2 = $(CH_2)_2$; R^2 = Et

3.2.5 Heck arylation of *N*-vinylpyrroles by arylhalogenides

Heck direct arylation of *N*-vinylpyrroles with aryl iodides at the double bond in the presence of Pd catalysts was observed (96RCB1497, 97MI245, 98MI200), thus opening a possible shortcut to *N*-(α-arylethenyl)pyrroles **170** and pyrrole stylbene analogs **171** (Eq. (54)).



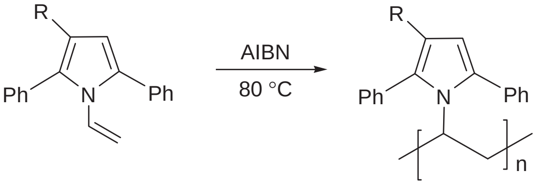
(54)

R^1 = H, Alk, Aryl; R^2 = H, Alk; Ar = Ph, 4-Ph-C_6H_4, 4-I-C_6H_4

The reaction resulted in high yield and regioselectivity, proceeding mainly at α-position of the *N*-vinyl group.

3.3 Polymerization and copolymerization of *N*-vinylpyrroles

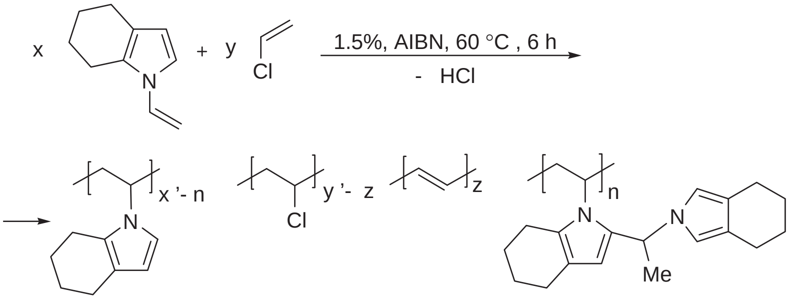
2,5-Diphenyl-*N*-vinyl- and 2,3,5-triphenyl-*N*-vinylpyrroles were polymerized by a free-radical mechanism to afford oligomers in 11% and 27% yields, respectively (Equation (55)) (09IZV115).



(55)

R= H, Ph; n = 5–6

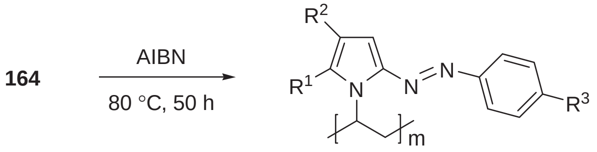
The radical copolymerization of *N*-vinyl-4,5,6,7-tetrahydroindole with vinyl chloride was accompanied by dehydrochlorination of polyvinyl chloride blocks (Equation (56)) (08MI315).



(56)

The copolymers obtained surpass the commercial poly(vinyl chloride) in terms of thermal stability and solubility in organic solvents.

2-Arylazo-*N*-vinylpyrroles **164** were polymerized under heating (80 °C) without initiators and in the presence of AIBN to form intensely colored paramagnetic and conducting polymers in a yield of 92% (Equation (57)) (07MI292).



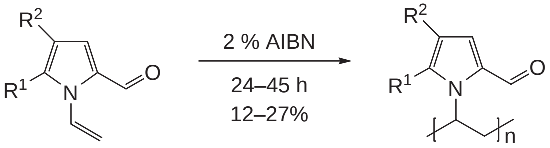
(57)

R^1= H, Me, Ph; R^2 = H; R^1-R^2 = $(CH_2)_4$; R^3 = H, OEt

Arylazo groups of the monomers were assumed to decompose upon heating and generate radicals capable of initiating the polymerization to afford homopolymers. These radicals underwent recombination to yield 2-aryl-*N*-vinylpyrroles (Scheme 14).

By the example of the thermal copolymerization with *N*-vinylpyrrolidone, it was shown that 2-arylazo-*N*-vinylpyrroles may simultaneously play the roles of initiators and comonomers to deliver the intrinsically colored copolymers.

N-Vinylpyrrole-2-carbaldehydes **157** were polymerized to give soluble paramagnetic oligomers (molecular weights 1800–3200) (Equation (58)) (07RCR2209).

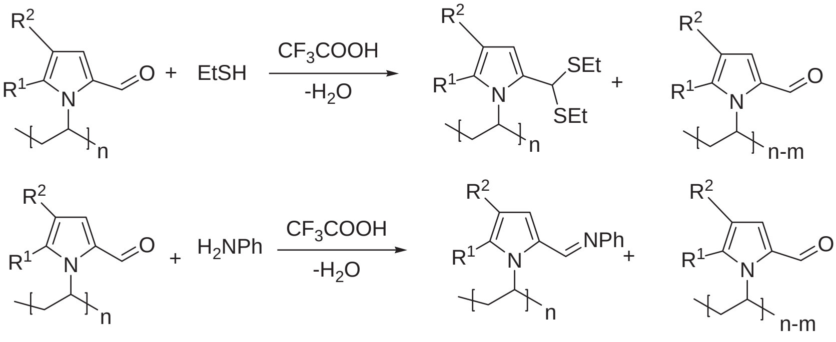


(157)

(58)

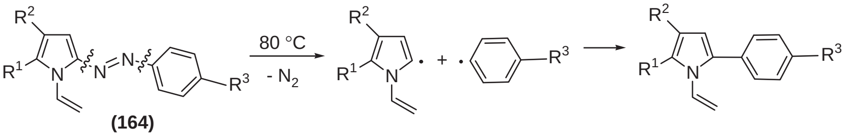
R^1 = Ph, 2-thienyl; R^2 = H; R^1-R^2 = $(CH_2)_4$; n = 5–12; yield 12–27%

The oligomers were further modified by the reactions with thiols and amines (Equation (59)) (07RCR2209).



R^1 = Ph, 2-thienyl, R^2 = H; R^1-R^2 = $(CH_2)_4$

(59)



(164)

Scheme 14

4. PHYSICOCHEMICAL AND QUANTUM CHEMICAL STUDIES OF KETOXIMES AND PYRROLES

The synthesis of *NH*- and *N*-vinylpyrroles from ketones (ketoximes) and acetylenes has stimulated physicochemical and theoretical studies of ketoximes as well as pyrroles and *N*-vinylpyrroles. The easy access to diversely substituted representatives of pyrrole series made it possible to systematically examine the structural effect on their reactivity and spectral properties. This section is a concise account on the research related to *NH*- and *N*-vinylpyrroles originated from the reaction of ketones with acetylenes along with investigation of stereoelectronic properties of intermediate ketoximes.

4.1 Spatial structure of ketoximes

High-level nonempirical quantum chemical calculations of ^{13}C–^{13}C coupling constants (J_{CC}) of heteroaromatic ketoximes are well consistent with the experimental data, the effect of the nitrogen lone electron pair on J_{CC} values being strongly predominant over conformational and electronic effects (07RJO872).

The chemical shifts of carbon atoms in ^{13}C NMR spectra of the oximes having pyrrolyl, furyl, benzofuryl, thienyl and pyridyl substituents change specifically on going from the *E*- to the *Z*-isomer. This makes it possible to use the chemical shifts for assignment of the oximes configuration and studying the special features of their electronic structure (08CHE1238).

4.2 Conformational structure of substituted pyrroles

In 2-(furan-2-yl)- and 2-(thiophen-2-yl)pyrroles, the heterocycles are involved in efficient π,π-conjugation. The $COCF_3$ group in position 2 of the pyrrole ring is *syn*-oriented with respect to the nitrogen atom, and the orientation is fixed by an intramolecular hydrogen bond NH···OC (02RJO1655).

In pyrrol-2-yl-pyridines, effective π,π-conjugation between the pyrrole and pyridine cycles takes place, the former being a π-donor (00RJO1074). A noticeable transmittance of the $COCF_3$ electronic effect through the pyrrole moiety to the pyridine cycle was observed. For 3-(pyrrol-2-yl)pyridine, s*yn*- and *anti*-conformations were registered, while for 2-(pyrrol-2-yl)pyridine only *syn*-conformation, stabilized by the intramolecular NH···N bond, was detectable.

Conformational analysis of *N*-vinylpyrroles was performed on the basis of experimental ^{13}C–^{1}H and ^{13}C–^{13}C coupling constants and their calculated values (07RJO880). A dependency between the J_{CC} and J_{CH} values and stereochemistry of these compounds were revealed

(07RJO880). The compounds were shown to adopt predominantly skewed *s-trans*-conformation. The exception is 2-*tert*-butyl-*N*-vinylpyrrole which exists almost entirely as skewed *s-trans*-conformation (07AJC583).

Conformational study of 2-(pyrrol-2-yl)pyridine and 2,6-di(pyrrol-2-yl)pyridine was performed using the experimental measurements and high-level *ab initio* calculations of ^{13}C–^{13}C, ^{13}C–^{1}H and ^{15}N–^{1}H spin–spin coupling constants showing remarkable stereochemical behavior upon the internal rotation around the pyrrole–pyridine bonds. Both compounds are predominantly in *s-cis*-conformations without noticeable out-of-plane deviations (06MRC692). The same approach was employed for the conformational study of 2-phenylazo-*N*-vinylpyrrole and 2-(4-bromophenylazo)-5-methyl-*N*-vinylpyrrole (06EJO4021, 07MRC142).

The N–H···X (X = N, O, S) intramolecular hydrogen bonding in the series of 2-heteroarylpyrroles and their trifluoroacetyl derivatives was examined by the ^{1}H, ^{13}C, ^{15}N NMR spectroscopy and density functional theory (DFT) calculations (08MRC441).

Electronic and spatial structure of a series of 2-(heteroaryl)-*N*-vinylpyrroles was analyzed by ^{1}H and ^{13}C NMR spectroscopy (02MRC114). The C–H···N intramolecular hydrogen bonding between the α-hydrogen of the vinyl group and the pyridine nitrogen was detected in 2-(*N*-vinylpyrrol-2-yl-)pyridine.

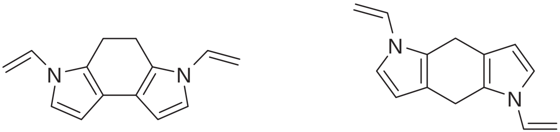
4.3 Association and solvatochromic behavior of functionalized pyrroles

2-(1,2,2-Tricyanoethenyl)-5-phenylpyrrole in hydrocarbons is sandwich-like associated, in solid state being additionally H-bonded (00RJO1504). In the ESR spectra, the radical anions generated by electron transfer between the associated molecules were fixed.

IR and UV spectrosocopy and quantum chemical investigations revealed a bifurcate (three-center) hydrogen bond in the complexes of 2-(1,2,2-tricyanoethenyl)pyrrole with hydrogen-bond acceptors. In the gas phase and aprotic inert solvents, this compound exists predominantly as the *sp* conformer stabilized by intramolecular hydrogen bond (01RJC234, 01RJC1701). Three-center hydrogen bonding with an aprotic protophilic solvent shifts the conformational equilibrium to the *ap* conformer. Solvatochromism of the long-wave absorption band in the electronic spectra of the *sp* and *ap* conformers was studied.

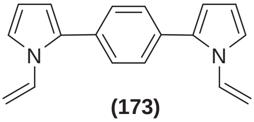
4.4 Conformational and electronic structure of fused pyrrole systems and assemblies

DFT B3LYP (6–311++G(*d*, *p*) and 6–311++G(3*df*, *p*) basis sets) calculation of chemical isomeric 3,6-divinyl-3,4,5,6-tetrahydropyrrolo[3,2-*e*]indole



(172) **(84)**

Figure 2



(173)

Figure 3

(**172**) and 1,5-divinyl-4,8-dihydropyrrolo[3,2-*f*]indole (**84**) showed the energy preference of **84** over **172** (1.3 kcal/mol and 1.5 kcal/mol, respectively) (06ZSK616). The structure of molecule **84** is planar while molecule **172** is nonplanar (Figure 2).

A hindered internal rotation of dipyrrole **173** (Figure 3) was assumed to cause a high quantum yield of its fluorescence. Both rotational conformations of dipyrrole **173** (*cis* and *trans*) are essentially nonplanar with the pyrrole rings being out of the benzene plane by *ca*. 44° (05T7756).

The vinyl groups are rotated relative to the pyrrole ring plane by *ca*. 17° in both conformations. The energy difference between the *cis*- and *trans*-conformations has been calculated to be only *ca*. 0.4 kcal/mol that implies essential population of the *cis*-form (05T7756).

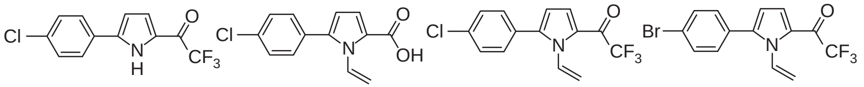
For 2,6-di(pyrrol-2-yl)pyridine (**91**), three stationary points are located on the potential energy surface corresponding to *cis–cis*, *cis–trans* and *trans–trans* rotamers (05EJO4338).

4.5 NLO properties, fluorescence and photochemistry of pyrroles

For pyrroles **174–177** (Figure 4), the second harmonic ($\lambda = 532\,\text{nm}$) is observed. The highest intensity (which was still five times lower than that for $LiIO_3$) was measured for pyrrole **177** (05DOC(402)86).

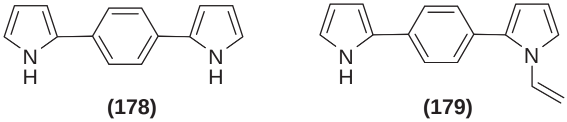
Exposing 2,6-di(pyrrol-2-yl)pyridine (**91**) to infrared light (1064 nm) resulted in the second harmonic generation ($\lambda = 532\,\text{nm}$) with the intensity comparable to that of $LiIO_3$ (05EJO4338).

Fluorescence quenching of dipyrroles **173, 178** and **179** (Figure 5) with chloromethanes (methylene chloride, chloroform and carbon tetrachloride) in solvents of different polarities follows electron-transfer mechanism (07RJC1386).



(174) **(175)** **(176)** **(177)**

Figure 4



(178) **(179)**

Figure 5

The electron-transfer step was confirmed by detection of short-living pyrrolylbenzene radical cations. An exception is the quenching of fluorescence of dipyrrole **173** in *n*-hexane in the presence of CCl_4, or $CHCl_3$ and in pure CCl_4. In this case, the neutral radical is formed *via* recombination of dipyrrole **173** radical cation and chloride anion. A relation was found between the nature of the short-living species detected by laser photolysis and stable product obtained by stationary photolysis (07RJC1386).

Deprotonation reaction of dipyrrole **179** was studied by nanosecond laser photolysis. The bimolecular rate constants of proton transfer to heterocyclic bases were determined. The inhibiting of the radical cation reaction by bases occurs during the radical cation formation (09CHE554).

5. CONCLUSION

The synthesis of pyrroles from ketones and acetylenes keeps gaining strength as a powerful tool of pyrrole chemistry, being cited in encyclopedia (92MI(9)27), monographs (84MI7, 90MI(8)105), reviews (80KG1299, 86ZC41, 87MI12, 89CHE237, 89UK275, 90AHC177, 92MI(10)131, 94H(37)1193, 94PS145, 96ZOR1127, 98ZOR967, 98ZOR1767, 98MI30, 99UK506, 01OPP411, 02MI(1)334) and handbooks (88MI(13)9, 09MI(11)336).

The success of this approach to construction of the pyrrole nucleus comes by complementing existing methods for the synthesis of pyrroles, enabling one to easily synthesize pyrroles with alkyl, aryl and hetaryl substituents, as well as various annulated pyrroles. For the first time this reaction makes available practically an unlimited series of *N*-vinylpyrroles which are readily protected *NH*-pyrroles and pyrrole ring-carriers and monomers having a wide and as yet almost unrealized synthetic potential.

The scope of the reaction has been extended as is evidenced by the recent syntheses involving acyladamantane, acylcyclophanes, acylbenzothiophenes, acylselenophenes (09CEJ6435), steroid ketones, diketones, methylacetylene, allene and phenylacetylene.

An important advantage of the Trofimov pyrrole synthesis is its technological feasibility, that is, the opportunity of applying it for the commercial production of difficultly accessible, though pharmaceutically and technically useful pyrroles. This was convincingly demonstrated and proved by *N*-vinyl-4,5,6,7-tetrahydroindole piloting (84MI7).

REFERENCES

74MI4	A. Gossauer, "*Die Chemie der Pyrrole*", Springer-Verlag, Berlin, Heidelberg, New York (1974).
77MI5	R. A. Jones and G. P. Bean, "*The Chemistry of Pyrroles*", Academic Press, New York (1977).
80KG1299	B. A. Trofimov and A. I. Mikhaleva, *Khim. Geterotsikl. Soed.*, **1**, 1299 (1980).
81MI6	B. A. Trofimov, "*Heteroatomic Derivatives of Acetylene. New Polyfunctional Monomers, Reagents and Intermediates*", Nauka, Moscow (1981).
84MI7	B. A. Trofimov and A. I. Mikhaleva, "N-*Vinylpyrroles*", Nauka, Siberian Branch, Novosibirsk (1984).
86ZC41	B. A. Trofimov, *Z. Chem.*, **26**, 41 (1986).
87MI12	B. A. Trofimov, L. N. Sobenina, and A. I. Mikhaleva, in "*Itogi Nauki i Tekhniki, Organicheskaya Khimia*" (A. I. Mikhailov, ed.), vol. 7, p. 79, VINITY, Moscow (1987).
88MI(13)9	A. F. Pozharsky, V. A. Anisimova, and E. V. Tsupak, "*Prakticheskie Raboty po Khimii Geterotsiklov (Manual for Heterocyclic Chemistry)*", p. 9. Izd. Rostovskogo Universiteta, Rostov (1988).
87MM958	J. R. Reynolds, P. A. Poropatic, and R. L. Toyooka, *Macromolecules*, **20**, 958 (1987).
89CHE237	L. N. Sobenina, A. I. Mikhaleva, and B. A. Trofimov, *Chem. Heterocycl. Compd. (Engl. Transl.)*, **25**, 237 (1989).
89UK275	L. N. Sobenina, A. I. Mikhaleva, and B. A. Trofimov, *Usp. Khim.*, **58**, 275 (1989).
90AHC177	B. A. Trofimov, in "*Adv. Heterocycl. Chem.*" (A. R. Katritzky, ed.), vol. 51, p. 177, Academic Press, San Diego (1990).
90MI(8)105	G. P. Bean, in "*The Synthesis of 1*H*-Pyrroles. Part. 1. The Synthesis and the Chemical and Physical Aspects Pyrrole Ring*" (R. A. Jones, ed.), p. 105, Wiley, New York (1990).
92MI(9)27	R. J. Tedeschi, "*Encyclopedia of Physical Science and Technology*", Vol. 2, p. 27, Academic Press, San Diego (1992).
92MI(10)131	B. A. Trofimov, in "*The Chemistry of Heterocyclic Compounds. 48. Pyrroles. Part 2*" (R. A. Jones, ed.), p. 131, Wiley, New York (1992).
92H(34)2003	R. E. Nizuski-Mann and M. P. Cava, *Heterocycles*, **34**, 2003 (1992).

93MI2 H. Takohata and T. Momose, in *"The Alkaloids"* (G. A. Cordel, ed.), Academic Press, San Diego (1993).

94H(37)1193 B. A. Trofimov and A. I. Mikhaleva, *Heterocycles*, **37**, 1193 (1994).

94PS145 B. A. Trofimov, *Phosphorus, Sulfur, Silicon*, **95–97**, 145 (1994).

95JOC6637 A. Furstner, H. Weintritt, and A. Huppert, *J. Org. Chem.*, **60**, 6637 (1995).

95TL1401 J. A. H. Lainton, J. W. Huffman, B. R. Martin, and D. R. Compton, *Tetrahedron Lett.*, **36**, 1401 (1995).

96AHC207 P. Lue and J. V. Greenhill, *Adv. Heterocycl. Chem.*, **67**, 207 (1996).

96CHEC(2)119 R. J. Sundberg, in *"Comprehensive Heterocyclic Chemistry II"* (A. R. Katritzky, C. W. Rees, and E. F. V. Scriven, eds.), Vol. 2, p. 119, Pergamon Press, Oxford (1996).

96HCO9 S. H. Leung, L. T. Nguyen, and K. M. Smith, *Heterocycl. Commun.*, **2**, 9 (1996).

96JP(1)2103 A. C. Spivey, C. S. Frampton, and A. R. Battersby, *J. Chem. Soc., Perkin Trans. 1*, 2103 (1996).

96OPP641 G. Casiraghi, F. Zanardi, G. Rassu, and L. Pinna, *Org. Prep. Proced. Int.*, **28**, 641 (1996).

96PHC103 R. J. Sundberg, in *"Prog. Heterocycl. Chem."* (H. Suschitzky and G. W. Gribble, eds.), Vol. 8, p. 103, Pergamon, Oxford (1996).

96RCB1497 A. F. Shmidt, T. A. Vladimirova, E. Yu. Shmidt, and T. V. Dmitrieva, *Russ. Chem. Bull. (Engl. Transl.)*, **66**, 1497 (1996).

96ZOR1127 B. A. Trofimov and A. I. Mikhaleva, *Zh. Org. Khim.*, **32**, 1127 (1996).

97JME1578 J. R. Carson, R. J. Carmosin, P. M. Pitis, J. L. Vaught, H. R. Alamond, J. P. Stables, H. H. Wolf, E. A. Swinyard, and H. S. White, *J. Med. Chem.*, **40**, 1578 (1997).

97JME1619 I. K. Khanna, R. M. Weier, Y. Yu, P. W. Collins, J. M. Miyashiro, C. M. Koboldt, A. W. Veenhuizen, J. L. Currie, K. Seibert, and P. C. Isakson, *J. Med. Chem.*, **40**, 1619 (1997).

97JOC2894 P. A. Jacobi, S. C. Buddhu, D. Fry, and S. Rajeswari, *J. Org. Chem.*, **62**, 2894 (1997).

97MI245 A. F. Shmidt, T. A. Vladimirova, E. Yu. Shmidt, and T. V. Dmitrieva, *Kinet. Catal.*, **38**, 245 (1997).

97T7731 C. Y. DeLeon and B. Ganem, *Tetrahedron*, **53**, 7731 (1997).

98ACS1040 J. Breinholt, H. Gurtler, A. Kjar, S. E. Nielsen, and C. E. Olsen, *Acta Chem. Scand.*, **52**, 1040 (1998).

98JOC6715 C. D. Silva and D. A. Walker, *J. Org. Chem.*, **63**, 6715 (1998).

98JOC10022 R. Settambolo, M. Mariani, and A. Gaiazzo, *J. Org. Chem.*, **63**, 10022 (1998).

98JP(1)615 T. L. Gilchrist, *J. Chem. Soc., Perkin Trans. 1*, 615 (1998).

98MI30 B. A. Trofimov and M. V. Sigalov, *Main Group Chem. News.*, **6**, 30 (1998).

98MI200 A. F. Shmidt, A. Halaika, L. O. Nindakova, and E. Yu. Shmidt, *Kinet. Catal.*, **39**, 200 (1998).

98MI324 O. Hoshino, in *"The Alkaloids"* (G. A. Cordel, ed.), Vol. 51, p. 324, Academic Press, San Diego (1998).

98T5075 G. T. Gupton, K. E. Krumpe, B. S. Burnham, and K. A. Dwornik, *Tetrahedron*, **54**, 5075 (1998).

98ZOR967 S. E. Korostova, A. I. Mikhaleva, A. M. Vasil'tsov, and B. A. Trofimov, *Zh. Org. Khim.*, **34**, 967 (1998).

98ZOR1767 S. E. Korostova, A. I. Mikhaleva, A. M. Vasil'tsov, and B. A. Trofimov, *Zh. Org. Khim.*, **34**, 1767 (1998).

99CC1039 M. E. Raggatt, T. J. Simpson, and S. K. Wrigley, *Chem. Commun.*, **11**, 1039 (1999).

99CHE613 A. V. Varlamov, L. G. Voskresenskii, T. N. Borisova, A. I. Chernyshev, and A. N. Levov, *Chem. Heterocycl. Compd. (Engl. Transl.)*, **35**, 613 (1999).

99CHE1107 B. A. Trofimov, Z. V. Stepanova, L. N. Sobenina, A. I. Mikhaleva, I. A. Ushakov, and D. -S. D. Toryashinova, *Chem. Heterocycl. Compd. (Engl. Transl.)*, **35**, 1107 (1999).

99J(P1)2669 D. Passarela, G. Lesma, M. Deleo, M. Martinelli, and A. Silvani, *J. Chem. Soc., Perkin Trans. 1*, 2669 (1999).

99JP(1)2849 T. L. Gilchrist, *J. Chem. Soc., Perkin Trans. 1*, 2849 (1999).

99RCB1542 B. A. Trofimov, Z. V. Stepanova, L. N. Sobenina, A. I. Mikhaleva, T. I. Vakul'skaya, V. N. Elokhina, I. A. Ushakov, D. -S. D. Toryashinova, and E. I. Kositsina, *Russ. Chem. Bull., Int. Ed. (Engl. Transl.)*, **48**, 1542 (1999).

99RJO916 L. N. Sobenina, S. G. D'yachkova, Z. V. Stepanova, D. -S. D. Toryashinova, A. I. Albanov, I. A. Ushakov, A. P. Demenev, A. I. Mikhaleva, and B. A. Trofimov, *Russ. J. Org. Chem. (Engl. Transl.)*, **35**, 916 (1999).

99RJO1214 L. N. Sobenina, A. I. Mikhaleva, O. V. Petrova, D. -S. D. Toryashinova, L. I. Larina, L. N. Il'icheva, and B. A. Trofimov, *Russ. J. Org. Chem. (Engl. Transl.)*, **35**, 1214 (1999).

99TL4519 F. Gonzalez, J. F. Sanz-Cervera, and R. M. Williams, *Tetrahedron Lett.*, **40**, 4519 (1999).

99UK506 S. E. Korostova, A. I. Mikhaleva, and B. A. Trofimov, *Usp. Khim.*, **68**, 506 (1999).

99ZOR1226 L. N. Sobenina, L. A. Es'kova, A. I. Mikhaleva, D. S. -D. Toryashinova, A. I. Albanov, B. A. Trofimov, and N. S. Zefirov, *Zh. Org. Khim.*, **35**, 1226 (1999).

99ZOR1534 L. N. Sobenina, A. I. Mikhaleva, O. V. Petrova, D. -S. D. Toryashinova, and B. A. Trofimov, *Zh. Org. Khim.*, **35**, 1534 (1999).

00H(53)2285 E. Abele and E. Lucevics, *Heterocycles*, **53**, 2285 (2000).

00IZV1945 N. N. Chipanina, Z. V. Stepanova, G. A. Gavrilova, L. N. Sobenina, and A. I. Mikhaleva, *Izv. Acad. Nauk, Ser. Khim.*, 1945 (2000).

00JAN1 S. J. Trew, S. K. Wrigley, and L. Paire, *J. Antibiot.*, **53**, 1 (2000).

00JME4582 B. Portevin, C. Tordjman, P. Pastoureau, J. Bonnet, and G. De Nanteuil, *J. Med. Chem.*, **43**, 4582 (2000).

00JNP7 D. Faulkner, *J. Nat. Prod. Rep.*, **17**, 7 (2000).

00JOC205 P. A. Jacobi, L. D. Coutts, J. S. Gou, S. L. Hauck, and S. H. Leung, *J. Org. Chem.*, **65**, 205 (2000).

00JOC2900 J. Chen, A. Burghart, A. Derecskei-Kovacs, and K. Burges, *J. Org. Chem.*, **65**, 2900 (2000).

00JP(1)2845 I. Collins, *J. Chem. Soc., Perkin Trans. 1*, 2845 (2000).

00RJO1074 A. V. Afonin, I. A. Ushakov, O. V. Petrova, L. N. Sobenina, A. I. Mikhaleva, V. K. Voronov, and B. A. Trofimov, *Russ. J. Org. Chem. (Engl. Transl.)*, **36**, 1074 (2000).

00RJO1504 A. I. Vokin, T. I. Vakul'skaya, N. M. Murzina, A. P. Demenev, L. N. Sobenina, A. I. Mikhaleva, and B. A. Trofimov, *Russ. J. Org. Chem. (Engl. Transl.)*, **36**, 1504 (2000).

00S1585 B. A. Trofimov, O. A. Tarasova, A. I. Mikhaleva, N. A. Kalinina, L. M. Sinegovskaya, and J. Henkelmann, *Synthesis*, 1585 (2000).

00SM181 P. Evans, B. P. J. de Lacy, N. Guernion, N. M. Ratcliffe, P. S. Sivanand, and G. S. Teare, *Synth. Met.*, **114**, 181 (2000).

00SUL1 L. N. Sobenina, A. P. Demenev, A. I. Mikhaleva, O. V. Petrova, L. I. Larina, G. P. Chernykh, D. -S. D. Toryashinova, A. V. Vashchenko, and B. A. Trofimov, *Sulfur Lett.*, **24**, 1 (2000).

00T7325 B. A. Trofimov, L. N. Sobenina, A. I. Mikhaleva, A. P. Demenev, O. A. Tarasova, I. A. Ushakov, and S. V. Zinchenko, *Tetrahedron*, **56**, 7325 (2000).

01ARK(ix)37 B. A. Trofimov, L. N. Sobenina, A. P. Demenev, A. I. Mikhaleva, I. A. Ushakov, O. A. Tarasova, V. I. Smirnov, K. B. Petrushenko, A. I. Vokin, N. M. Murzina, and G. F. Myachina, *Arkivoc (Arkive for Organic Chemistry)*, **ix**, 37 (2001).

01CHE141 E. Abele and E. Lucevics, *Chem. Heterocycl. Compd. (Engl. Transl.)*, **37**, 141 (2001).

01CHE1488 A. M. Vasil'tsov, E. Yu. Shmidt, A. I. Mikhaleva, A. V. Afonin, and A. B. Zaitsev, *Chem. Heterocycl. Compd. (Engl. Transl.)*, **37**, 1488 (2001).

01JP(1)2491 T. L. Gilchrist, *J. Chem. Soc., Perkin Trans. 1*, 2491 (2001).

01MC74 A. M. Vasil'tsov, A. B. Zaitsev, E. Schmidt, A. I. Mikhaleva, and A. V. Afonin, *Mendeleev Commun.*, 74 (2001).

01MI125 L. -X. Wang, X. -G. Li, and Y. Y. -L. Yang, *React. Funct. Polym.*, **47**, 125 (2001).

01OPP411 V. F. Ferreira, M. C. B. V. De Souza, A. C. Cunha, L. O. R. Pareira, and M. L. G. Feriera, *Org. Prep. Proced. Int.*, **33**, 411 (2001).

01RJC234 V. K. Turchaninov, N. M. Murzina, A. I. Vokin, T. N. Aksamentova, and B. A. Trofimov, *Russ. J. Gen. Chem. (Engl. Transl.)*, **71**, 234 (2001).

01RJC1701 V. K. Turchaninov, N. M. Murzina, A. I. Vokin, and B. A. Trofimov, *Russ. J. Gen. Chem. (Engl. Transl.)*, **71**, 1701 (2001).

01RJO547 L. N. Sobenina, A. P. Demenev, A. I. Mikhaleva, V. N. Elokhina, Z. V. Stepanova, A. G. Mal'kina, I. A. Ushakov, and B. A. Trofimov, *Russ. J. Org. Chem. (Engl. Transl.)*, **37**, 547 (2001).

01RJO1736 L. V. Baikalova, L. N. Sobenina, A. I. Mikhaleva, I. A. Zuryanova, N. N. Chipanina, A. V. Afonin, and B. A. Trofimov, *Russ. J. Org. Chem. (Engl. Transl.)*, **37**, 1736 (2001).

01S293 L. N. Sobenina, A. P. Demenev, A. I. Mikhaleva, V. N. Elokhina, A. G. Mal'kina, O. A. Tarasova, I. A. Ushakov, and B. A. Trofimov, *Synthesis*, 293 (2001).

01S1878 B. A. Trofimov, Z. V. Stepanova, L. N. Sobenina, A. I. Mikhaleva, I. A. Ushakov, and V. N. Elokhina, *Synthesis*, 1878 (2001).

01SUL181 B. A. Trofimov, N. M. Vitkovskaya, V. B. Kobychev, E. Yu. Larionova, L. N. Sobenina, A. I. Mikhaleva, and A. P. Demenev, *Sulfur Lett.*, **24**, 181 (2001).

01TL1309 S. -S. P. Hou and Y. -H. Yeh, *Tetrahedron Lett.*, **42**, 1309 (2001).

01TL3139 B. Gabriele, G. Salerno, A. Fazio, and M. R. Bossio, *Tetrahedron Lett.*, **42**, 3139 (2001).

01TL6027 B. Lagu, M. Pan, and M. P. Wachter, *Tetrahedron Lett.*, **42**, 6027 (2001).

01ZSK645 V. B. Kobychev, N. M. Vitkovskaya, I. L. Zaitseva, E. Yu. Larionova, and B. A. Trofimov, *Zh. Struct. Khim.*, **42**, 645 (2001).

02CHE60 A. M. Vasil'tsov, A. B. Zaitsev, A. I. Mikhaleva, E. Yu. Shmidt, and A. V. Afonin, *Chem. Heterocycl. Compd. (Engl. Transl.)*, **38**, 60 (2002).

02CHE86 L. N. Sobenina, A. P. Demenev, A. I. Mikhaleva, I. A. Ushakov, A. V. Afonin, S. G. D'yachkova, E. A. Beskrylaya, L. A. Oparina, V. N. Elokhina, K. A. Volkova, O. V. Petrova, and B. A. Trofimov, *Chem. Heterocycl. Compd. (Engl. Transl.)*, **38**, 86 (2002).

02COR1121 B. A. Trofimov, *Curr. Org. Chem.*, **6**, 1121 (2002).

02CPB711 R. M. Williams, *Chem. Pharm. Bull.*, **50**, 711 (2002).

02JQC542 V. B. Kobychev, N. M. Vitkovskaya, I. L. Zaitseva, E. Yu. Larionova, and B. A. Trofimov, *Int. J. Quant. Chem.*, **88**, 542 (2002).

02MI(1)334 A. I. Mikhaleva and E. Yu. Schmidt, in "*Selected Methods for Synthesis and Modification of Heterocycles*" (V. G. Kartsev, ed.), Vol. 1, p. 334, IBS Press, Moscow (2002).

02MRC114 A. V. Afonin, I. A. Ushakov, S. Yu. Kuznetsova, O. V. Petrova, E. Yu. Schmidt, and A. I. Mikhaleva, *Magn. Reson. Chem.*, **40**, 114 (2002).

02RCB111 N. N. Chipanina, V. K. Turchaninov, I. I. Vorontsov, M. Yu. Antipin, Z. V. Stepanova, L. N. Sobenina, A. I. Mikhaleva, and B. A. Trofimov, *Russ. Chem. Bull., Int. Ed. (Engl. Transl.)*, **51**, 111 (2002).

02RCR563 L. N. Sobenina, A. P. Demenev, A. I. Mikhaleva, and B. A. Trofimov, *Russ. Chem. Rev. (Engl. Transl.)*, **71**, 563 (2002).

02RJO1655 A. V. Afonin, S. Yu. Kuznetsova, I. A. Ushakov, V. K. Voronov, A. I. Mikhaleva, and E. Yu. Shmidt, *Russ. J. Org. Chem. (Engl. Transl.)*, **38**, 1655 (2002).

02RJO1775 I. A. Ushakov, A. V. Afonin, V. K. Voronov, Z. V. Stepanova, L. N. Sobenina, A. I. Mikhaleva, and B. A. Trofimov, *Russ. J. Org. Chem. (Engl. Transl.)*, **38**, 1775 (2002).

02SUL87 L. N. Sobenina, A. P. Demenev, A. I. Mikhaleva, I. A. Ushakov, A. V. Afonin, O. V. Petrova, V. N. Elokhina, K. A. Volkova, D. -S. D. Toryashinova, and B. A. Trofimov, *Sulfur Lett.*, **25**, 87 (2002).

02ZOB848 N. M. Murzina, A. I. Vokin, L. N. Sobenina, and V. K. Turchaninov, *Zh. Obshch. Khim.*, **72**, 848 (2002).

02ZOB1011 N. M. Murzina, A. I. Vokin, S. V. Fedorov, A. P. Demenev, L. N. Sobenina, and V. K. Turchaninov, *Zh. Obshch. Khim.*, **72**, 1011 (2002).

03CHE1115 L. N. Sobenina, A. I. Mikhaleva, I. A. Ushakov, V. N. Elokhina, and B. A. Trofimov, *Chem. Heterocycl. Compd. (Engl. Transl.)*, **39**, 1115 (2003).

03DOC(390)137 T. I. Vakul'skaya, L. N. Sobenina, A. I. Mikhaleva, V. N. Elokhina, A. G. Mal'kina, and B. A. Trofimov, *Dokl. Chem. (Engl. Transl.)*, **390**, 137 (2003).

03MI127 B. A. Trofimov, in "*Oxygen- and Sulfur-Containing Heterocycles*" (V. G. Kartsev, ed.), Vol. 1, p. 127, IBS Press, Moscow (2003).

03RJO1195 L. N. Sobenina, A. I. Mikhaleva, I. A. Ushakov, V. N. Elokhina, and B. A. Trofimov, *Russ. J. Org. Chem. (Engl. Transl.)*, **39**, 1195 (2003).

03RJO1406 A. B. Zaitsev, A. M. Vasil'tsov, E. Yu. Shmidt, A. I. Mikhaleva, A. V. Afonin, and L. N. Il'icheva, *Russ. J. Org. Chem. (Engl. Transl.)*, **39**, 1406 (2003).

03RJO1471 O. V. Petrova, L. N. Sobenina, A. P. Demenev, A. I. Mikhaleva, and I. A. Ushakov, *Russ. J. Org. Chem. (Engl. Transl.)*, **39**, 1471 (2003).

03RJO1636 Z. V. Stepanova, L. N. Sobenina, A. I. Mikhaleva, I. A. Ushakov, V. N. Elokhina, I. I. Vorontsov, M. Yu. Antipin, and B. A. Trofimov, *Russ. J. Org. Chem. (Engl. Transl.)*, **39**, 1636 (2003).

03S1272 B. A. Trofimov, L. N. Sobenina, A. I. Mikhaleva, I. A. Ushakov, T. I. Vakul'skaya, Z. V. Stepanova, D. -S. D. Toryashinova, A. G. Mal'kina, and V. N. Elokhina, *Synthesis*, 1272 (2003).

03SUL95 A. P. Demenev, L. N. Sobenina, A. I. Mikhaleva, and B. A. Trofimov, *Sulfur Lett.*, **26**, 95 (2003).

03TL2629 B. A. Trofimov, S. F. Malysheva, B. G. Sukhov, N. A. Belogorlova, E. Yu. Schmidt, L. N. Sobenina, V. A. Kuimov, and N. K. Gusarova, *Tetrahedron Lett.*, **44**, 2629 (2003).

03TL3501 B. A. Trofimov, A. P. Demenev, L. N. Sobenina, A. I. Mikhaleva, and O. A. Tarasova, *Tetrahedron Lett.*, **44**, 3501 (2003).

03ZOB471 V. K. Turchaninov, N. N. Chipanina, Z. V. Stepanova, L. V. Kanitskaya, S. V. Fedorov, G. A. Gavrilova, N. M. Murzina, T. N. Aksamentova, L. N. Sobenina, and A. I. Mikhaleva, *Zh. Obshch. Khim.*, **73**, 471 (2003).

03ZOR1391 I. A. Ushakov, A. V. Afonin, V. K. Voronov, Z. V. Stepanova, and L. N. Sobenina, *Zh. Org. Khim.*, **39**, 1391 (2003).

04CHE326 L. G. Voskressensky, T. N. Borisova, and A. V. Varlamov, *Chem. Heterocycl. Compd. (Engl. Transl.)*, **40**, 326 (2004).

04CRV2481 B. A. Trofimov, L. N. Sobenina, A. P. Demenev, and A. I. Mikhaleva, *Chem. Rev.*, **104**, 2481 (2004).

04JQC360 V. B. Kobychev, N. M. Vitkovskaya, I. L. Zaitseva, and B. A. Trofimov, *Int. J. Quant. Chem.*, **100**, 360 (2004).

04S2736 Z. V. Stepanova, L. N. Sobenina, A. I. Mikhaleva, I. A. Ushakov, N. N. Chipanina, V. N. Elokhina, V. K. Voronov, and B. A. Trofimov, *Synthesis*, 2736 (2004).

04TL3789 B. A. Trofimov, A. B. Zaitsev, E. Yu. Schmidt, A. M. Vasil'tsov, A. I. Mikhaleva, I. A. Ushakov, A. V. Vashchenko, and N. V. Zorina, *Tetrahedron Lett.*, **45**, 3789 (2004).

04TL5489 E. Yu. Schmidt, N. V. Zorina, A. B. Zaitsev, A. I. Mikhaleva, A. M. Vasil'tsov, P. Audebert, G. Clavier, R. Meallet-Renault, and R. B. Pansu, *Tetrahedron Lett.*, **45**, 5489 (2004).

04TL6513 B. A. Trofimov, Z. V. Stepanova, L. N. Sobenina, A. I. Mikhaleva, and I. A. Ushakov, *Tetrahedron Lett.*, **45**, 6513 (2004).

04ZSK990 V. B. Kobychev, N. M. Vitkovskaya, I. L. Zaitseva, and B. A. Trofimov, *Zh. Struct. Khim.*, **45**, 990 (2004).

05ARK(vii)11 E. Yu. Schmidt, A. I. Mikhaleva, A. B. Zaitsev, A. M. Vasil'tsov, and N. V. Zorina, *Arkivoc (Arkive for Organic Chemistry)*, **vii**, 11 (2005).

05ARK(vii)28 L. N. Sobenina, V. N. Drichkov, A. I. Mikhaleva, O. V. Petrova, I. A. Ushakov, and B. A. Trofimov, *Arkivoc (Arkive for Organic Chemistry)*, **vii**, 28 (2005).

05CHE444 A. B. Zaitsev, E. Yu. Shmidt, A. M. Vasil'tsov, A. I. Mikhaleva, A. V. Afonin, I. A. Ushakov, and D. -S. D. Toryashinova, *Chem. Heterocycl. Compd. (Engl. Transl.)*, **41**, 444 (2005).

05CHE722 A. B. Zaitsev, E. Yu. Schmidt, A. M. Mikhaleva, A. V. Afonin, and I. A. Ushakov, *Chem. Heterocycl. Compd. (Engl. Transl.)*, 722 (2005).

05DOC(402)86 V. M. Khulugurov, L. I. Bryukvina, K. B. Petrushenko, A. I. Mikhaleva, A. M. Vasil'tsov, L. N. Sobenina, E. Yu. Shmidt, and A. B. Zaitsev, *Dokl. Chem. (Engl. Transl.)*, **402**, 86 (2005).

05EJO4338 B. A. Trofimov, A. M. Vasil'tsov, E. Yu. Schmidt, N. V. Zorina, A. V. Afonin, A. I. Mikhaleva, K. B. Petrushenko, I. A. Ushakov, L. B. Krivdin, V. K. Belsky, and L. I. Bryukvina, *Eur. J. Org. Chem.*, 4338 (2005).

05MC229 B. A. Trofimov, Z. V. Stepanova, L. N. Sobenina, A. I. Mikhaleva, L. M. Sinegovskaya, K. A. Potekhin, and I. V. Fedyanin, *Mendeleev Commun.*, 229 (2005).

05MI97 L. N. Sobenina, A. I. Mikhaleva, and B. A. Trofimov, *Ross. Khim. Zh.*, **49**, 97 (2005).

07RJC1386 I. K. Petrushenko, V. I. Smirnov, K. B. Petrushenko, E. Yu. Shmidt, N. V. Zorina, Yu. Yu. Rusakov, A. M. Vasil'tsov, A. I. Mikhaleva, and B. A. Trofimov, *Russ. J. Gen. Chem. (Engl. Transl.)*, **77**, 1386 (2007).

05T2683 A. B. Zaitsev, R. Méallet-Renault, E. Yu. Schmidt, A. I. Mikhaleva, S. Badré, C. Dumas, A. M. Vasil'tsov, N. V. Zorina, and R. B. Pansu, *Tetrahedron*, **61**, 2683 (2005).

05T4841 L. N. Sobenina, V. N. Drichkov, A. I. Mikhaleva, O. V. Petrova, I. A. Ushakov, and B. A. Trofimov, *Tetrahedron*, **61**, 4841 (2005).

05T7756 A. M. Vasil'tsov, E. Yu. Schmidt, A. I. Mikhaleva, N. V. Zorina, A. B. Zaitsev, O. V. Petrova, L. B. Krivdin, K. B. Petrushenko, I. A. Ushakov, C. Pozo-Gonzalo, J. A. Pomposo, and H. -J. Grande, *Tetrahedron*, **61**, 7756 (2005).

06CHE34 A. B. Zaitsev, E. Yu. Schmidt, A. M. Vasil'tsov, A. I. Mikhaleva, O. V. Petrova, A. V. Afonin, and N. V. Zorina, *Chem. Heterocycl. Compd. (Engl. Transl.)*, **42**, 34 (2006).

06EJO4021 B. A. Trofimov, E. Yu. Schmidt, A. I. Mikhaleva, A. M. Vasil'tsov, A. B. Zaitsev, N. S. Smoljanina, E. Yu. Senotrusova, A. V. Afonin, I. A. Ushakov, K. B. Petrushenko, O. N. Kazheva, O. A. D'yachenko, V. V. Smirnov, A. F. Schmidt, M. V. Markova, and L. V. Morozova, *Eur. J. Org. Chem.*, 4021 (2006).

06JPH238 S. Badré, V. Monnier, R. Méallet-Renault, C. Dumas-Verdes, E. Yu. Schmidt, A. I. Mikhaleva, G. Laurent, G. Levi, A. Ibanez, B. A. Trofimov, and R. B. Pansu, *J. Photochem. Photobiol., A.*, 238 (2006).

06MRC692 Yu. Yu. Rusakov, L. B. Krivdin, E. Yu. Schmidt, A. I. Mikhaleva, and B. A. Trofimov, *Magn. Reson. Chem.*, **44**, 692 (2006).

06RJO1348 B. A. Trofimov, L. N. Sobenina, Z. V. Stepanova, A. P. Demenev, A. I. Mikhaleva, I. A. Ushakov, T. I. Vakul'skaya, and O. V. Petrova, *Russ. J. Org. Chem. (Engl. Transl.)*, **42**, 1348 (2006).

06T4146 B. A. Trofimov, O. V. Petrova, L. N. Sobenina, V. N. Drichkov, A. I. Mikhaleva, I. A. Ushakov, O. A. Tarasova, O. N. Kazheva, A. N. Chekhlov, and O. A. Dyachenko, *Tetrahedron*, **62**, 4146 (2006).

06T7213 F. Bellina and R. Rossi, *Tetrahedron*, **62**, 7213 (2006).

06TL795 M. A. Ismail, D. W. Boykin, and C. E. Stephens, *Tetrahedron Lett.*, **47**, 795 (2006).

06TL3645 B. A. Trofimov, O. V. Petrova, L. N. Sobenina, I. A. Ushakov, A. I. Mikhaleva, Yu. Yu. Rusakov, and L. B Krivdin, *Tetrahedron Lett.*, **47**, 3645 (2006).

06TL3693 A. I. Mikhaleva, A. B. Zaitsev, A. V. Ivanov, E. Yu. Schmidt, A. M. Vasil'tsov, and B. A. Trofimov, *Tetrahedron Lett.*, **47**, 3693 (2006).

06TL7139 L. N. Sobenina, A. P. Demenev, A. I. Mikhaleva, I. A. Ushakov, A. M. Vasil'tsov, A. V. Ivanov, and B. A. Trofimov, *Tetrahedron Lett.*, **47**, 7139 (2006).

06ZSK616 A. V. Vashchenko, A. M. Vasil'tsov, E. Yu. Shmidt, A. I. Mikhaleva, and B. A. Trofimov, *Zh. Strukt. Khim.*, **47**, 616 (2006).

07AJC583 L. B. Krivdin, Yu. Yu. Rusakov, E. Yu. Schmidt, A. I. Mikhaleva, and B. A. Trofimov, *Aust. J. Chem.*, **60**, 583 (2007).

07CRV4891 A. Loudet and K. Burgess, *Chem. Rev.*, **107**, 4891 (2007).

07JHC505 B. A. Trofimov, L. N. Sobenina, A. I. Mikhaleva, O. V. Petrova, V. N. Drichkov, I. A. Ushakov, O. A. Tarasova, D. -S. D. Toryashiniva, Yu. Yu. Rusakov, and L. B. Krivdin, *J. Heterocycl. Chem.*, **44**, 505 (2007).

07MC40 B. A. Trofimov, E. Yu. Schmidt, A. I. Mikhaleva, N. V. Zorina, I. A. Ushakov, A. V. Afonin, and A. M. Vasil'tsov, *Mendeleev Commun.*, **17**, 40 (2007).

07MI292 B. A. Trofimov, M. V. Markova, L. V. Morozova, E. Yu. Shmidt, E. Yu. Senotrusova, G. F. Myachina, Yu. A. Myachin, T. I. Vakul'skaya, and A. I. Mikhaleva, *Polym. Sci., Ser. B*, **49**, 292 (2007).

07MI3 T. A. Skotheim and J. R. Reynolds, *"Handbook of Conducting Polymers: Conjugated Polymers: Theory, Synthesis, Properties, and Characterization"*, CRC Press, Boca Raton, London, New York (2007).

07MRC142 Yu. Yu. Rusakov, L. B. Krivdin, E. Yu. Senotrusova, E. Yu. Schmidt, A. M. Vasiltsov, A. I. Mikhaleva, B. A. Trofimov, O. A. D'yachenko, and A. N. Cheklov, *Magn. Reson. Chem.*, **45**, 142 (2007).

07RCB2209 L. V. Morozova, I. V. Tatarinova, M. V. Markova, A. M. Vasil'tsov, A. V. Ivanov, T. I. Vakul'skaya, A. I. Mikhaleva, and B. A. Trofimov, *Russ. Chem. Bull. (Engl. Transl.)*, **56**, 2209 (2007).

07RJO228 A. I. Mikhaleva, E. Yu. Shmidt, A. V. Ivanov, A. M. Vasil'tsov, E. Yu. Senotrusova, and N. I. Protsuk, *Russ. J. Org. Chem. (Engl. Transl.)*, **43**, 228 (2007).

07RJO872 N. A. Shcherbina, N. V. Istomina, L. B. Krivdin, E. Yu. Shmidt, A. I. Mikhaleva, and B. A. Trofimov, *Russ. J. Org. Chem. (Engl. Transl.)*, **43**, 872 (2007).

07RJO880 Yu. Yu. Rusakov, L. B. Krivdin, E. Yu. Shmidt, A. M. Vasil'tsov, A. I. Mikhaleva, and B. A. Trofimov, *Russ. J. Org. Chem. (Engl. Transl.)*, **43**, 880 (2007).

07RJO1495 E. Yu. Shmidt, E. Yu. Senotrusova, I. A. Ushakov, N. I. Protsuk, A. I. Mikhaleva, and B. A. Trofimov, *Russ. J. Org. Chem. (Engl. Transl.)*, **43**, 1495 (2007).

07S447 B. A. Trofimov, L. N. Sobenina, Z. V. Stepanova, I. A. Ushakov, O. V. Petrova, O. A. Tarasova, K. A. Volkova, and A. I. Mikhaleva, *Synthesis*, 447 (2007).

07S452 A. M. Vasil'tsov, A. V. Ivanov, I. A. Ushakov, A. I. Mikhaleva, and B. A. Trofimov, *Synthesis*, 452 (2007).

07TL4661 B. A. Trofimov, L. N. Sobenina, A. P. Demenev, Z. V. Stepanova, O. V. Petrova, I. A. Ushakov, and A. I. Mikhaleva, *Tetrahedron Lett.*, **48**, 4661 (2007).

08CHE1117 A. I. Mikhaleva, A. V. Ivanov, A. M. Vasil'tsov, I. A. Ushakov, J. S. Ma, and G. Yang, *Chem. Heterocycl. Compd. (Engl. Transl.)*, **44**, 1117 (2008).

08CHE1238	A. V. Afonin, I. A. Ushakov, D. E. Simonenko, E. Yu. Schmidt, N. V. Zorina, A. V. Ivanov, A. M. Vasil'tsov, and A. I. Mikhaleva, *Chem. Heterocycl. Compd. (Engl. Transl.)*, **44**, 1238 (2008).
08DOC(423)66	A. I. Mikhaleva, E. Yu. Schmidt, N. I. Protsuk, N. V. Zorina, and B. A. Trofimov, *Dokl. Chem. (Engl. Transl.)*, **423**, 66 (2008).
08DOC(423)273	E. Yu. Schmidt, A. I. Mikhaleva, N. V. Zorina, O. N. Kazheva, G. V. Shilov, O. A. D'yachenko, and B. A. Trofimov, *Dokl. Chem. (Engl. Transl.)*, **423**, 273 (2008).
08MRC441	A. V. Afonin, A. V. Vashchenko, I. A. Ushakov, N. V. Zorina, and E. Yu. Schmidt, *Magn. Reson. Chem.*, **46**, 441 (2008).
08RJC2247	R. Meallet-Renault, G. Clavier, C. Dumas-Verdes, S. Badre, E. Yu. Shmidt, A. I. Mikhaleva, C. Laprent, R. Pansu, P. Audebert, and B. A. Trofimov, *Russ. J. Gen. Chem. (Engl. Transl.)*, 2247 (2008).
08RJO237	L. N. Sobenina, V. N. Drichkov, O. V. Petrova, I. A. Ushakov, T. V. Kashik, L. B. Krivdin, Yu. Yu. Rusakov, E. V. Zukova, A. I. Mikhaleva, and B. A. Trofimov, *Russ. J. Org. Chem. (Engl. Transl.)*, **44**, 237 (2008).
08RJO1247	B. A. Trofimov, E. Yu. Shmidt, A. I. Mikhaleva, N. V. Zorina, and E. Yu. Senotrusova, *Russ. J. Org. Chem. (Engl. Transl.)*, **44**, 1247 (2008).
08RJO1338	S. S. Khutsishvili, Yu. Yu. Rusakov, L. B. Krivdin, N. V. Istomina, O. V. Petrova, L. N. Sobenina, and A. I. Mikhaleva, *Russ. J. Org. Chem. (Engl. Transl.)*, **44**, 1338 (2008).
08RJO1395	E. Yu. Shmidt, A. I. Mikhaleva, E. Yu. Senotrusova, A. M. Vasil'tsov, A. V. Ivanov, and B. A. Trofimov, *Russ. J. Org. Chem. (Engl. Transl.)*, **44**, 1395 (2008).
08RJO1512	O. V. Petrova, L. N. Sobenina, I. A. Ushakov, and A. I. Mikhaleva, *Russ. J. Org. Chem. (Engl. Transl.)*, **44**, 1512 (2008).
08S2631	V. N. Drichkov, L. N. Sobenina, T. I. Vakulskaya, A. I. Mikhaleva, and B. A. Trofimov, *Synthesis*, 2631 (2008).
08T5541	B. A. Trofimov, L. N. Sobenina, Z. V. Stepanova, T. I. Vakul'skaya, O. N. Kazheva, G. G. Alexandrov, O. A. D'yachenko, and A. I. Mikhaleva, *Tetrahedron*, **64**, 5541 (2008).
08TL3946	B. A. Trofimov, L. N. Sobenina, Z. V. Stepanova, O. V. Petrova, I. A. Ushakov, and A. I. Mikhaleva, *Tetrahedron Lett.*, **49**, 3946 (2008).
08TL4362	B. A. Trofimov, E. Yu. Schmidt, N. V. Zorina, E. Yu. Senotrusova, N. I. Protsuk, I. A. Ushakov, A. I. Mikhaleva, R. Méallet-Renault, and G. Clavier, *Tetrahedron Lett.*, **49**, 4362 (2008).
08MI315	N. S. Shaglaeva, O. V. Lebedeva, Yu. N. Pozhidaev, R. G. Sultangareev, M. V. Markova, and V. N. Salaurov, *Polym. Sci., Ser. B*, **50**, 315 (2008).
09ARK(iv)14	O. V. Petrova, L. N. Sobenina, I. A. Ushakov, A. I. Mikhaleva, S. H. Hyun, and B. A. Trofimov, *Arkivoc (Arkive for Organic Chemistry)*, **iv**, 14 (2009).
09CEJ5823	E. Yu. Schmidt, B. A. Trofimov, A. I. Mikhaleva, N. V. Zorina, N. I. Protzuk, K. B. Petrushenko, I. A. Ushakov, M. Yu. Dvorko, R. Méallet-Renault, G. Clavier, T. V. Thanh, T. T. T. Ha, and R. B. Pansu, *Chem. Eur. J.*, **15**, 5823 (2009).
09CEJ6435	B. A. Trofimov, E. Yu. Schmidt, A. I. Mikhaleva, C. Pozo-Gonzalo, J. A. Pomposo, M. Salsamendi, N. I. Protzuk, N. V. Zorina, A.

V. Levkovskaya, A. V. Vashchenko, E. P. Levanova, and G. G. Levkovskaya, *Chem. Eur. J.*, **15**, 6435 (2009).

09CHE554 I. K. Petrushenko, K. B. Petrushenko, V. I. Smirnov, E. Yu. Shmidt, and A. I. Mikhaleva, *Chem. Heterocycl. Compd. (Engl. Transl.)*, 554 (2009).

09IZV115 O. V. Petrova, M. V. Markova, L. N. Sobenina, L. V. Morozova, A. I. Mikhaleva, S. H. Hyun, and B. A. Trofimov, *Izv. AN. Ser. Khim.*, **58**, 115 (2009).

09MI(11)336 V. V. Razin and R. R. Kostikov, "*Exercises on Organic Chemistry*", p. 336, Khimizdat, St. Petersbourg (2009).

09S587 A. I. Mikhaleva, A. V. Ivanov, E. V. Skitaltseva, I. A. Ushakov, A. M. Vasiltsov, and B. A. Trofimov, *Synthesis*, 587 (2009).

09T4326 B. A. Trofimov, L. N. Sobenina, V. N. Drichkov, I. A. Ushakov, and A. I. Mikhaleva, *Tetrahedron*, **65**, 4326 (2009).

09T4855 E. Yu. Schmidt, E. Yu. Senotrusova, I. A. Ushakov, A. I. Mikhaleva, and B. A. Trofimov, *Tetrahedron*, **65**, 4855 (2009).

09TL97 B. A. Trofimov, A. M. Vasiltsov, A. I. Mikhaleva, A. V. Ivanov, E. V. Skitaltseva, E. Yu. Schmidt, E. Yu. Senotrusova, I. A. Ushakov, and K. B. Petrushenko, *Tetrahedron Lett.*, **50**, 97 (2009).

SUBJECT INDEX