

3.01

Pyrazoles

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3.01.1 INTRODUCTION

The exponential increase in literature that has affected organic chemistry as a whole has its foundation in pyrazole chemistry. Between 1984, the year of the publication of the first edition of *Comprehensive Heterocyclic Chemistry* (CHEC-I) (where, however, only a few 1983 references were reported) and 1994, the number of publications has almost doubled. Fortunately, since the really new discoveries have not increased at the same pace, it is not necessary to summarize in 70 pages what required 137 pages <84CHEC-I(5)167>. Pyrazole chemistry can be described in a shorter number of pages due to the existence of a series of excellent reviews (see Table 1); although this is not intended to be a review of reviews, the information already available in the form of a review will be only very briefly reported.

3.01.1.1 Survey of Possible Structures

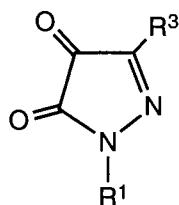
With regard to the CHEC-I <84CHEC-I(5)167>, the only real advance regarding new structures belongs to the section entitled "Three double bonds." Then, two examples were quoted, pyrazoline-4,5-diones (**1**) and pyrazolidine-3,4,5-triones (**2**).

But in 1993 appeared a review by Costero <93AHC(58)171> which contains much information on two other related systems, namely 2,3-diaza-2,4-cyclopentadienone (**3**) and 3,4-diaza-2,4-cyclopentadienone (**4**). The chemistry of these systems is discussed in the appropriate sections.

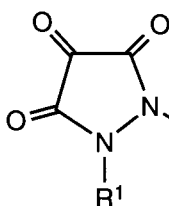
On the other hand, the group of Alcalde has developed new families of betaines of the azolate-

Table 1 Reviews on pyrazoles and related topics.

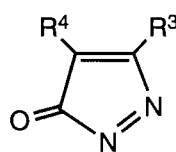
Main author	Title	Ref.
Katritzky	3 <i>H</i> -Pyrazoles	83AHC(34)1
Katritzky	4 <i>H</i> -Pyrazoles	83AHC(34)53
Trofimenko	Coordination chemistry of pyrazoles	86MI 301-01
Niedenzu	Pyrazole derivatives of boron	86TCC1
Catalán	Basicity and acidity of azoles	87AHC(41)187
Begtrup	¹³ C NMR of azoles	88MRC134
Constable	<i>N,N'</i> -Chelating ligands (azoles)	89CCR205
Bonati	X-ray geometries of pyrazoles	89G291
Katritzky	Electrophilic substitution (azoles)	90AHC(47)139
Cirincione	Diazoazoles	90AHC(48)65
Katritzky	Prototropic tautomerism	91H(32)329
Claramunt	Chemistry of pyrazolidinones	91OPP273
Pozharskii	<i>N</i> -Aminoazoles	92AHC(53)85
Sviridova	Pyrazolidines	92KGS829
Canty	Polydentate <i>N</i> -donor ligands	92AOC(34)1
Grimmett	Halogenation of heterocycles (five)	93AHC(57)291
Costero	Unsaturated heterocycles with CO groups	93AHC(58)171
Hurst	Nitration phenyl substituted heterocycles	93AHC(58)215
Trofimenko	Poly(pyrazolyl)borate chemistry	93CRV943
Begtrup	¹³ C NMR of pyrazoles	93MRC107
Nagai	3 <i>H</i> -Pyrazoles	93OPP403
Grimmett	Halogenation of fused heterocycles	94AHC(59)245
Burger	Fluoro heterocycles five-membered rings	94AHC(60)1
Grimmett	Lithiated pyrazoles: synthesis and reactions	94H(37)2087
Foces-Foces	X-ray geometries of pyrazoles	94JST(319)231
Fruchier	Trifluoromethylazoles	95OPP33



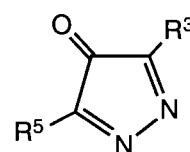
(1)



(2)

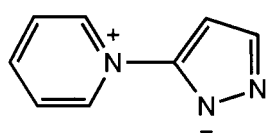


(3)

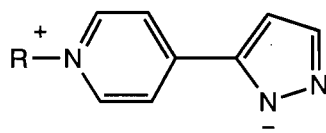


(4)

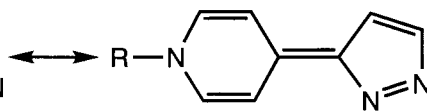
azinium and azolate–azolium class where the negative charge is in the azole ring and the positive one in a pyridine-like or azole-like ring <95AHC(60)197>. Two main classes can be recognized, depending on the nature of the single bond between the two rings: N—C (5) and C—C (6) (illustrated with a pyridinium ring). A spacer (for instance a CH₂, a CH=CH group, or a *p*-disubstituted phenyl ring) can be present in these structures.



(5)



(6a)



(6b)

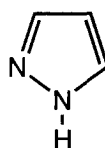
These systems, which are azaanalogues of sesquifulvalene, have been thoroughly explored for different azole rings, pyrazole being one of the less suitable for obtaining stable derivatives <87JOC5009>.

A few papers deal with comparative studies of azoles which generally include pyrazole and both indazoles. This is the case with the chemometric study of the effect of the heteroaromatic moiety on spectroscopic properties, *pK_a* and reactivity of azoles <90JPO651>, the comparison of ¹³C NMR chemical shifts and coupling constants of parent azoles differing only by the substituent on the nitrogen atom <93MRC791>.

3.01.2 THEORETICAL METHODS

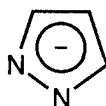
3.01.2.1 Structure and Reactivity of Pyrazoles

The microwave geometry of pyrazole (**7**) <84CHEC-I(5)167> has been used as a test for *ab initio* calculations carried out at different levels of accuracy <95MI 301-01>. At the HF level, the performance of several basis sets, namely 3-21G, 6-31G, 6-31G**, and 6-311G** was investigated. The influence of the electron correlation effects was also studied by carrying out geometry optimizations at the MP2, MP4, and QCISD levels. The performance of density functional methods was also evaluated. From these analyses, it was concluded that there is no asymptotic approach to the experimental geometry by increasing the quality of the theoretical model, although, as expected, the more reliable structures are those obtained at the MP2, MP4, and QCISD levels, as well as those obtained by the B3LYP density functional method.

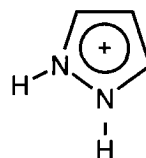


(7)

Geometries, protonation sites, basicity, and acidity of all parent azoles, including pyrazole itself have been calculated using the INDO and STO-3G methods <84CS84>. Theoretical studies of the basicity of pyrazoles, using the semiempirical approximations as well as the STO-3G and 4-31G methods have been published <83JCS(P2)1869, 84JA6552, 90JA1303, 90JST(205)367>. These studies have allowed the understanding of the differences in basicity between the gas phase and the aqueous solution <84JOC4379>. To understand the relative gas-phase and solution basicity and acidity of pyrazole, it is necessary to take into account the lone pair/lone pair repulsion in pyrazolate anion (**8**) (6.5 kcal mol⁻¹), the adjacent NH/lone pair attraction in pyrazole (**7**) (1.0 kcal mol⁻¹) and the NH⁺/NH⁺ repulsion in pyrazolium cation (**9**) (6.5 kcal mol⁻¹). Solvation by water, and to a lesser extent by DMSO, modifies these values to the point that the position of the equilibria can be reversed <86JA3237>.

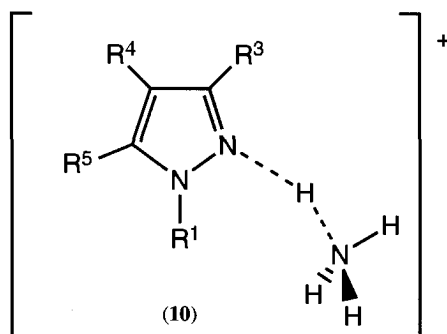


(8)



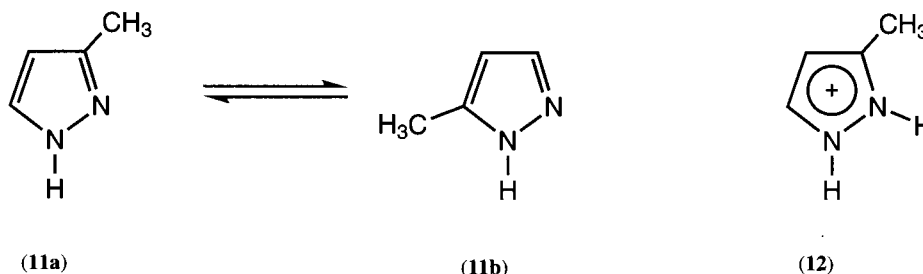
(9)

Ab initio calculations (STO-3G and 4-31G) were carried out for methylpyrazoles-NH₄⁺ complexes (**10**) <87JOC1713>. In the equilibrium geometry of these complexes, the proton of the NH₄⁺ system was partially transferred to the pyrazole. Their hydrogen bond energies increase with the proton affinity of the pyrazole, but they are smaller than the corresponding proton affinities, this fact being related to the degree of hardness of these heterocyclic bases.

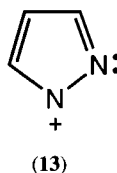


(10)

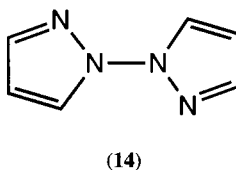
On the two tautomers of 3(5)-methylpyrazole (**11a**) and (**11b**), and their common cation (**12**) 6-31G**//6-31G calculations (which are 6-31G** calculations on 6-31G fully optimized geometries) were carried out <89MI 301-01>. Information about the geometries, dipole moments ((**11a**) $\mu = 2.02$ D, (**11b**) $\mu = 2.73$ D), and energies ((**11a**) $E = -263.84583$ Hartrees, (**11b**) $E = -263.84653$ Hartrees, (**12**) $E = -264.203834$ Hartrees) were collected.



Theoretical calculations at the *ab initio* level on simple trifluoromethylpyrazoles have been carried out <93JFC(63)271, 93JST(291)211> as well as on cation (**13**) <87JOC4058>. Very high level computational calculations (up to MP4) have been carried out on the four tautomers of pyrazolinone (see Section 3.01.7.5.1) <93JA2352>.



The conformation of *N,N*-linked biazoles, including 1,1'-bipyrazole, (**14**) has been calculated within the framework of the MNDO method: the energy minimum for compound (**14**) is for a dihedral angle of 108° (N atoms in opposite positions) <84CJC687>. A similar study has been reported for a 1-(2-pyridinyl)-1*H*-pyrazole (**24**) derivative <93JHC865>. The complete potential surface of 3,5-bis(4-methylpyrazol-1-yl)-4-methylpyrazole (**106**; $R = \text{CH}_3$) (see Section 3.01.5.3.5(v)) has been calculated at the AM1 level <93CJC1443>.

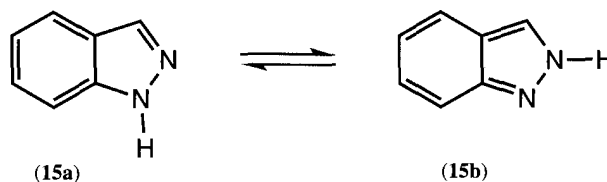


Both INDO and AM1 calculations have been carried out on pyrazolidinones with special emphasis on the stability of their conjugated acids (protonation site) <91BSB291>.

3.01.2.2 Structure and Reactivity of Indazoles

Photophysical experiments and theoretical calculations have been used to determine the tautomeric equilibrium between 1*H*- and 2*H*-indazoles (**15a**) and (**15b**) both in the ground (S_0) and in the excited state (S_1) <94JPC10606>. The measurement of sublimation and solution enthalpies in water at 25°C , basicities in the excited state of 1-methylindazole ($\text{p}K_a^* = 1.61$) and 2-methylindazole ($\text{p}K_a^* = 3.00$), and MP2//6-31G**//6-31G* calculations of the difference in energy between their conjugated acids in the ground state allows the complete thermodynamic cycle to be established. Indazole in the excited state is 3.0 $\text{p}K_a$ units more acid ($\text{p}K_a^* = 11.08$) and 1.8 $\text{p}K_a$ units more basic

($pK_a^* = 2.87$) than in the ground state. The conclusion is that the *1H*-tautomer is always the most stable, although the difference in energy is lower in the excited ($1.6 \text{ kcal mol}^{-1}$) than in the ground state ($2.3 \text{ kcal mol}^{-1}$) $\langle 94JPC10606 \rangle$.



3.01.2.3 Dipole Moments

Betaines such as (5) have very high dipole moments (10–12 D) $\langle 86CC734 \rangle$. The dipole moments of very few neutral pyrazoles (e.g., those of some *N*-adamantylpyrazoles $\langle 86JHC999 \rangle$) have been determined (this is a field where more effort is necessary).

3.01.3 EXPERIMENTAL STRUCTURAL METHODS

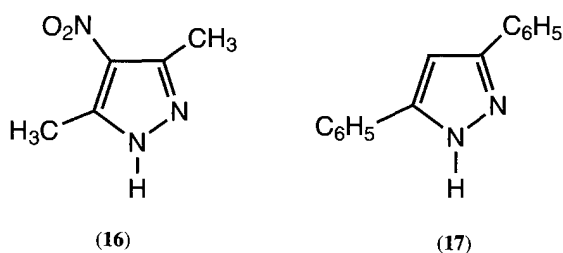
A ^{199}Hg NMR study of 1-phenylpyrazole and 1-phenyl-3,4,5-trimethylpyrazole organomercuric complexes (138) and (139) (see Section 3.01.5.4.7) has been published $\langle 93AJC1323 \rangle$.

3.01.3.1 X-ray Diffraction

A total of 209 structures of neutral pyrazoles have been analyzed (metal complexes being excluded) $\langle 94JST(319)231 \rangle$. The structures of these pyrazoles were classified according to the substituent R^1 on the nitrogen ($R^1 = \text{H}$, boron, methyl, a sugar, adamantane, phenyl, aryl, heteroaryl, acyl, alkoxy carbonyl, amino, nitro, sulfonyl); indazoles and [5.5] bicyclic pyrazoles were also considered. The averaged geometries were compared with those obtained at the 6-31G* level for $R^1 = \text{H}$, Me, CHO, NH_2 , NO_2 , PH_2 , BH_2 and BH_3^- . One of the most significant conclusions of this study was that the substituent effect through the nitrogen atom in pyrazoles parallels that of substituents through a carbon atom in benzenes with the exception of the amino group.

One of the most interesting structures of *NH*-pyrazoles is that of 3,5-dimethyl-4-nitropyrazole (16) $\langle 93G477 \rangle$; this compound crystallizes in a noncentrosymmetric group (a chiral helix) and owing to its high dipole moment shows nonlinear optical properties in the solid state. The structures of other *NH*-pyrazoles bearing a 4-nitro substituent were determined and compared with those of the corresponding 4-unsubstituted-pyrazoles (pyrazole itself (7), 3,5-dimethyl (19), 3,5-diphenyl (17), 3,5-di-*t*-butyl) $\langle 94AX(B)746 \rangle$, as well as 3,5-dicarboxylic acid and its monosodium salt (it involves the 3-carboxylic acid) $\langle 94MI 301-01 \rangle$. Amongst perfluoroalkylated pyrazoles, the x-ray structures of 1-(4-chlorophenyl)-4-*N*-methylcarboxamido-5-trifluoromethylpyrazole $\langle 87JHC739 \rangle$ and that of 1-phenyl-3-(CF_2) $_3\text{CF}_2\text{H}$ -5-hydroxypyrazole have been reported $\langle 90IZV640 \rangle$. The structure of the magenta dye (3*H*-indazol-3-one 1-[4-(diethylamino) phenyl] imine) was established definitely by x-ray crystallography $\langle 91JOC5278 \rangle$.

One of the most significant advances in the crystallography of *NH*-pyrazoles concerns the problem



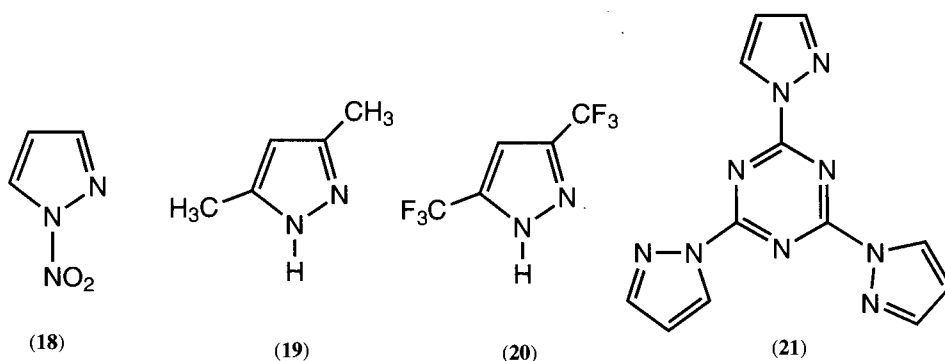
of the disorder of the NH proton and its relationship with dynamic CPMAS-NMR spectroscopy (see Section 3.01.3.7) and annular tautomerism in the solid state (see Section 3.01.4.4.1) <89JA7304, 92JA9657>.

3.01.3.2 Microwave Spectroscopy and Electron Diffraction

In 1984 at the time of CHEC-I, only the structure of pyrazole itself (**7**) had been determined in the gas phase by MW spectroscopy <84CHEC-I(5)167> (afterwards, a high resolution rotational Zeeman effect study was carried out on 1-[²H]-pyrazole <90ZN(A)1248>). Five more structures have been determined since then. First the MW spectrum of indazole was determined by Velino <92JST(155)1> at 70 °C: the spectrum corresponds to 1*H*-tautomer (**15a**). Afterwards, the MW spectra and *ab initio* calculations (MP2/6-31G**) have been obtained for 1-nitropyrazole (**18**) by Alonso *et al.* <95JST241>: the whole molecule is planar as in the solid state but presents clear differences in bond lengths and bond angles with regard to x-ray structure <94JST(319)231>.

The electron diffraction structures of 3,5-dimethylpyrazole (**19**) and 3,5-bis(trifluoromethyl)-pyrazole (**20**) have been determined <93JST(291)211>. The last pyrazole is a compound with a pungent odor which is too volatile to collect diffractometric data even in a sealed capillary.

Finally, in the case of tris(pyrazol-1-yl)-*s*-triazine (TPT) (**21**) the structure has been determined both in the solid state (x-ray) and in the gas phase (electron diffraction) <94MI 301-02>, both being remarkably similar and close to the conformation of minimum energy (AM1 calculations).



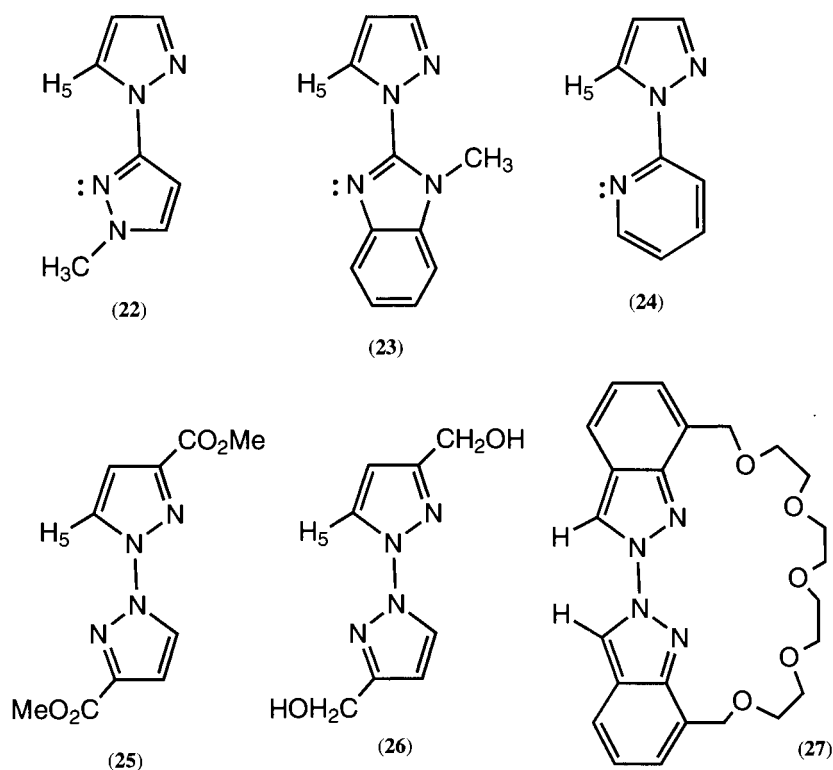
3.01.3.3 ¹H NMR Spectroscopy

3.01.3.3.1 Aromatic systems

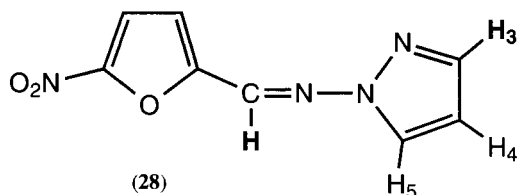
Unambiguous assignment of 1,3- and 1,5-disubstituted pyrazoles constitutes a classical problem which has usually been resolved by ¹H NMR spectroscopy. A revision <87T4663> examines the different criteria and shows that some rules (for instance, the sensitivity of H₃ chemical shift to solvent polarity) do not hold when a nitrogen lone pair lies very close to the measured proton, in *N,C*-compounds (**22**), (**23**), and (**24**). On the other hand, *N,N'*-bonded pyrazoles like (**25**) and (**26**), and even more clearly the macrocycle (**27**), follow the rule <87T4663>.

One of the most significant changes in ¹H NMR spectroscopy of *NH*-pyrazoles, is the systematic use of low temperature to block the proton transfer and, thus, determine by simple integration of signals the tautomeric equilibrium constant. In this way, the *K_T* values of 3(5)-phenylpyrazole (**57**) <91G477> and 3(5)-phenyl-5(3)-methylpyrazole (**64**) <92JCS(P2)1737> were determined (see Section 3.01.4.4.1). In the last case and using the [¹⁵N₂] derivative, the ¹H—¹⁵N coupling constant of each tautomer were measured.

Compound (**28**) presents an unusual long range ⁶*J*(¹H—¹H) coupling constant between pyrazole H₃ and =CH protons <87AP(320)115>. A systematic study of *ortho*-benzylic coupling constants ⁴*J*_{Me—C=C—H} has been published <92JHC935>: 1,3-dimethylpyrazole (−0.55 Hz), 1,4-dimethylpyrazole



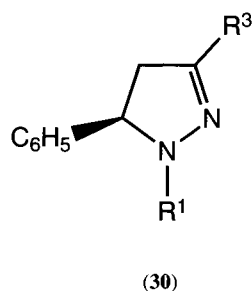
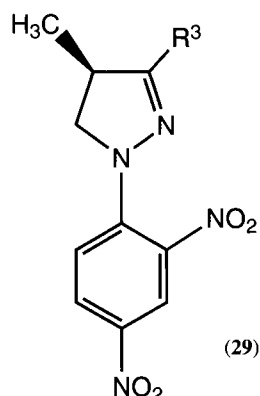
(-0.68 Hz with H_3 , and -0.92 Hz with H_5), 1,5-dimethylpyrazole (-0.83 Hz), the coupling values being linearly related to bond orders.



Heinisch and Holzer have used systematically NOE difference spectroscopy for assignment purposes in pyrazole derivatives <90M837, 93JHC865>.

3.01.3.3.2 Nonaromatic systems

The complex system present in 4-methyl- Δ^2 -pyrazolines (**29**; $R^3 = H, Br$) requires at least 360 MHz spectra, to be analyzed <86BSB73>. To determine the protonation site of Δ^2 -pyrazolines (**30**; $R^1 = H, CH_3, C_6H_5$, $R^3 = H, CH_3, C_6H_5$) ^1H NMR spectroscopy (chemical shifts and ^1H — ^1H coupling constants) has been used <87CS283>. The ^1H NMR spectra of 128 Δ^2 -pyrazolines have been reported <90JCR(S)200>; concerning the chemical shifts, additive contributions of substituents were calculated which allowed the prediction of those of unknown pyrazolines. Concerning the J_{gem} , J_{cis} , and J_{trans} coupling constants of the protons at positions 4 and 5, it was shown that they are quite sensitive to the nature of the substituent on the nitrogen atom. A series of papers by Tóth <89JCS(P2)319, 93T863> deal with the conformational analysis of fused- and spiropyrazolines using ^1H , ^{13}C , and two-dimensional methods.

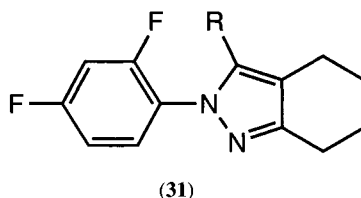


3.01.3.4 ^{19}F NMR Spectroscopy

In this chapter, all ^{19}F chemical shifts are expressed from CFCl_3 with positive values for signals at higher frequencies than the reference signal and solvent will be CDCl_3 unless stated otherwise. Conversion factors from some references to CFCl_3 are, according to Wray <83MI 301-01>: TFA: -78.5 ; C_6F_6 : -162.9 ; $\text{C}_6\text{H}_5\text{CF}_3$: -63.9 ; $\text{C}_6\text{H}_5\text{F}$: -113.15 ; F_3CCl_3 : -82.2 .

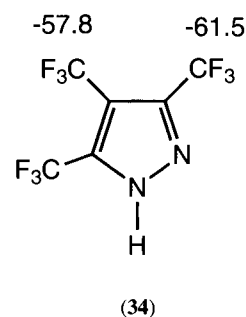
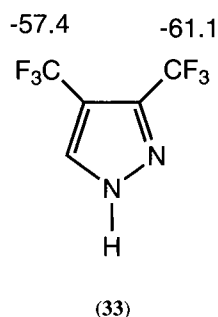
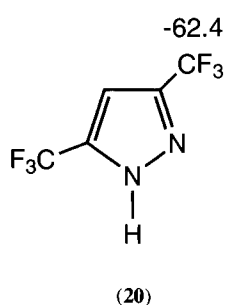
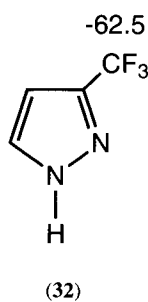
3.01.3.4.1 Aromatic systems

If only one trifluoromethylpyrazole isomer is available with various substituents at other positions, the fluorine chemical shift is not by itself characteristic of the position of the CF_3 group. The situation is different in a homogeneous series. For instance, it has been shown <93JHC365> that in 1,5-disubstituted pyrazoles bearing CF_3 substituents in the other positions, the mean ^{19}F chemical shifts at positions 3 and 4 are -60.0 and -55.3 ppm, respectively. In compounds (31) there are long range coupling constants ($^6J(^1\text{H}-^{19}\text{F})$ and $^6J(^{19}\text{F}-^{19}\text{F})$) between the *ortho* fluorine atom and R (R = CH_3 , CHF_2 , and CF_3) <93MRC323>; these couplings were assigned to “trough-space” spin-spin couplings.

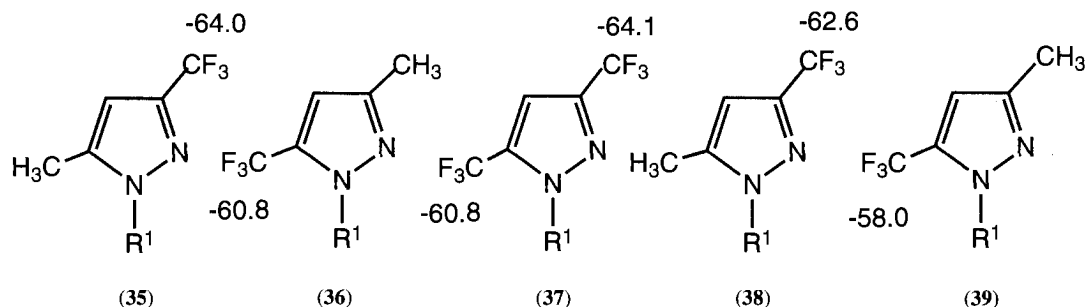


Other 4-trifluoromethylpyrazoles present CF_3 chemical shifts between -53.2 ppm and -58.1 ppm <90BSF843, 90JFC(47)45, 93JFC(62)39>. At room temperature in *NH* pyrazoles, positions 3 and 5 are equivalent due to rapid protropy (see Section 3.01.4.4.1). This is the case for compounds (32), (20), (33), and (34). In compounds (32) and (33), tautomers 3(5)- CF_3 on the one hand, and tautomers 3(5),4-(CF_3)₂ on the other hand, give average signals in ^{19}F NMR spectroscopy <95OPP33>.

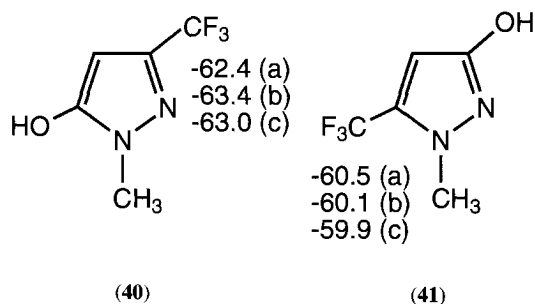
All things being equal, a significant difference is also observed between 3- CF_3 and 5- CF_3 for



compounds (35)–(37) on the one hand (R^1 = benzothiazol-2-yl) <93JCR(S)163>, and (38) and (39) on the other hand (R^1 = aryl) <90JHC919>.

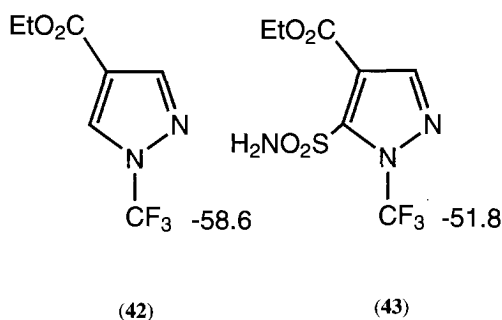


The Δ^2 -pyrazolin-5-one/ Δ^3 -pyrazolin-5-one/5-hydroxypyrazole tautomerism <84CHEC-I(5)167> has not been considered by the different authors, when discussing the chemical shifts of 3- and 5-pyrazolinones <93JHC49>. The values reported for compounds (40) and (41) in CDCl_3 (a) <93JHC49>, in $[\text{D}_6]\text{acetone}$ (b) <92JOC5680>, and in $[\text{D}_6]\text{DMSO}$ (c) <90JHC243> are given.



The results concerning (40) and (41) show the low sensitivity of the trifluoromethyl group to solvent effects. However, in the case of 3(5)-trifluoromethyl-5(3)-methylpyrazole (44), very different chemical shifts have been observed in the same group of solvents <83JC774>: -41.2 in CDCl_3 , -61.6 in $[\text{D}_6]\text{acetone}$, and -51.9 in $[\text{D}_6]\text{DMSO}$. This may be due to a modification in the tautomeric equilibrium constant (44a)/(44b) (see Section 3.01.4.4.1).

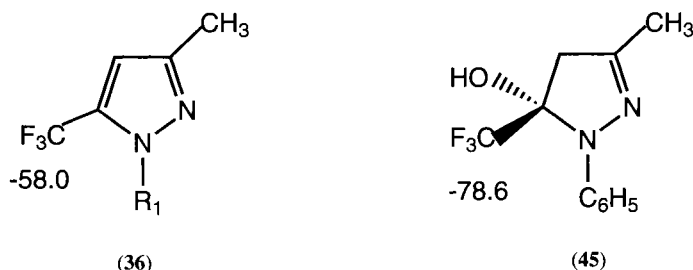
Finally, it appears that the order of appearance of signals from upfield to downfield is $3\text{-CF}_3 > 5\text{-CF}_3 > 4\text{-CF}_3$. Other data about 3- and/or 5- CF_3 pyrazoles can be found in references <89TL2049, 90JFC(48)123, 91JFC(51)141>; for $\text{C}_n\text{F}_{2n+1}$ substituted pyrazoles see references <93JHC49>. For a trifluoromethyl group at position 1 (i.e., linked to the nitrogen) the only available data, compounds (42) and (43), came from reference <90JHC807>.



3.01.3.4.2 Nonaromatic systems

Some examples of Δ^1 - <92JCR(S)40> and Δ^2 -pyrazolines <89TL2049, 90BSF843, 90JCR(S)120, 90JHC919, 92JCR(S)40, 92ZOR1380> substituted by trifluoromethyl groups are described in the literature, but the

most interesting point is probably the possibility to differentiate between Structures (36; $R^1 = C_6H_5$) and (45) using the chemical shift of the CF_3 group ($CDCl_3$) $\langle 89TL2049, 90JHC919 \rangle$.



This characteristic 20 ppm upfield shift of a $-C(OH)-CF_3$ compared to a $=C-CF_3$ at the 5-position of a pyrazole ring has been pointed out by Singh *et al.* $\langle 93JCR(S)163 \rangle$ who demonstrated that the 5- CF_3 pyrazoles described in references $\langle 91JFC(51)283 \rangle$ and $\langle 88JHC1641 \rangle$ were in fact the corresponding Δ^2 -pyrazolines.

3.01.3.5 ^{13}C NMR Spectroscopy

3.01.3.5.1 Aromatic systems

Long range $^1H-^{13}C$ coupling constants in pyrazoles have been carefully analyzed $\langle 84MI 301-03 \rangle$ as well as $^1J(^{13}C-^{13}C)$ ($C_3, C_4 = 51.5$ Hz, $C_4, C_5: 64.6$ Hz) coupling constants in 1-methylpyrazole $\langle 94MRC62 \rangle$. The best method to assign isomeric 1,3- and 1,5-disubstituted pyrazoles is a proton-coupled ^{13}C NMR spectrum $\langle 87T4663 \rangle$. A great effort has been done to systematically determine and collect ^{13}C NMR data for pyrazoles $\langle 84OMR(22)603, 93MRC107 \rangle$. For more precise information on *N*-adamantyl and *N*-arylpayrazoles, and indazoles see $\langle 85MI 301-01, 92MRC455, 93JHC957 \rangle$. A comparative study of the ^{13}C chemical shifts of methanes bearing 1-azolyl and/or phenyl rings ($n = 1-4$) has been published $\langle 87MRC260 \rangle$. The azolyl residues comprises 1-pyrazolyl and 1- and 2-indazolyl; the chemical shift of the central sp^3 carbon atom depend on the substituents in an additive manner (in tetrapyrazolylmethane (98) it appears at 95.8 ppm). A similar type of model has been used to analyze the ^{13}C chemical shifts of the CH_2-CH_2 bridge in 1,2-bisazolyethanes $\langle 88JHC771 \rangle$.

A systematic study of $\delta^{13}C$ and $^1H-^{13}C$ coupling constants of 1,4-disubstituted pyrazoles ($R^1 = SO_2Ph, C_6H_5, CH_2Ph$; $R^4 = H, Br, I, Me, NO_2, C\equiv C-Ph, C\equiv C-TMS$) was carried out by Heinisch and Holzer $\langle 88H(27)2443 \rangle$. The ^{13}C NMR chemical data of compound (28) have been reported $\langle 87MRC737 \rangle$. There is a linear relationship of the form $\delta C_4 = 106.7 + 5.1 \sigma_p$ for a series of pyrazoles *N*- R^1 (with $R^1 = N=PPh_3, NHCH_3, NH_2, CH_3, adamantyl, C_6H_5, 2,4,6$ -trinitrophenyl, $CONH_2, COCH_3, NO_2$, and SO_2CF_3) $\langle 90ICA195 \rangle$. This equation allows to calculate σ_p for BH_3^- (-0.36), $pzBH_2^-$ (-0.21), pz_2BH^- (-0.13), and pz_3B^- (0.04) (pz = anion pyrazolate). Chemical shifts and $^1H-^{13}C$ coupling constants of pyrazole, 1-phenylpyrazole, indazole, 1-methyl, and 2-methylindazoles have been recorded in sulfuric acid to obtain information on azolium cations $\langle 90MRC807 \rangle$; in these conditions coupling with the *NH* atoms can be measured.

The effect of *N*-substituents on the ^{13}C NMR parameters of azoles has been studied with a collection of 169 azoles with no other substitution in the ring $\langle 88MRC134 \rangle$. Pyrazole and both isomers of indazole are amongst the azoles studied with a large collection of *N*-substituents [$CH_3, C(CH_3)_3, CH_2C_6H_5, CH_2OH, C(CD_3)_2OH, C_6H_5, C_6H_4NO_2, C_6H_3(NO_2)_2, C_6H_2(NO_2)_3, CN, COCH_3, CO_2R, CONH_2, NH_2, NO_2, OCH_3, Si(CH_3)_3, SO_2C_6H_4CH_3, SO_2CF_3, Cl$, and $Sn(C_4H_9)_3$]. The analysis of the chemical shifts and $^1H-^{13}C$ coupling constants leads to a classification of azoles into three to six families, depending on the parameter used. Pyrazole and 2*H*-indazole belong to the same family while 1*H*-indazole belongs to another one. The ^{13}C NMR spectra of 1-methylpyrazole have been recorded in 11 solvents $\langle 91SA(A)785 \rangle$; the solvent induced shifts of the three heterocyclic carbons and those of the *N*-methyl groups were discussed using the Kamlet-Taft-Abboud formalism. As reported in Table 1, a review on ^{13}C NMR spectroscopy of pyrazoles (1168 compounds) has been published; the reported data were discussed on the basis of statistical treatments $\langle 93MRC107 \rangle$. Data concerning trifluoromethylpyrazoles from ^{13}C NMR spectroscopy can be summarized as follows $\langle 83IC774, 88TL5281, 90JFC(47)45, 90JHC243, 91JOC3942, 92H(34)791, 92IJC(B)233, 92JOC5680, 93JCR(S)163, 93JFC(62)39, 93JHC49 \rangle$; neither the chemical shift of the CF_3 group (about 122 ± 2 ppm)

nor the $^1J_{\text{CF}}$ (267 ± 1 Hz) can be considered as characteristic of the position of the substituent on the pyrazole ring. Coupling constants of ^{13}C — ^{31}P have been reported for 5-triphenylphosphoranilydeneaminopyrazoles <91MRC517>.

The effect of the positive charge and steric effect of substituents at positions 2 and 4 has been studied by ^{13}C NMR spectroscopy for 1-arylpyrazolium cations <89MRC603>. The protonation site of *N*-methylazoles and benzazoles was determined by ^{13}C NMR, ^{15}N NMR (see Section 3.01.3.6.1) and, 6-31G *ab initio* calculations <93MRC791>.

Pyrazolinones have been much less studied than pyrazoles. In a paper dealing with the comparison between 1,2,6-thiadiazinones and pyrazolinones, the ^{13}C chemical shifts of 10 pyrazolinones were reported <88JCR(S)94>.

3.01.3.5.2 Nonaromatic systems

Carbon-13 NMR spectroscopy has been used to determine the structure of 3-(3,5-dimethylfuryl)-2-1,5-diaryl- Δ^2 -pyrazolines <94MI 301-03>; the assignments were substantiated by means of ^{15}N labeling.

Data on pyrazolidines and Δ^2 -pyrazolines (46)–(49) are reported in Table 2.

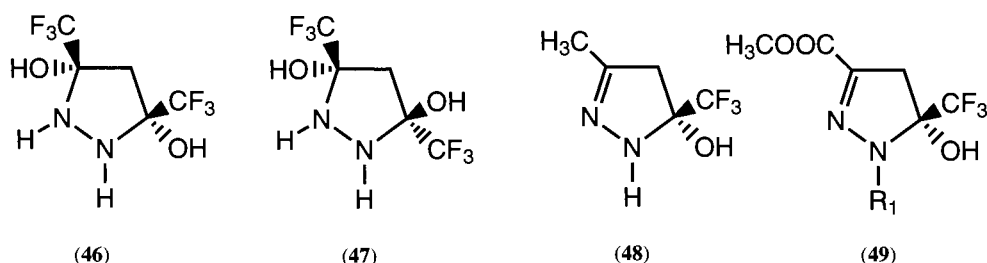
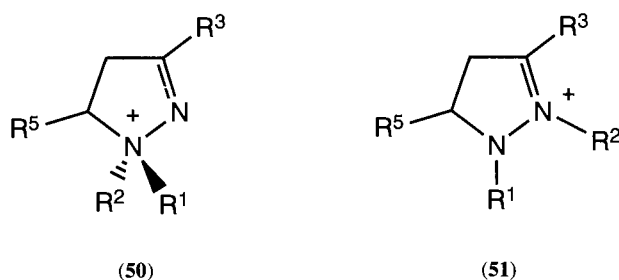


Table 2 ^{13}C Chemical shifts (δ) and ^{13}C – ^{19}F coupling constants (Hz, in parentheses) of pyrazolidines and Δ^2 -pyrazolines.

No	C ₃	C ₄	C ₅	CF ₃	Ref.
(46) ^a	92.4(30.1)	45.6	92.4(30.1)	124.9(285.9)	90JCR(S)120
(47)	92.6(29.8)	45.1	92.6(29.8)	124.4(285.2)	90JCR(S)120
(48)	148.4	45.1	91.1(30.1)	124.4(282.3)	90JCR(S)120
(49) (R = H) ^b			93.0(31.7)	124.5(281.6)	92ZOR1380
(49) (R = C ₆ H ₅) ^c			94.8(32.9)	122.9(285.3)	92ZOR1380

^a[²H₆]DMSO. ^b[²H₆]acetone. ^cCDCl₃.

The protonation site on N₁ of Δ^2 -pyrazolines has been determined using ^{13}C NMR spectroscopy <83MI 301-02>. This general rule is not followed in the case of 1-phenyl-3-aminopyrazolines which protonates on N₂ <95JCS(P2)1875>. Carbon-13 NMR spectroscopy easily differentiates the two classes of pyrazolinium cations, namely the 1,1- and the 1,2-disubstituted (50) and (51) <86MRC551>. For instance, the *N*-methyl groups (R¹ = R^{1'} = R² = R³ = CH₃, R⁵ = H) appear at 54.1 ppm for (50), and at 42.1 ppm (position 1) and 36.0 ppm (position 2) for (51).



3.01.3.6 ^{15}N NMR Spectroscopy

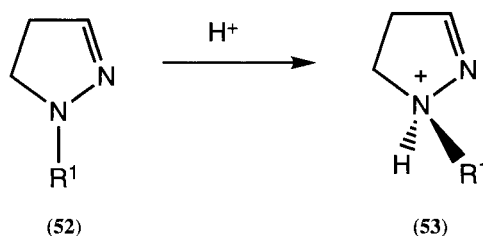
3.01.3.6.1 Aromatic systems

As well as ^{13}C — ^{15}N and ^{15}N — ^{15}N coupling constants ^{15}N chemical shifts have been measured for [$^{15}\text{N}_2$]pyrazole and some of its derivatives $\langle 84\text{OMR}(22)473 \rangle$ (for ^{14}N quadrupole coupling tensors in pyrazole, see $\langle 85\text{CPH}103 \rangle$); ^{14}N , ^{15}N , ^{17}O chemical shifts, and related coupling constants have been reported for 1-nitropyrazole (**18**) $\langle 93\text{MC}109 \rangle$. Both ^{15}N chemical shifts and some ^{11}B — ^{15}N coupling constants have been reported for bis-, tris-, and tetrakispyrazolylborates $\langle 90\text{ICA}195 \rangle$. The chemical shifts and $^1J(\text{H}$ — $^{15}\text{N})$ coupling constants of 1-aminopyrazole, 1- and 2-aminoindazoles as well as those of their cations have also been reported $\langle 90\text{JCS}(\text{P}2)237, 93\text{JCS}(\text{P}2)1687 \rangle$. A statistical survey (Principal Component Analysis, Hammett, Taft, and Swain-Lupton models) of the ^{15}N chemical shifts (as well as $\delta^{13}\text{C}$ and ^1H — ^{13}C coupling constants) of *N*-substituted pyrazoles concludes that 1-trifluorosulfonylpyrazole must have a strong 1-azadiene character $\langle 93\text{MI} 301-01 \rangle$. The protonation site of *N*-methylazoles and benzazoles was determined by ^{15}N NMR, ^{13}C NMR (see Section 3.01.3.5.1), and 6-31G *ab initio* calculations $\langle 93\text{MRC}791 \rangle$ while protonation of aminopyrazoles was studied by ^{15}N NMR spectroscopy $\langle 89\text{JCS}(\text{P}2)1941 \rangle$.

Low temperature studies, for instance in THF at 175 K, gives information on the annular tautomerism of *NH*-pyrazoles (see Section 3.01.4.4.1) $\langle 92\text{JCS}(\text{P}2)1737 \rangle$; a large collection of ^{15}N chemical shifts of *NH*-pyrazoles (frozen tautomerism) has been published $\langle 94\text{MRC}699 \rangle$.

3.01.3.6.2 Nonaromatic systems

The ^{15}N NMR spectroscopy of Δ^2 -pyrazolines and their salts has been reported $\langle 87\text{MI} 301-01 \rangle$. Using as model *N,N*-dimethylaniline (for protonation on N_1) and pyridine (for protonation on N_2), the protonation effects were calculated (+8 ppm and −111 ppm, respectively). Since the protonation effects in *C*-unsubstituted Δ^2 -pyrazolines are −12 ppm to −20 ppm on N_1 and −20 ppm to −30 ppm on N_2 (it depends on the nature of R^1), it was concluded that Δ^2 -pyrazolines (**52**) protonates on N_1 (**53**) but, owing to the conjugated aza-enamine structure, protonation on N_1 affects both nitrogen chemical shifts.

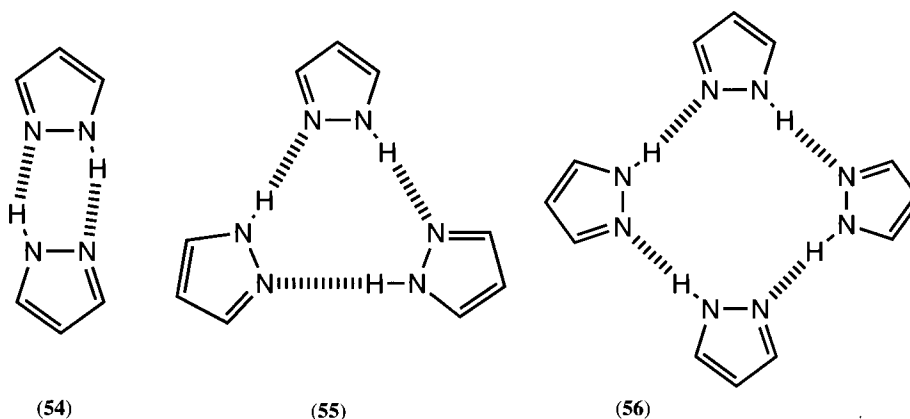


3.01.3.7 CPMAS NMR Spectroscopy

The discovery, by the combined use of crystallography and CPMAS NMR, of the dynamic properties of 3,5-dimethylpyrazole (a trimer like **55**) in the solid state opened a new field of research $\langle 85\text{JA}5290, 92\text{JA}9657 \rangle$. Other cyclic structures, dimers like **54** and tetramers like **56** were discovered $\langle 94\text{JHC}695 \rangle$. At the beginning, only ^{13}C CPMAS was used but afterwards ^{15}N CPMAS (with labeled derivatives) proved to be superior.

3.01.3.7.1 ^{13}C NMR spectroscopy

The ^{13}C CPMAS NMR spectra of antipyrine, 1-phenyl-3-hydroxypyrazole and 1-*p*-bromophenyl-3-methylpyrazolin-5-one have been recorded $\langle 87\text{H}(26)333 \rangle$. The last compound presents the most interesting case, since it is known by crystallography to be a mixture of *NH* and *OH* tautomers (see Section 3.01.4.4.2); the ^{13}C chemical shifts of both are observed as narrow signals (no proton transfer in the solid state between different tautomers).



A systematic study of annular tautomerism of *NH*-pyrazoles in the solid state has been published <88CJC1141>: in each case the tautomer present in the solid state was identified and the conclusion is always in agreement with the result obtained by x-ray crystallography, when available. The only compound for which the solution was not clear was 3(5)-phenyl-5(3)-methylpyrazole (**64**) (Section 3.01.4.4.1), but afterwards the problem was solved. The structure of (**64**) (polymorph B) in the solid state cannot be determined by x-ray crystallography due to the lack of suitable monocrystals. The combined use of CPMAS NMR, DSC, and powder diffraction provides information about the behavior of these pyrazoles in the solid state, particularly, about N—H···N intermolecular proton transfer <95JHC451>. Pyrazole (**64**) is an example of the influence of polymorphism on the proton exchange since polymorph A (a tetramer formed by a mixture of both tautomers (**64a**) and (**64b**) and whose x-ray structure is known <94JST(319)231>) presents the phenomenon but polymorph B (formed exclusively by tautomer (**64a**)) is devoid of it. The study by ¹³C CPMAS NMR of *NH*-pyrazoles and indazoles was extended to many more derivatives <93CJC678>; the conclusions of this study were: (i) the tautomer present in the solid is also the major tautomer in solution (the possible exception of 3(5)-phenylpyrazole (**57**) is probably related to a new case of desmotropy (see Section 3.01.3.1)); (ii) 3(5)-ferrocenylpyrazole should be a 50:50 mixture of both tautomers in the solid state; (iii) certain pyrazole *C*-substituents (CF₃, Br, Ar, Het) prefer the position 3 (that is, they are 3-substituted pyrazoles), others (Bu^t, Prⁱ, CH₃) prefer the position 5 (that is, they are 5-substituted pyrazoles).

Some splittings observed for 4-chloropyrazoles were satisfactorily explained considering ³⁵Cl quadrupolar effects transferred to ¹³C spin-1/2 MAS spectra of solids <94JPC5207>.

3.01.3.7.2 ¹⁵N NMR spectroscopy

A combination of ¹⁵N CPMAS NMR, ¹⁴N quadrupole double resonance, and x-ray studies of solid 3,5-dimethylpyrazole (**19**) between 270 K and 350 K has been necessary to discuss the intermolecular proton transfer in a structure like (**55**) <89JA7304>; the experimental evidence (species HHH and DDD) is consistent with a correlated triple hydrogen jump with an activation energy of 11 kcal mol⁻¹. The cases of 3,5-diphenyl-4-bromopyrazole (a dimer like (**54**)) and 3,5-diphenylpyrazole (a tetramer like (**56**)) were subsequently studied <92JA9657>; here also proton jumps were found with activation energies similar to those found for (**19**). The dynamic behavior of pyrazole (**7**) included in a host <93CC1139> is discussed afterwards (see Section 3.01.4.4.1).

Two other publications examine the effect of alumina and silicagel on the dynamic behavior of pyrazole (**7**) and 3,5-dimethylpyrazole (**19**) <94JPC8752> and collect all ¹⁵N chemical shifts of pyrazoles in the solid state and in solution (frozen tautomerism) <94MRC699>.

3.01.3.8 UV and IR Spectroscopies

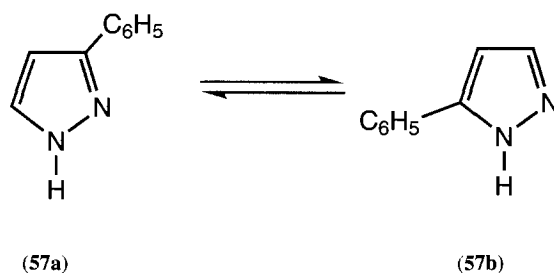
Since the mid-1980s great progress has been made in the field of electronic spectroscopy due to theoretical calculations, to the interest of gathering information about the excited state, and to advances in related techniques like fluorescence and phosphorescence. On the other hand,

vibrational–rotational spectroscopy, as far as IR is concerned, has mainly produced routine work showing a decline in this spectroscopy as a structural tool. Nevertheless, two important works appeared: (i) the complete spectrum assignment of the gas-phase IR spectrum of indazole <93JCS(F1)4005>; and (ii) IR spectral data were used to determine the enthalpies of O—H···N and N—H···O bonds in complexes of formic acid and 3,5-dimethylpyrazole <87MI 301-01>. Moreover, an important contribution has been made concerning the Raman spectrum of polycrystalline pyrazole <92MI 301-01> where the vibrational assignment is based on 3-21G calculations (see, for a preceding contribution <89MI 301-02>).

The only systematic study of the electronic absorption spectra of pyrazoles has been carried out by Cativiela *et al.* <86G119, 89G41, 91G477>. In the first of these papers, the main absorption band (wavelength and wavenumber) of 30 *N*H-pyrazoles was examined. An additive model was proposed which accounted for most of the information available. In nanometers, the model is $\lambda_{\max} = \lambda_{\max}(0) + \sum \sum G_{ij} X_{ij}$, where $\lambda_{\max}(0)$ is the value for pyrazole itself (212.7 nm), G_{ij} is the contribution to the response of a substituent *i* at position *j* (*j* = 3, 4, 5), and X_{ij} represents the presence ($X_{ij} = 1$), or the absence ($X_{ij} = 0$) of the substituent *i* at position *j*. Due to the fact that the pyrazoles were unsubstituted on the nitrogen, tautomerism made positions 3 and 5 equivalent. Some representative values are: Br(3,5) = +3.2 nm, Br(4) = +5.9 nm, NO₂(4) = +61.8 nm, OH(4) = −1.5 nm. Some deviations from the additive model (for instance, 3,5-dimethyl-4-iodopyrazole, $\lambda_{\max}(\text{calc}) = 231.0$ nm, $\lambda_{\max}(\text{exp}) = 222.5$ nm) were assigned to steric effects. To complete the experimental values, the previously unknown 4-*t*-butylpyrazole was synthesized and its UV spectrum measured ($\lambda_{\max} = 218$ nm).

In the second paper <89G41> a set of 48 *N*-methylpyrazoles and 20 new *N*H-pyrazoles were measured. In this case, the *N*-methyl derivatives allow the study of positions 3 and 5 independently. For *N*-methylpyrazoles, $\lambda_{\max}(0) = 217.5$ nm. The most interesting conclusion concerns the *C*-phenyl substituents: the effects they produce on the main absorption band depend on their conformation (planar, twisted, perpendicular) but not on their position (3, 4, 5) on the pyrazole ring.

The last paper <91G477> deals more specifically with the problem of tautomerism of 3(5)-phenylpyrazole (**57**). By the use of UV spectroscopy, semiempirical calculations (CNDO/S//CNDO/2) and low temperature ¹³C NMR spectroscopy the tautomeric equilibrium (80% (**57a**), 20% (**57b**)) was determined. One of the most important conclusions of this work, as far as electronic spectra are concerned, is that the absorption of phenylpyrazoles is much more dependent on the conformation of the phenyl ring than on its position, 3, 4, or 5.



The 290 nm electronic band of indazole (**15a**) has been assigned to a π – π^* transition <92JST(155)307>. There is much interest in the fluorescence of 1,3,5-triaryl- Δ^2 -pyrazolines. The work of de Silva must be quoted in this respect: fluorescent pH indicators <89CC1054>, fluorescent PET sensors <90CC186>, fluorescent sensors for physiological levels of magnesium <94CC1213>, and even a molecular photoionic “and” gate <93NAT42>.

The definitive assignment of the photoelectron spectra (PES) of pyrazole <84CHEC-I(5)167> has been made using *ab initio* CI calculations <87CPH249>. Other PES studies include 4-methylene- Δ^1 -pyrazolines <90CB1161>.

3.01.3.9 Mass Spectrometry and Ion Cyclotron Resonance Studies

Van Thuijl has continued his studies of mass spectrometry of pyrazoles <84CHEC-I(5)167> determining the structure of $[\text{C}_3\text{H}_3\text{N}_2]^+$ ions formed from 1-nitropyrazole, 3(5)-bromopyrazole, and 4-bromopyrazole by collision-induced dissociation MS <84OMS(19)569>. Other MS studies of Δ^1 - and Δ^2 -trifluoromethylpyrazolines, and of 1-thiocarbamoyl- and 1-carbamoylpyrazolidines have been reported <92G397, 93JHC1641>.

Thanks to the work of Taft in California and Abboud in Madrid, the gas-phase basicity of many pyrazoles has been determined by ICR and in some cases, using Cooks' method, by mass spectrometry <84OMS(19)627>. Both methods afford basicities (termed thermodynamic vs. kinetic basicity) which have been compared in <91JOC179>.

The experimental proton affinity of 3(5)-methylpyrazole (**11**), 216.0 kcal mol⁻¹ is in agreement with those calculated (see Section 3.01.2.1) for tautomers 3-methyl (**11a**) 217.2 kcal mol⁻¹, and 5-methyl (**11b**) 217.6 kcal mol⁻¹ <89MI 301-01>.

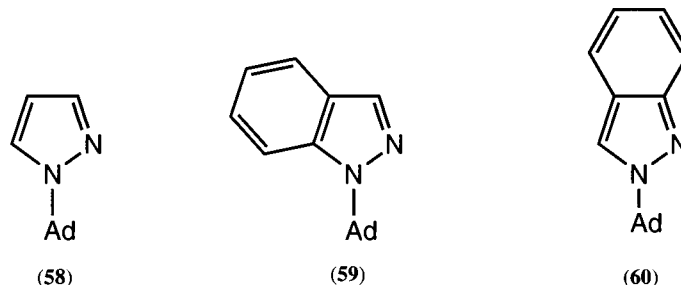
Other structural studies by ICR include basicity of methylpyrazoles (13 compounds) <90JA1303>; acid-base properties of trifluoromethylpyrazoles in the gas phase <91JOC3942>; the determination of the gas-phase proton affinities of 32 *N*-H and *N*-methyl pyrazoles and the analysis of these data by comparison with *ab initio* 6-31G calculations <92JOC3938>. The gas-phase basicities of eight pyrazoles substituted only at position 4 (R⁴ = H, NO₂, F, Cl, CO₂Et, CH₃, NH₂, 1-adamantyl) were measured and the experimental values discussed in two ways: (i) by comparing these values with AM1 calculated proton affinities; and (ii) within the framework of the Taft-Topsom analysis of substituent effects <95JCS(P2)1875>.

3.01.4 THERMODYNAMIC ASPECTS

3.01.4.1 Intermolecular Forces

The most significant contribution to this section comes from studies of partition coefficients made necessary by QSAR modeling.

The log *P* of 3-hydroxy-4-amino-5-trifluoromethylpyrazole has been determined <89JMC2116>. The log *P* values of 1-(1-adamantyl)pyrazole, 3.05 (**58**), 1-(1-adamantyl)indazole, 4.33 (**59**), and 2-(1-adamantyl)indazole, 3.68 (**60**) were determined by HPLC. From these values, the π value of the 1-adamantyl substituent was calculated: as an aromatic substituent $\pi_{Ad} = 3.49$ <87FES915>.



The π value of the pyrazol-1-yl substituent has been determined (−0.81, shake-flask; −0.77 HPLC) <92JPS577>. log *P* and $\pi_{pyrazole}$ (Hansch hydrophobic constant calculated on *C*-substituted pyrazole derivatives) have been calculated from 66 *N*-arylpyrazoles using mainly HPLC <94QSAR165>. It has been shown that $\pi_{pyrazole}$ is roughly 0.23 times $\pi_{benzene}$ plus a term representing the pyrazole position (3, 4, or 5).

3.01.4.2 Stability and Stabilization

3.01.4.2.1 Thermochemistry

The enthalpies of combustion, vapour pressures, enthalpies of sublimation, and enthalpies of formation ($\Delta_f H_m^\circ(g) = 42.9$ and 55.9 kcal mol⁻¹, respectively) of pyrazole and indazole have been measured <87MI 301-03>. The effect of *N*-methylation on acid-base properties of azoles, including the pyrazole/*N*-methylpyrazole pair, has been studied by calorimetry in water and in DMSO (enthalpies of solution, enthalpies of vaporization or sublimation, and enthalpies of solvation) <89JPO646>.

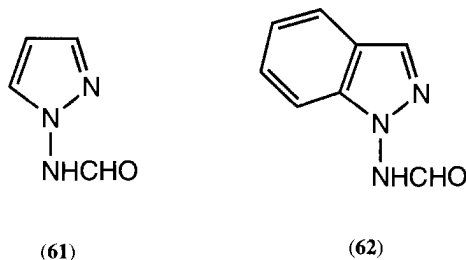
3.01.4.2.2 Aromaticity

Aromaticity, the property resulting from cyclic conjugation, is an important concept in organic chemistry. The fundamental work of Bird <85T1409> and Katritzky <89JA7> included information about pyrazole. Based on absolute hardness, or HOMO-LUMO gap, and on relative hardness, Zhou and Parr <89JA7371> have estimated the aromaticity of pyrazole and imidazole, the former being a little more aromatic ($\eta = 0.783$) than the latter ($\eta = 0.762$). The $^4J_{\text{Me}-\text{C}=\text{C}-\text{H}}$ coupling constants have been used to determine the aromaticity of 1,4-dimethylpyrazole (73%) <92JHC935>.

3.01.4.3 Conformation and Configuration

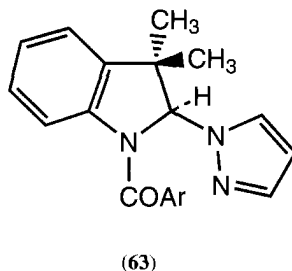
The conformation of *N*-heteroarylpyrazoles (for instance, compounds (22)–(24)) is governed by the possibility of having a hydrogen bond between an acidic hydrogen and the lone pair of a pyridine type nitrogen <89JHC733>. A conformational study of bis-(88), tris-(94), and tetrakis-pyrazolylmethane (98) was carried out using crystallography, NMR (Lanthanide Shift Reagents) and MM2 and MNDO calculations <89T7805>. The different interconversion paths were calculated and analyzed by analogy with polyarylmethanes.

The existence of *N*-formylaminoazoles (pyrazoles and indazoles) in the *Z* configuration <93JCS(P2)377> has been proved (x-ray structures) for *N*-(pyrazol-1-yl)formamide (61) and *N*-(indazol-1-yl)formamide (62); the rotation barriers about the amide bond are similar although a little lower than those of *N*-phenylformamide.



A combination of methods which include MM2 and MNDO calculations, NMR spectroscopy in the solid state (CPMAS) and in solution (^1H , ^{13}C , LSR, chiral solvents, and NOE experiments), DSC and x-ray powder diffraction, has been used to study the conformation of tris(pyrazol-1-yl)methanes (94) and ethanes <89T7805>. It has been shown that tris(3,5-dimethylpyrazol-1-yl)methane exists in two isolable isomers, the abb and the bbb (a or b depending on the orientation of the lone pair with regard to the substituent, H or CH_3 , on the sp^3 carbon), whose interconversion by melting, crystallization, and sublimation has been studied.

In a study of diastereomeric atropisomers, compound (63) was prepared by reaction of 2-hydroxyindoline with pyrazole in the presence of boron trifluoride diethyl ether <92CPB2255>.



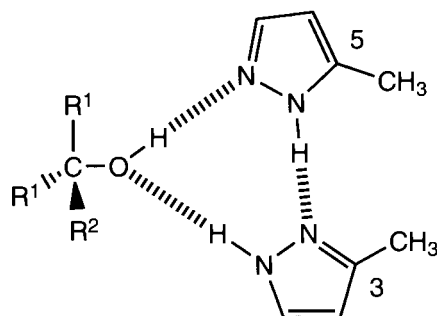
3.01.4.4 Tautomerism

3.01.4.4.1 Annular tautomerism

The discovery that 3,5-dimethylpyrazole shows prototropic tautomerism in the solid state (crystallography and CPMAS NMR) has been one of the most important discoveries since the mid-

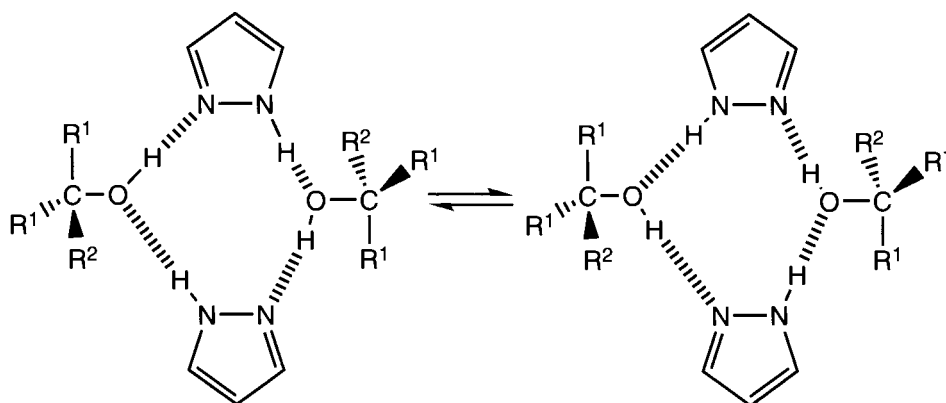
1980s <85JA5290>. Afterwards, other NH-pyrazoles were discovered which share this property: 3,5-diphenyl (**17**) and 3,5-diphenyl-4-bromopyrazole <92JA9657>. A theoretical study (INDO, STO-3G) has been published on pyrazole and its nonaromatic tautomers (pyrazolenines and isopyrazoles <86BSF429>. An important conclusion of this study is that 1,2-proton shift is forbidden, thus, annular tautomerism of pyrazoles (including in the gas phase) always implies other entities (water, alcohols, formic acid, benzoic acid, other pyrazole molecules in the form of cyclic dimers, trimers, and tetramers, etc.). Golubev's contribution <87MI 301-02, 90MI 301-01> to the effect of carboxylic acids on the proton transfer in pyrazoles is essential for the understanding of these processes.

One of the rare NH-pyrazoles which is liquid at room temperature is 3(5)-methylpyrazole (**11**). The pure liquid is probably a 50 : 50 mixture of both tautomers in solution <92JOC3938> (the same conclusion is true for 3(5),4-dimethylpyrazole <90JA1303>). The inclusion of the compound in a host affords a 1 : 1 : 1 complex of the host with both tautomers present in the crystal. This has allowed the determination of the x-ray structure of (**11a**) and (**11b**) simultaneously <88CL1061>. Theoretical calculations at the 6-31G**//6-31G level (see Section 3.01.2.1) on 3(5)-methylpyrazole (**11**) lead to the conclusion that 3-methyl tautomer (**11a**) is slightly more stable than 5-methyl tautomer (**11b**) by 0.4 kcal mol⁻¹ <89MI 301-01>. Moreover, the 3-methyl tautomer appears to be more acidic and more basic than the 5-methyl one.



(Host-11a-11b)

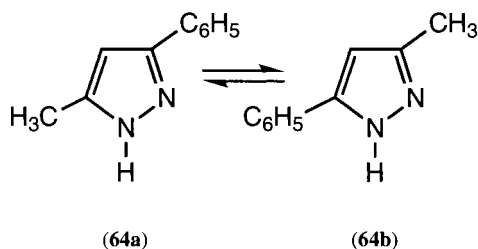
Two related compounds were prepared afterwards <93CC1139> and one of them, a 1 : 1 complex of the host and pyrazole (**7**) crystallizes in the form of a tetramer which presents proton transfer in the solid state involving nitrogen and oxygen atoms. The system has been studied by a combination of x-ray crystallography and dynamic high resolution solid state ¹³C/¹⁵N NMR spectroscopy.



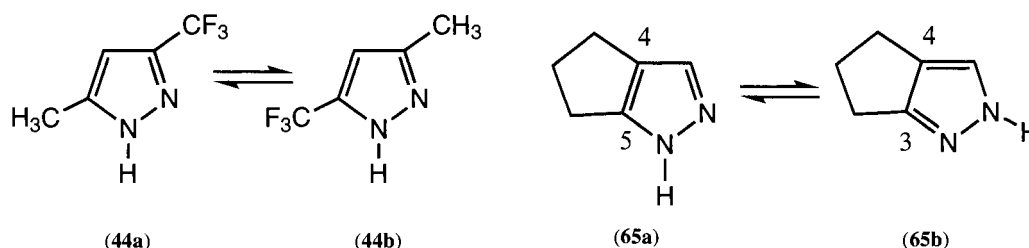
(Host-7)₂

In the gas phase 1*H*-indazole (**15a**) is 4.7 kcal mol⁻¹ more stable than 2*H*-indazole (**15b**), while in water the difference is reduced to 2.2 kcal mol⁻¹, thus, water more effectively stabilizes the 2*H*-tautomer because of the high dipole moment <88JA4105, 94JPC10606> (see <92JST(155)1> for the existence of (**15a**) in the gas phase). The observation that 2-indazolylpropanamides isomerize into 1-indazolylpropanamides (by a retro-Michael addition on acrylamide) is consistent with the greater stability of 1*H*-indazole <88JHC225>.

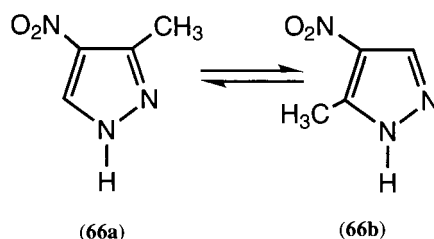
The use of low temperature ^1H NMR (see Section 3.01.3.3.1) to determine K_T deserves special mention. This is the simplest and most straightforward method which only requires that the proton transfer be slow enough to observe separate signals for both tautomers, and that the equilibrium is not shifted too much towards one of the tautomers (about 5% of the minor one seems the limit). Using this method $\langle 91\text{G}477 \rangle$, the case of 3(5)-phenylpyrazole (**57**) was studied; at -20°C in a 50:50 mixture of HMPT and $[\text{D}_6]\text{acetone}$, there is a mixture of 80% of 3-phenyl tautomer (**57a**) and 20% of 5-phenyl tautomer (**57b**) ($\Delta G_{253} = 0.8 \text{ kcal mol}^{-1}$). The case of 3(5)-phenyl-5(3)-methylpyrazole (**64**) was studied by ^1H and ^{15}N NMR spectroscopy (see Sections 3.01.3.3.1 and 3.01.3.6.1) $\langle 92\text{JCS(P}2)1737 \rangle$.



The tautomerism between 3-trifluoromethyl-5-methylpyrazole (**44a**) and 3-methyl-5-trifluoromethylpyrazole (**44b**) has been discussed in detail $\langle 83\text{IC}774 \rangle$; the authors favor tautomer (**44a**). In the case of 3(5),4-polymethylenepyrazoles $\langle 91\text{JHC}647 \rangle$, the position of the tautomeric equilibrium is directed by the Mills–Nixon effect; thus, the 3,4-trimethylene tautomer (**65b**) is much more stable than the 4,5-one (**65a**) ($\Delta G = 1.3 \text{ kcal mol}^{-1}$) $\langle 94\text{NJC}269 \rangle$ (the x-ray structure of its hydrochloride has been determined $\langle 93\text{MI} 301-02 \rangle$). The fact that campho[c]pyrazole (**221**) (see Section 3.01.10.1.2(ii)) exists in the solid state and in solution as the 2*H*-tautomer is another consequence of the Mills–Nixon effect $\langle 93\text{AX(C)}724 \rangle$.



The first example of desmotropy (two tautomers that crystallize in two different crystals) in azoles has been found by x-ray crystallography: it concerns 3-methyl-4-nitropyrazole (**66a**) and its tautomer, 5-methyl-4-nitropyrazole (**66b**) $\langle 94\text{CC}1143 \rangle$.



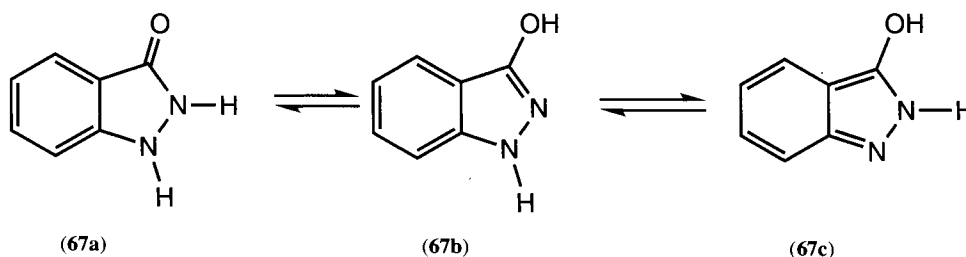
The tautomerism of 3,5-bis(4-methylpyrazol-1-yl)-4-methylpyrazole (**106**; $\text{R} = \text{CH}_3$) (see Section 3.01.5.3.5(v)) involves the simultaneous rotation of the two lateral rings and has a value of 12 kcal mol^{-1} (in methanol), almost the same as 3,5-dimethyl-4-chloropyrazole and 3,5-dimethyl-4-nitropyrazole (**16**) $\langle 93\text{CJC}1443 \rangle$.

3.01.4.4.2 Substituent tautomerism

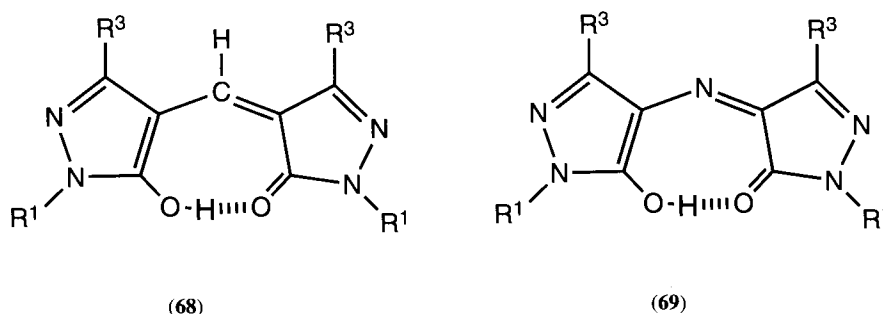
Although much work is still devoted to tautomerism of pyrazole derivatives, the methodology and the main conclusions remain unaltered. As an example of study of the tautomerism of pyrazolinones using ^{13}C NMR spectroscopy see $\langle 91\text{JHC}641 \rangle$ for the case of pyrazolone T. Katritzky

<91H(32)329> has provided a rationale for this type of tautomerism and has included solvent effects in the theoretical calculations <90JCS(P2)195> (see also <90ZN(A)1328>).

The structure of indazolinone and some of its derivatives was determined by the combined use of crystallography, ^{13}C CPMAS NMR, and ^{15}N NMR <86JCS(P2)1677>. It was concluded that indazolinone exists as such (**67a**) in the solid state but only as a minor isomer (15%) in DMSO solution, where the 3-hydroxy-1*H*-indazole tautomer (**67b**) predominates (85%). The 3-hydroxy-2*H*-indazole tautomer (**67c**) has never been observed. The equilibrium between 2-hydroxy-3-methylindazole and 1*H*-3-methylindazole-2-oxide has been studied in DMSO, methanol, and trifluoromethanol by ^{13}C and ^{15}N NMR spectroscopy <87MRC721>. The position of the equilibrium was found to be dependent on the acidity of the solvent, the hydroxy form being predominant in weakly acidic media.



The old problem of the autotropic tautomerism (both tautomers are identical) of rubazotic acid derivatives (**68**) and (**69**) has been studied by NMR in solution and in the solid state <93JCS(P2)1597>.



Another example of the very rare case where two pyrazolinone tautomers are present in the same unit cell <84CHEC-1(5)167> has been described: 1*H*-3-hydroxy-4-*R*-5-methylpyrazole (*OH* tautomer)/1,2-*H*₂-3-methyl-4-*R*-Δ³-pyrazolin-5-one (*NH* tautomer) <94MI 301-04>.

The long-standing problem of the very broad signals present when the ^1H NMR spectra of 1-aryl-3-amino-Δ²-pyrazolines were recorded <84CHEC-1(5)167> has been clarified <95JCS(P2)1875>: the broadening is not due to an amine/imine tautomerism but to a slow equilibrium between the neutral form and the protonated one (in this case, on N_2). Even minute quantities of acid (for instance, DCI present in CDCl_3) suffice.

3.01.5 REACTIVITY OF FULLY CONJUGATED RINGS

3.01.5.1 General Survey of Reactivity

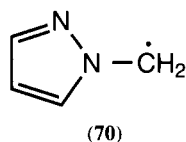
Since the mid-1980s, the most significant aspect regarding pyrazoles reactivity concerns the publication of a series of papers dealing with gas phase studies and the enormous increase in the use of pyrazoles as ligands in metallo-organic and coordination chemistry.

3.01.5.2 Thermal and Photochemical Reactions

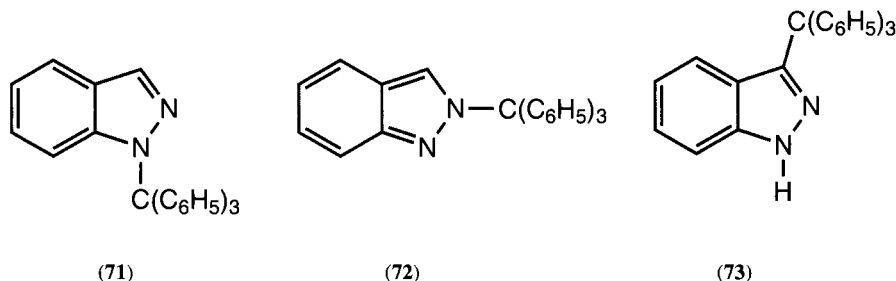
The main difference with regard to CHEC-I is a series of papers by Pérez and Yranzo on the flash vacuum pyrolysis (FVP) of pyrazole derivatives <85BSF473, 86BSF129, 86BSF473, 87MI 301-04, 88MI 301-01, 89JPO225, 91BSF592, 93JFC(63)271>.

Flash vacuum pyrolysis of bis- and tris-(pyrazol-1-yl)methane follows a radical mechanism

<88T6429>. Pyrolysis of trispyrazolymethane (**94**) affords bispyrazolymethane (**88**; R = H) and, probably, *N,N'*-bipyrazole (**14**) while pyrolysis of bispyrazolymethane (**88**; R = H) affords NH-pyrazole (**7**), trispyrazolymethane (**94**), 1-methylpyrazole and, at higher temperatures, pyrimidine. To explain the formation of pyrimidine a radical mechanism involving the rearrangement of radical (**70**) was proposed. Trichloromethyl radicals react with 3(5)-methyl-pyrazole to afford 4-methylpyrimidine and its 2-chloro derivative <89PJS377>.

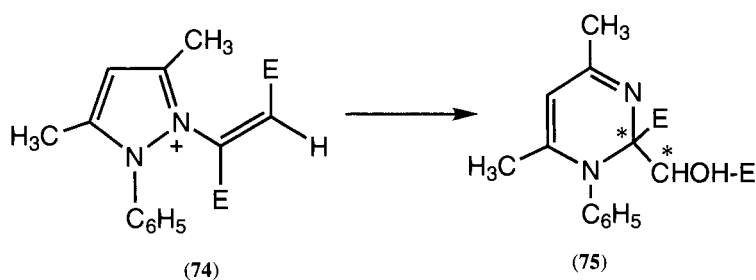


Flash vacuum pyrolysis of 1- (**71**), 2- (**72**) and 3-tritylindazole (**73**) was carried out at 300°C and 400°C. The experimental results show that (**73**) isomerizes to (**71**) and (**72**); (**72**) isomerizes to (**71**) at 300°C, and (**71**) remains unchanged at 300°C and at 400°C gives (**72**) and by-products <89BSB349>. A reaction profile consistent with these observations was proposed which involves indazole aromatic and nonaromatic (3*H*) tautomers. Under FVP conditions *N*-adamantylindazoles (**59**) and (**60**) interconverted mutually <91BSF592>.



A theoretical and experimental study of the FVP of trifluoromethyl-pyrazoles has been published <93JFC(63)271>: the reaction affords fluorinated alkenes and alkynes. Flash vacuum pyrolysis of 1-(alkyn-2'-oyl)-3-methylpyrazoles forms pyrazolo[1,5-*a*]pyridin-5-ols <94AJC991>.

Treatment of 2-vinylpyrazolium salts (**74**) in basic medium yields the 1,2-dihydropyrimidine (**75**) <85TL3869, 86CCA153> (see Section 3.01.10).



The photophysics (fluorescence and phosphorescence) of hydroquinones (**114**)–(**116**) was reported <90JA747> by Catalán and Claramunt. In a related study, they described a new family of UV stabilizers, the 3- and 5-(2'-hydroxyphenyl)pyrazoles <92JA5039>. A series of papers by Pavlik <91JOC6313, 93JA7645> reappraised the problem of the phototransposition of pyrazoles into imidazoles and *N*-methylenaminonitriles <84CHEC-I(5)167>.

3.01.5.3 Electrophilic Attack at Nitrogen

3.01.5.3.1 Introduction

As indicated in CHEC-I <84CHEC-I(5)167>, electrophilic attack at nitrogen is the most characteristic of the whole pyrazole reactivity. Several protecting groups have been used in pyrazole chemistry: *p*-methoxybenzyl <88BSB573>, pyrrolidinomethyl <89PHC1>, [2-(trimethylsilyl)ethoxy]methyl <92H(34)303>.

3.01.5.3.2 Reaction sequence

Since in general two isomers are obtained from 3(5)-substituted pyrazoles and from indazoles, some effort has been directed in trying to obtain regiospecific reactions; for instance, Seela <91HCA315> has discussed the problem of the regioisomerism in the glycosylation of indazole and 4-nitroindazole, and Beck has proposed the use of tertiary carbocations to regioselectively alkylate pyrazoles <89JHC3>. In the case of pyrazolinones, after protecting the OH group in the form of a tetrahydropyranyl acetal, selective *N*-alkylation has been achieved <93JHC1097>. It is possible to obtain 1-methyl-5-nitropyrazole regiospecifically by methylation of 3(5)-nitropyrazole if the reaction is monitored by polarography <94H(37)2009>.

3.01.5.3.3 Effect of substituents

These effects modify the reactivity of pyrazoles and indazoles and several examples are found in the next sections.

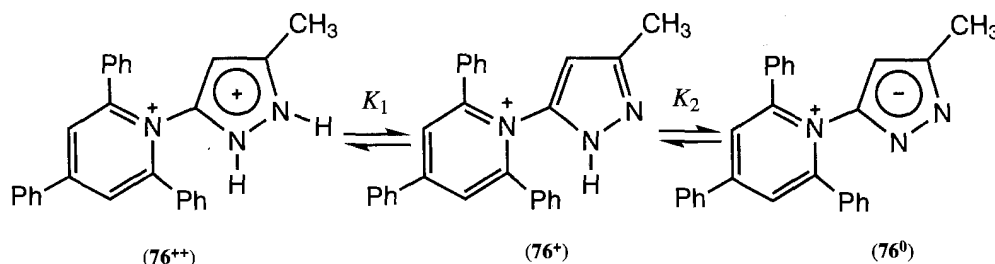
3.01.5.3.4 Proton acids on neutral compounds

Five-membered rings containing nitrogen or oxygen show linear relationships between their ionization potential and their basicity: for pyrazole itself, $LP_N = 10.7$ eV and $pK_a = 2.54$ <84JHC269>. There is also a relationship between proton affinity and the charge on N_2 <84JST(108)161>. It has been established empirically that the acidity and the basicity of azoles are linearly related: for pyrazoles $pK_a(\text{acid}) = 0.938$, $pK_a(\text{basic}) = 11.48$ <85BSF30>. Moreover, the oxidation potentials of azole pentacyanoferrate(II) complexes are linearly related for pyrazoles (11 compounds) <90CJC958>.

The acidity and basicity in the gas phase and in aqueous solution of pyrazole (7), 1-methylpyrazole, indazole, 1-methyl-, and 2-methylindazole have been measured <88JA4105>. From these data it is possible to determine the annelation effect on going from an azole to the corresponding benzazole on the gas phase acidity (6–8 kcal mol⁻¹ increase) and on the gas phase basicity (2 kcal mol⁻¹ increase). These intrinsic differences explain why in aqueous solution the benzazoles are more acidic and less basic than the corresponding azoles <88JA4105>. The effect of solvation by five water molecules has been calculated (fully optimized INDO geometries) for a series of azoles including pyrazole itself (neutral molecule, anion, and cation): only the differences in energy between solvated molecules are linearly related to the aqueous pK_a s <88JST(166)415>.

The pyrazole/pyridine-*N*-oxide (which measures the HB acidity of the pyrazole NH) and the pyrazole/3,4-dinitrophenol (which measures the HB basicity of pyrazole N_2 lone pair) equilibrium constants were determined for several NH-pyrazoles in cyclohexane by UV spectroscopy <87CR(C)567>. The correlation between these equilibrium constants and the thermodynamic pK_a s is excellent, allowing the indirect determination of pK_a s of very lipophilic pyrazoles: pK_a of 1-(1-adamantyl)pyrazole = 3.12. The equilibrium constants, K_{pyO} (in dm³ mol⁻¹) pertaining to equilibrium ($AH + OPy \rightleftharpoons AH \cdots OPy$, $AH = NH$ -pyrazole, $OPy = \text{pyridine } N\text{-oxide}$) have been measured for pyrazole, 3(5)-methylpyrazole, 4-methylpyrazole, 3,5-dimethylpyrazole, 3,4,5-trimethylpyrazole, 4-bromopyrazole, and 3,5-dimethyl-4-bromopyrazole <90JOC2230>. These values allow the determination of α^H_2 values (HB acidity parameter): it shows that pyrazole is as acidic as trifluoroethanol as far as HB acidity is concerned.

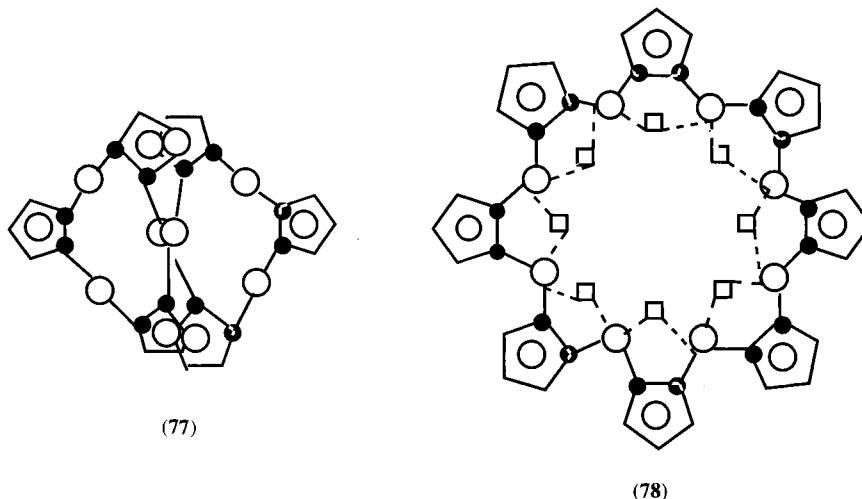
The pK_a s corresponding to the mono- and diprotonation of betaines of the azolate–triphenylpyridinium class have been determined. In the case of the 3-methylpyrazole derivative (**76**⁺), the pK_a values corresponding to both equilibria are $pK_a(1) = -2.50$ and $pK_a(2) = 11.42$ <87BSF604>. Assuming a Hammett relationship $\Delta pK_a = a + r\sigma_m$, these pK_a s indicate that the triphenylpyridinium substituent has $\sigma_m = 0.67 \pm 0.12$.



3.01.5.3.5 Metal ions

(i) Ionic compounds of electropositive metals

Since the choice is difficult due to the huge amount of examples, the selection is based either on aesthetic criteria (77) and (78), or on important applications. In a review, "Synthetic Models for Binuclear Copper Proteins," Sorrell reports his previous results with pyrazole ligands which mimics histidyl-imidazole <89T3>.



Fackler has described $[\text{Au}_3(\text{dppz})_3]$ and $[\text{Au}_6(\text{dppz})_6]$ (77) ($\text{dppz} = (17)$) <87CC737>, while Italian inorganic chemists have described $[\text{Cu}_8(\text{dmpz})_8(\text{OH})_8]$ (78) ($\text{dmpz} = (19)$) <90CC1021>. The hexamer has an x-ray structure like an eight while the octamer has a toroidal shape (black dots: nitrogen atoms; white dots: metals; white squares: OH groups).

Gray has used pyrazole-iridium complexes for his studies of photophysics and photochemistry <84JA3027, 86JA2263>, while Mann <86JA1779> uses these complexes for electrochemical studies. Lalor <86JCS(D)103> is one of the few to report the use of pyrazole-4-diazonium and 3-pyrazolin-5-one-4-diazonium ligands (see Section 3.01.7.4.5). Pyrazole complexes of yttrium, lutetium <91OM215>, and osmium <94IC787> have been reported, as well as the structure of a hydroperoxo complex of iridium and rhodium <94CC575>.

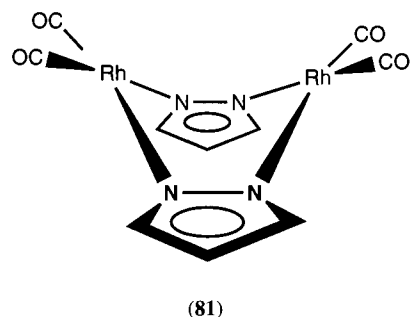
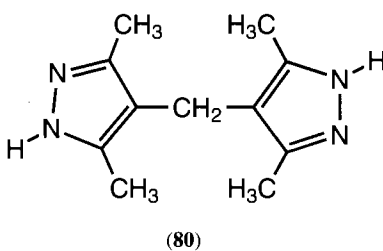
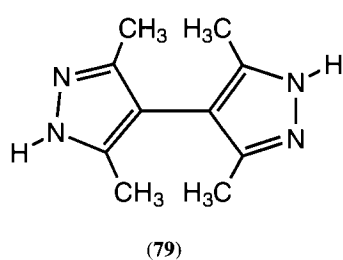
(ii) Simple complexes

Cobalt(II) and nickel(II) complexes of bipyrazoles, like (79), and bispyrazoles, like (80), are either dimeric or polymeric <84ICA99>. The x-ray structure and ^{13}C CPMAS NMR spectra of (79) and (80) were reported <94SA(A)727>. Ligands similar to (80) have also been used to prepare rhodium(I) complexes <84JOM(276)79>.

Rhodium(I) complexes of pyrazole, such as (81) have been studied by ^1H and ^{13}C NMR: the boat conformation of the metallocycle was thus established <84JCPB251>. Ruthenium(II) complexes of pyrazole, 3-methylpyrazole, 3,5-dimethylpyrazole, and indazole were described (x-ray crystallography and a careful ^1H and ^{13}C NMR study) in <90JCS(D)1463>.

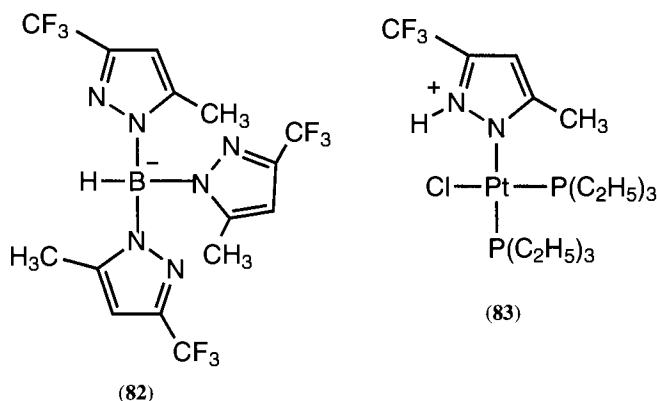
One of the most fascinating aspects of pyrazole complexes is their fluxional behavior. Among these compounds are: tris(pyrazolyl)borate complexes of yttrium <88IC3923>; copper(I)-pyrazole complexes like $[\text{Cu}(\text{pzH})_2(\text{CO})\text{Cl}]$ <89JOM(363)409>; dinuclear ruthenium(I) and osmium(I) complexes containing poly(pyrazolyl)borato ligands <90JCS(D)2991>; chromium, molybdenum, and tungsten derivatives of pyrazolylgallato compounds <90CJC109>, and bis[hydrotris(pyrazolyl)borate] thorium(IV) aryloxy derivatives <92POL909>.

(Pentamethylcyclopentadienyl)iridium complexes ($\text{pzH} = (7)$ and $\text{dmpzH} = (19)$) $[(\text{C}_5\text{Me}_5)\text{Ir}(\text{pz})_2(\text{Hpz})]$ and $[(\text{C}_5\text{Me}_5)\text{Ir}(\text{dmpz})_2(\text{Hdmpz})]$ show prototropism in solution depending on the substituents on the pyrazole rings <86AG(E)1114>. The dynamic properties of the complex $[\eta^6\text{-p-}$



cymene)Ru(μ -pz)₃Ag(PPh₃)] were used to determine the free activation energy (11 kcal mol⁻¹) for the breaking of the ³¹P—¹⁰⁷(¹⁰⁹)Ag bond <94JOM(470)271>.

Several trifluoromethylpyrazoles, for instance 3(5)-trifluoromethyl-5(3)-methylpyrazole (**44**) were used to prepare platinum complexes and the x-ray structure of the resulting complex reported <83IC774>. The ligand tris[3-trifluoromethyl-5-methyl(pyrazol-1-yl)]borate (**82**) yields a hydridovinyl iridium complex more stable than its η^2 -ethylene isomer <89JA5480>. The x-ray structure of the related platinum complex (**83**) has been described <83IC774>.



The dynamic behavior of heterobimetallic compounds [(η^5 -C₅Me₅)Ir(pz)₃Ag(PPh₃)] (**84**), [(η^5 -C₅Me₅)Ir(μ -pz)₃{Ag(PPh₃)₂}BF₄] (**85**), [(η^5 -C₅Me₅)Ir(pz)₂PPh₃] (**86**), and [(η^5 -C₅Me₅)Ir(PPh₃)(μ -pz)₂Ag(PPh₃)]BF₄ (**87**) has been studied by multinuclear (¹H, ¹³C, ¹⁵N, ³¹P, and ¹⁰⁹Ag) NMR <94IC2196>. The results demonstrate that argentotropism accounts for the observed spectra of compound (**84**) ($\Delta H^\ddagger = 8.3$ kcal mol⁻¹, $\Delta S^\ddagger = -13$ e.u.), and (**85**) ($\Delta H^\ddagger = 7.6$ kcal mol⁻¹, $\Delta S^\ddagger = -20$ e.u.); in the case of compound (**86**), the dynamic behavior is due to a slow rotation about the P—Ir bond and for compound (**87**) the dynamic behavior corresponds to a flipping of the central heteroring Ir(N)₄Ag. Several new heteronuclear coupling constants have been determined, some of them (such as ¹J(³¹P—¹⁰⁷(¹⁰⁹)Ag) being related to the structure and dynamical properties of the complex.

(iii) Polypyrazolylborates

The extraordinary success of polypyrazolylborate ligands (scorpionates) <93CRV943> was summarized with authority by their discoverer, Trofimenko. The bibliography is complete until 1992 including many references of 1993 as well as some unpublished results. In the present work, references already reported by Trofimenko may be mentioned, the main effort being devoted to new publications.

Trofimenko's review describes essentially the family of hydrotris(pyrazol-1-yl)borates with different substituents on the pyrazole ring and explores systematically their coordination chemistry (for crystallographic structure and NMR properties of the ligands see <90ICA195> and for their

behavior in FAB-MS see <91RCM113, 91RCM469>). In Table 3 the new results following Trofimenko's classification are summarized.

Table 3 Coordination chemistry of polypyrazolylborates.

Group	Metal	Ligand ^a	Content	Ref.
2	Be, Mg	Tp	Ion size discrimination	93JA4128 ^b
5	Nb	Tp*	α -Agostic interaction	94OM410
6	Mo	Tp, Tp*	Electron and proton transfer	93JA5559
6	W	Tp*	[Tp*W(CO) ₂ (S- <i>p</i> -C ₆ H ₄ NO ₂)]	93IC5437
6	W	Tp*	¹⁸³ W— ¹ H correlation	93MRC58
6	W	Tp*	¹⁸³ W— ¹ H correlation	94MRC415 ^c
8	Fe	Tp	Diiiron(III) proteins	94IC636
8	Ru	Tp, Tp*	Dihydrogen complex	93CC465
8	Ru	Tp*, Tp ^{vi}	Dihydrogen complexes	94JA2635
9	Co	Tp ⁱⁱⁱ	Inverse recrystallization	94IC2306
9	Rh	Tp*	Polyhydrido complex	90AG(E)548 ^d
9	Ir	Tp*	Dinitrogen complex	94JA791
10	Pd	Tp	[Pd ₂ {Tp} ₂ (μ -RNC) ₂]	94IC32
10	Pd	Tp	[<i>fac</i> -{PdMe ₃ (Tp)}]	94JOM(471)8
11	Cu	Tp ^{iv}	[Cu(SCPh ₃)Tp ^{iv}]	94CC623
11	Cu	Tp ^{iv}	Blue copper proteins model	94JA2585
12	Zn	Tp ^{iv}	Carbonic anhydrase	93JA4690
12	Zn	Tp ^v	Enzyme model activity	94CC135
12	Cd	Tp*	[CdTp* ₂]	93POL1193
14	Sn	Tp ⁱⁱ	[PhCl ₂ Sn(Tp ⁱⁱ)]	92JOM(440)27
Actinides	U	Tp*	[U ₁₂ {O(CH ₂) ₄ l}{Tp*}]	93JOM(463)103
Actinides	U	Tp*	U ^{III} and U ^{IV}	94OM654

^aTp = HB(pz)₃; Tp* = HB(3,5-Me₂pz)₃; Tpⁱⁱ = HB(3-Mepz)₃; Tpⁱⁱⁱ = HB(3-Prⁱ-5-Mepz)₃; Tp^{iv} = HB(3,5-Prⁱ₂pz)₃; Tp^v = HB(3-*p*-Prⁱphenyl-5-Mepz)₃; Tp^{vi} = HB(3-Prⁱ-4-Brpz)₃. ^bQuoted in <93CRV943> as ref. 435 (in press). ^cSolution and solid-state structural chemistry of tungsten pyrazolylborate π -allyl complexes (2D ¹⁸³W and ¹H NOESY NMR studies). ^dQuoted in <93CRV943> as ref. 309 (in press).

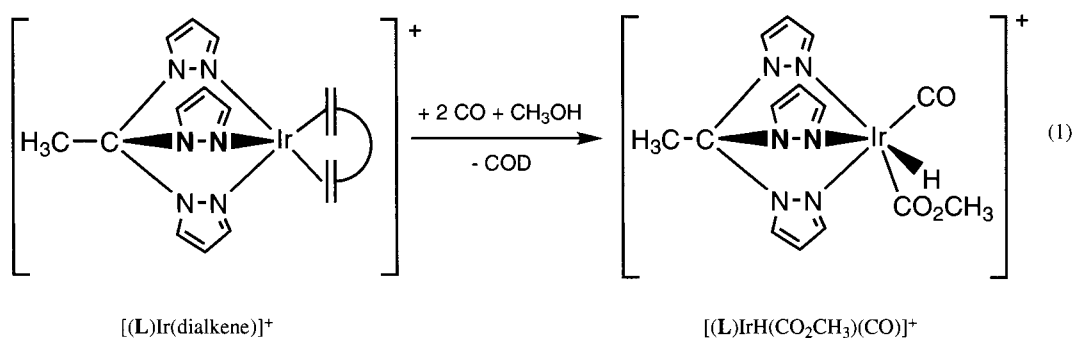
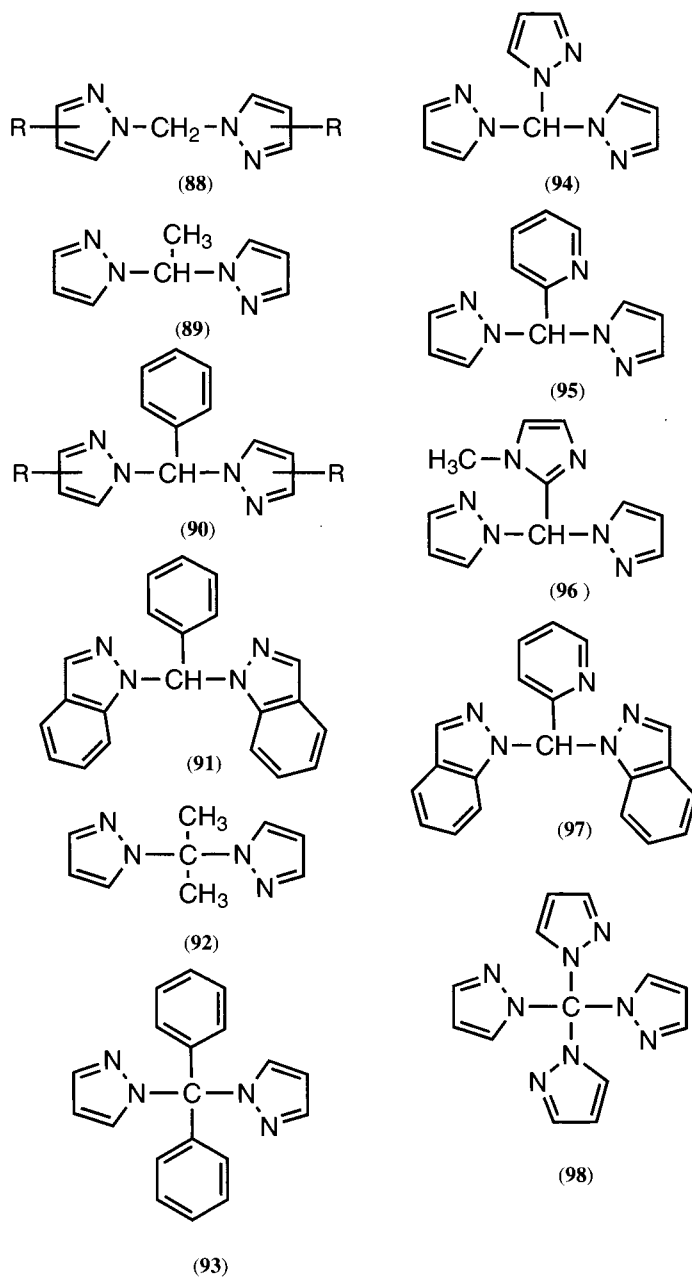
Amongst the publications reported in Table 3, two are worth a brief comment. First of all, the very important field of hydrogen-hydrido complexes has used the stabilization provided by scorpionate ligands to isolate and study these compounds <90AG(E)548, 93CC465, 94JA2635>. Second, thermally stable dinitrogen complexes have been isolated during the study of activation of benzene molecules <94JA791>.

(iv) Polypyrazolylmethanes and ethanes

The success of polypyrazolylborates prompted the development of the coordination chemistry of polyazolylmethanes, the neutral counterpart of anionic borates <86JCS(D)645>. This interest resulted in the preparation of a large family of ligands whose principal representatives are shown below (88)–(98) (for spectroscopic studies of the ligands themselves see <92G341>).

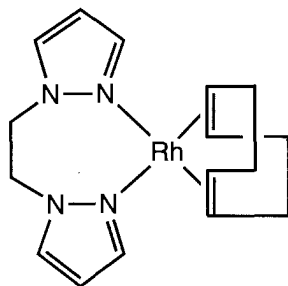
Ligand (94) is the most studied because it corresponds to the popular [HB(pz)₃][−]. It has been used to prepare *aqua* complexes of Ru^{II} <88IC514>, 14 Rh^I and Ir^I complexes <88JOM(344)93>, and a series of isomorphous complexes of Co, Ni, Cu, and Zn <93JCS(D)509>. Aluminum complexes of the type (94)Al(CH₃)₃ have been identified by ¹H NMR spectroscopy <90POL265>. The crystal structure of [RuCl(cod)(94)]Cl·EtOH has been determined <93JCS(D)1935>. Ligands related to (88) (with different R substituents) have been used to prepare cyclopalladated derivatives <89JOM(363)393, 90JOM(385)429>. (For related complexes with platinum(II) see <86ICAL39>). This last ligand has been reviewed, as a nitrogen donor, in its organometallic chemistry related to homogeneous catalysis <94AG(E)497> and has been used, together with (90), to prepare diamagnetic and paramagnetic Mo and W complexes <90OM669>. A derivative of (88) with azacrowns ethers at positions 5 of the pyrazole rings shows negative allosteric co-operation of Zn^{II} <94TL1295>.

Ligand (94) or its *C*-methyl derivative [tris(pyrazol-1-yl)ethane] (represented by L) affords iridium complexes which react with carbon monoxide and methanol to yield alkoxycarbonyl derivatives [(L)IrH(CO₂Me)(CO)]⁺ (Equation (1)) <89JOM(366)245>. This constitutes an interesting example of alcohol activation.



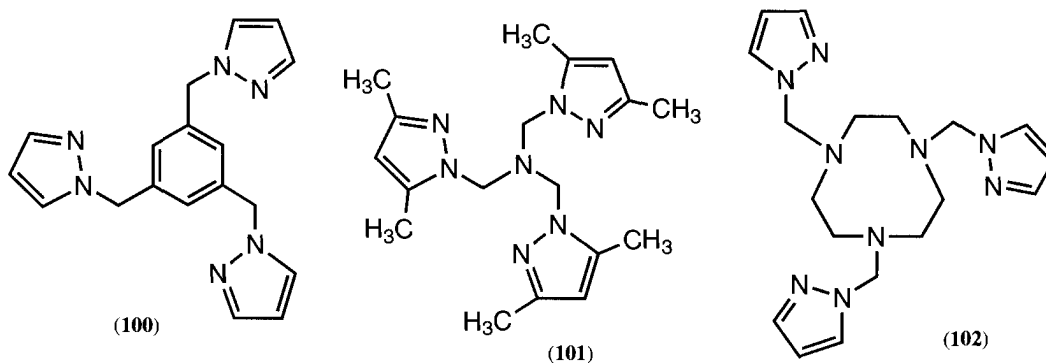
Indazole derivatives (**91**) and (**97**) <93JOM(450)237, 94OM289> allowed the comparison of the effect of benzo condensation on the properties of ligands (**90**) and (**95**) <90OM669, 90JOM(385)417>. Other examples of the ligands above reported are: (**89**) <89JOM(372)311>, (**92**) (x-ray structure of $\{(\mathbf{92})_2\text{Ag}\}\text{ClO}_4$), <90ICA199>, (**93**) (η^2 -arene complexes of molybdenum) <93JOM(460)203>, (**96**) and (**98**) (palladium(II) derivatives) <90JOM(385)417>.

The 1,2-bis(pyrazol-1-yl)ethanes, for instance (**99**) have been much less studied and the results published show that they are less interesting ligands <88JHC771, 89BSF472, 91RRC629, 94POL1553>. Complexes of (**99**) with Co^{II} , Ni^{II} , and Zn^{II} have been prepared and identified (the x-ray structure of $(\mathbf{99})\text{Ni}(\text{NO}_3)_2$ was determined), the complex with Rh^{II} , $[(\mathbf{99})\text{Rh}(\text{COD})]^+ \text{ClO}_4^-$, was characterized as exo-bidentated by ^1H and ^{13}C NMR in solution, and ^{13}C CPMAS NMR in the solid state <89BSF472>.



$[(\mathbf{99})\text{Rh}(\text{COD})]^+$

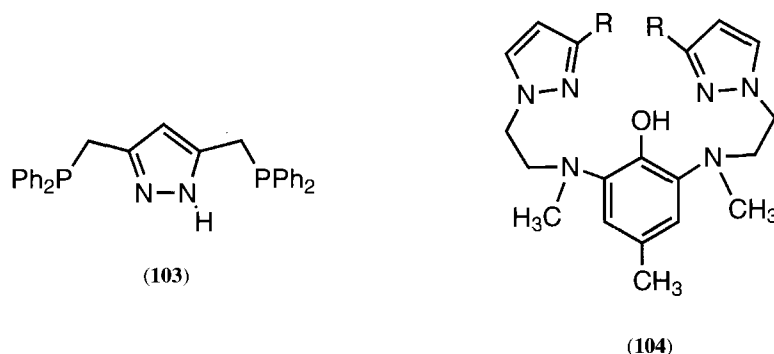
A characteristic feature of the progress made in the field of coordination chemistry of pyrazole derivatives is the use of more elaborate ligands such as (**100**)–(**102**). Copper(II) and cobalt(II) complexes have been prepared from 1,3,5-tris(pyrazol-1-ylmethyl)benzene (**100** = **L***), for instance $[\text{Cu}_2\text{CoL}^*\text{Cl}_6(\text{H}_2\text{O})_2]_n$ <93JCS(D)687>. Tripodal tetradentate ligand, tris(3,5-dimethylpyrazol-1-yl)methylamine (**101**) was prepared by one of the most creative groups in this field, that of Driessen and Reedijk <85IC2919> and used to prepare cobalt(II) complexes. The pyrazole-functionalized macrocyclic ligands, 1,4,7-tris(pyrazol-1-ylmethyl)-1,4,7-triazacyclononane (**102**) and the corresponding tetramer, form stable complexes with alkali-metal cations <91JCS(D)331>. A ligand related to (**101**) was used by Nolte <94JA5667> to prepare a novel metallohost which can be used for shape-selective oxidation of benzylic alcohols.



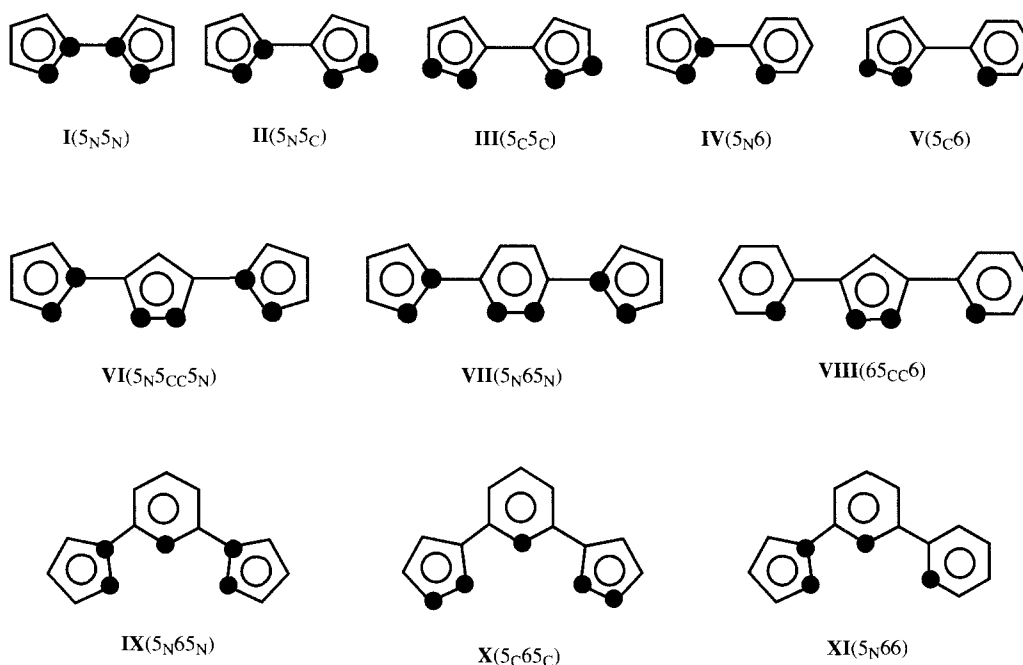
Another possibility are ligands which combine the properties of pyrazoles with those of other well known ligands, for instance, with triphenylphosphines (**103**) (this planar quadridentate ligand affords complexes with Pd^{II} , Rh^{I} , and Ir^{I} <85IC2334>) or phenols (**104**) <87IC1755>. Ligands similar to (**104**) but with two arms of the type $\text{CH}_2\text{—N}(\text{CH}_2\text{pz})_2$ or $\text{CH}_2\text{—N}(\text{CH}_2\text{dmpz})_2$ have been prepared <92H(34)1227>.

(v) Chelate complexes

Regarding chelating pyrazole ligands only compounds in which two or three heteroaromatic rings (one of them, at least, being a pyrazole) are directly linked are considered. The N atoms bearing the



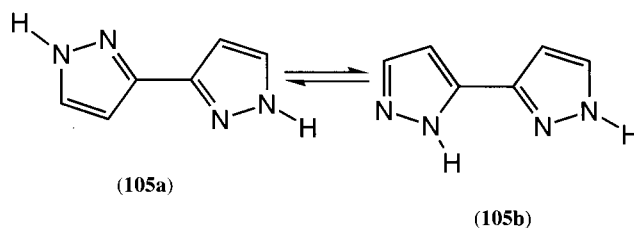
lone pairs (pyridine or pyridine-like) must be at positions α, α' . The general situations depicted in Scheme 1 can be found (black dots represents N atoms, 5_N corresponds to a pyrazole ring linked by the N_1 nitrogen, and 5_C to a pyrazole ring linked by C_3 or C_5 ; the six-membered ring is always linked by the carbon).



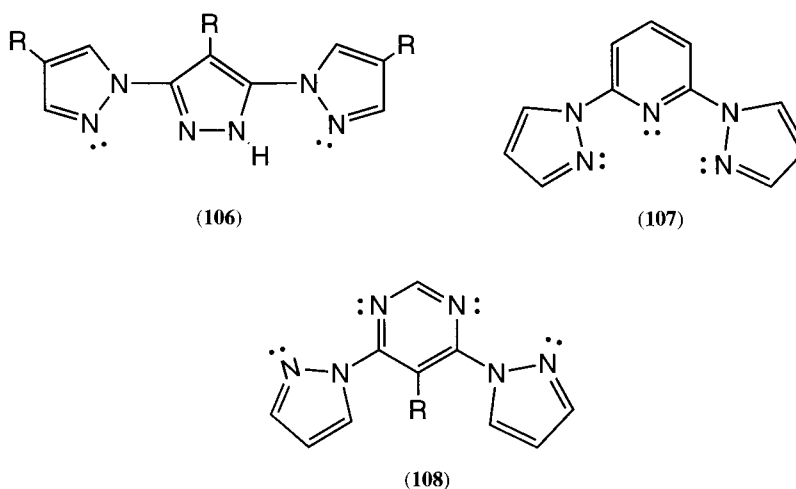
Scheme 1

This is a field in rapid development <90CCR227>. Amongst bidentate ligands, those of type I (14) and (27), type II (22), and type IV (21) and (24) have been reported previously. Ligand (105), a 3,3'-bipyrazole, belonging to type III is described in <94SA(A)727>, where x-ray crystallography shows that the compound exists in the tautomeric form (105a) in the solid state while in solution both tautomers (105a) and (105b) are present. Ligands of type IV are quite common; Steel and Constable, one of the most active groups in this field, have described several N, N' -chelating agents, all of them of general formulae IV, where the heterocyclic rings are pyrimidines, pyrazines, pyridazines, and even thiazoles, benzothiazoles, or benzoxazoles <89JCR(S)189>. Similar ligands have been reported in <90AF705, 92HCA1320>. A new synthesis of 2-(pyrazol-1-yl)pyridine (24) has been described <93JOC4476>. Ligands of type V have been reported by Potvin <94JOC1761>.

Amongst tridentate ligands, type VI, 3,5-bis(4-methylpyrazol-1-yl)-4-methylpyrazole (106; R = Me) has been used to prepare rhodium(I) complexes (one or two metals for one ligand) <91JOM(412)259>; the conformation of the free ligand and the effect of coordination over its conformation are discussed in <93CJC1443>. Type VII ligands like bis(pyrazol-1-yl)pyridazines have been used as ligands in Rh^I <84POL213>, Cu^I and Cu^{II} chemistry <90POL2603, 85IC4719>. Casabó has used 3,5-bis(2-pyridyl)pyrazole (type VIII) as ligand <89JCS(D)1401, 90POL2839>, while Jameson <90JOC4992>



has described the convenient synthesis of a family of planar tridentate ligands, for instance 2,6-bis(pyrazol-1-yl)pyridine (**107**), that are terpyridine analogues (type **IX**). Related to these last compounds are bis(pyrazol-1-yl)pyrimidines (**108**; R = H) <84POL213> and (**108**; R = Ph) <90JOM(395)375>; for these last ligands monocyclopalladation has been observed. Type **X** ligands have been described by Potvin <94JOC1766> and those of type **XI** by Steel <91IC3733>.



The products resulting from the addition of pyrazoles to quinones (**116**; R³ = R⁵ = H) (see Section 3.01.5.3.11) proved to be useful ligands in rhodium and iridium organometallic chemistry <94JOM(467)293>.

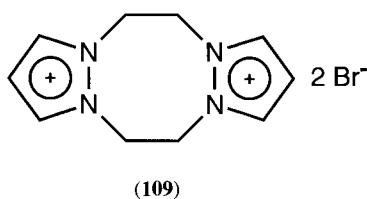
3.01.5.3.6 Azacrown ethers and porphyrinogens

A series of publications by Navarro and co-workers are devoted to crown ethers containing pyrazole subunits <84CL425, 85JCR(S)312> (see Section 3.01.13.1).

Another kind of crown ether is represented by compound (**27**) (see Section 3.01.3.3.1) where the two pyrazole derivatives (in this case, 1*H*-indazoles) are directly linked <87T4663>.

3.01.5.3.7 Alkyl halides and related compounds: compounds without a free NH group

Quaternization of 1,2-bispyrazolyethane (**99**) with methyl fluorosulfonate affords a mixture of mono and diquaternary salts <92BSB29>. A heterosubstituted cyclooctane (**109**) has also been obtained, the chair conformation of the eight-membered ring established by x-ray crystallography <91AX(C)2583> and its behavior in FAB-MS described <91BSB459>.



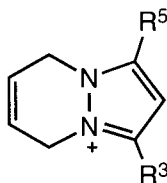
3.01.5.3.8 Alkyl halides and related compounds: compounds with a free NH group

Azoles containing an acidic NH-group, for instance 3,5-dimethyl-pyrazole, react with various alcohols in the presence of catalytic amounts of ruthenium-, rhodium-, and iridium-trialkylphosphite complexes to afford the corresponding *N*-alkyl derivatives with excellent yields <92CL575>. Regioselective *N*-alkylation was achieved using alkenes and sulfuric acid <89JHC3>. The key step of several pyrazoles prepared for their biological properties is a *N*-substitution, for instance, the synthesis of RP 70676 (an inhibitor of cholesterol *O*-acyl transferase) needs a $N-(CH_2)_5-Cl$ intermediate <92BMC375> and 3,4,5-triphenyl-1*H*-pyrazole-1-nonanoic acid (a nonprostanoid prostacyclin mimetic) is prepared from 3,4,5-triphenylpyrazole by *N*-alkylation <92JMC389>.

Polyhalogenoalkanes and dihalogenoethanes have been extensively used to prepare, under PTC conditions, poly(pyrazol-1-yl)alkanes (number of pyrazoles = 2,3,4) and 1,2-di(pyrazol-1-yl)ethanes <84OPP299, 86H(24)2233>. The reaction of pyrazoles with 1,2-dibromoethane in PTC conditions affords a mixture of *N*-ethenylpyrazoles and 1,2-bispyrazolyethanes <88JHC771>; it is also possible to carry out the reaction in two steps through 1-chloro-2-(pyrazol-1-yl)ethane. Indazole affords a mixture of 1,2-bis(indazol-1-yl)ethane and 1-(indazol-1-yl)-2-(indazol-2-yl)ethane.

The reaction of indazole with trityl chloride yields in addition of the 1- and 2-substituted derivatives, 3-tritylindazole (**73**) which is an unprecedented behavior in indazole chemistry <85BSB421>. Benzyl chloride and diphenylmethyl chloride behave classically in this respect <85H(23)2895>. Another *N*-substituent which has been subject to much study is the 1-adamantyl, for instance crystal structures, and ^{13}C NMR spectra have been reported <85T473>.

The possibility that both nitrogen atoms react with a double alkylating agent has been extended to the reaction with *cis*-1,4-dichlorobutene to afford salt (**110**) <89KGS497>.



(110)

Cross-conjugated mesomeric betaines (see formula 238 in <84CHEC-I(5)167>), first described by Potts and Friedrichsen continue to be the subject of much interest <88CB895, 88JOC2889, 88JOC2898>. Kappe <89S629> has described a very simple procedure to prepare these compounds by reacting pyrazoles and (commercially available) substituted diethylmalonates. For a representative publication of one of the leading groups in the field of bimanes see <93JCS(CC)1644>.

3.01.5.3.9 Aryl halides and related compounds

It has been shown that 1-(4-nitrophenyl)azoles (pyrazole, 1*H* and 2*H*-indazole amongst them) are obtained in good yields by direct arylation of the corresponding azole with *p*-fluoronitrobenzene using PTC without solvent <93SC1947>. A fascinating series of new compounds, the hexa(pyrazol-1-yl)benzenes, can be easily prepared from hexafluorobenzene and pyrazole anions <93H(35)415>.

3.01.5.3.10 Acyl halides and related compounds

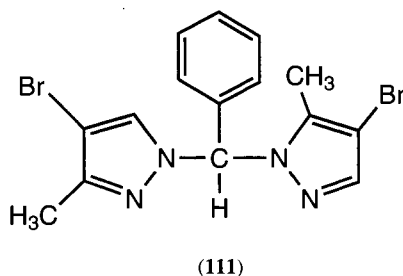
Reaction of 3(5)-aminopyrazole with chloroacetyl chloride gives a mixture of 3-amino-1-(chloroacetyl)pyrazole and 5-amino-1-(chloroacetyl)pyrazole, both of which rearrange in the solid state to 3-(chloroacetamido)pyrazole over a period of a few days; the course of the rearrangement was monitored directly by ^{13}C CPMAS NMR <94MRC255>. It has been shown that 3,5-dimethylpyrazole reacts with acetylcobalt tetracarbonyl under PTC conditions to give 1-acetyl-3,5-dimethylpyrazole <93JOM(451)169>. Both *N*-SO₂F pyrazoles and pz-SO₂-pz derivatives have been prepared from pyrazoles and *O*-fluorosulfonyl-*N,N*-difluorohydroxylamine <93MC14>.

3.01.5.3.11 Michael addition on double and triple bonds

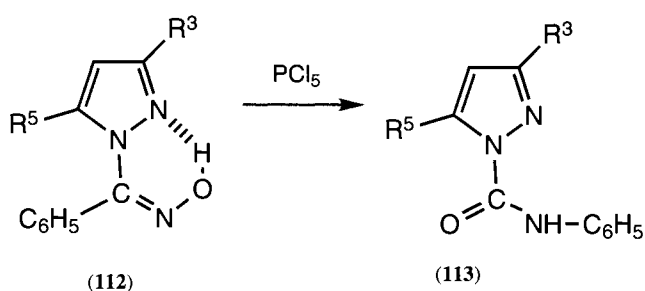
The reaction of *N*-substituted pyrazoles with alkynic esters in the presence of fluoroboric acid yields Michael addition salts and not Diels–Alder adducts as was previously reported in the literature <83T2193>. Addition of 3,5-dimethyl-pyrazole to DMAD (dimethyl acetylenedicarboxylate) is highly stereoselective in aprotic solvents, yielding mono- and bis-adducts <85JCS(P2)427>.

Michael addition of azoles on acrylamide affords *N*-azolypropanamides <88JHC225>. In this way derivatives of pyrazole (7), indazole, 5-chloroindazole, and 5-nitroindazole have been prepared and characterized by ^1H and ^{13}C NMR spectroscopy. In the case of indazoles, both isomers are formed which isomerize to the most stable 1*H*-derivative with activation energies high enough to observe both isomers but not to prevent their equilibration.

Some 1,1'-diindazolylphenylmethanes have been prepared from indazoles and benzaldehyde in presence of zinc chloride as catalyst <85T5955>. The reaction proceeds similarly with other azoles, like pyrazole, 4-bromopyrazole, and 3-methyl-4-bromopyrazole <88CPB2036>. When the resulting compound was chiral, for instance (111), its resolution was successfully carried out by liquid chromatography on triacetylcellulose <88H(27)351>.



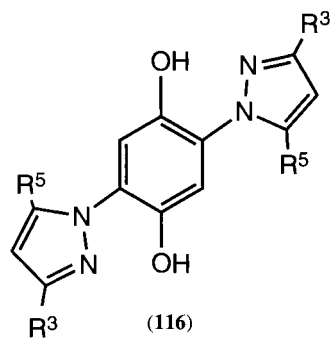
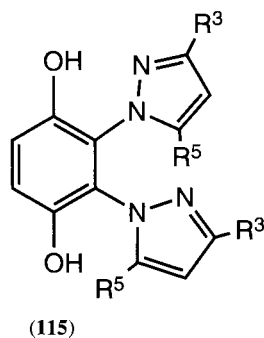
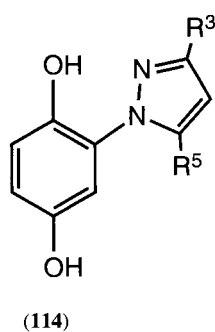
Reaction between pyrazoles and their derivatives and ketenes has been studied by Stephanidou-Stephanatou <90JCS(P1)025, 90JOC4732>. Reaction of pyrazole with diphenylnitrilimine (to afford the phenylhydrazone of *N*-benzoylpyrazole) was reported by Pardo <90JCR(S)294>. The reaction of benzonitrile oxide with 3,5-dimethylpyrazole, pyrazole, and 3(5)-methylpyrazole affords nucleophilic addition products (112) <87JCR(S)240> and not cycloadducts as was previously proposed for imidazole <83JCR(S)230>. Afterwards, the Italian authors acknowledged their error <93JCS(P1)2615>. The Beckmann rearrangement of oximes (112) affords 1-(*N*-phenylcarboxamido) pyrazoles (113) <87JCR(S)240>.



Addition of pyrazoles to quinones affords mono- (114) and bis- (*ortho* (115) and *para* (116)) pyrazol-1-yl-hydroquinones, NMR and crystallography were used to identify these compounds <90JA747>. The mechanism of the formation of these products involves Michael additions (mono-adducts) and oxidation by quinones (bis-adducts) <92JOC1873>.

3.01.5.3.12 Halogens

No significant progress has been made on *N*-halogenation of pyrazoles since <84CHEC-I(5)167>. However, *N*-trifluoromethylthiopyrazole and pzSCF₃, have been prepared from pyrazole and CF₃SCl <86MI 301-02>.



3.01.5.3.13 Peracids

Concerning the synthesis of *N*-hydroxypyrazoles and *N*-oxides of pyrazole, the authoritative publication of Begtrup <92ACS972> should be consulted.

3.01.5.3.14 Aminating and nitrating agents

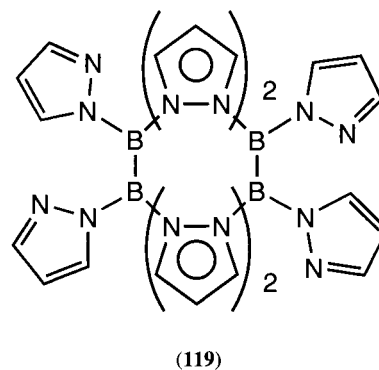
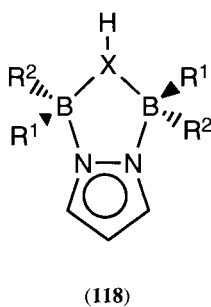
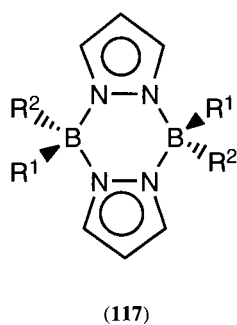
The knowledge of the synthesis of *N*-aminopyrazoles by amination of pyrazoles has been summarized by Kuzmenko and Pozharskii <92AHC(53)85>. The amino group has a sp^3 character in these compounds <89AX(C)1902>. The *N*-nitropyrazoles continue to be the research field of Habraken <86JOC4656, 94T865>, while *N*-nitroindazoles have been studied mainly by Wrzeciono <85PHA105, 92PHA15, 92PHA22>; in the last paper the nitration of 5-fluorindazole was reported to yield a mixture of 1-, 2-, and 3-nitro derivatives.

3.01.5.3.15 Other Lewis acids

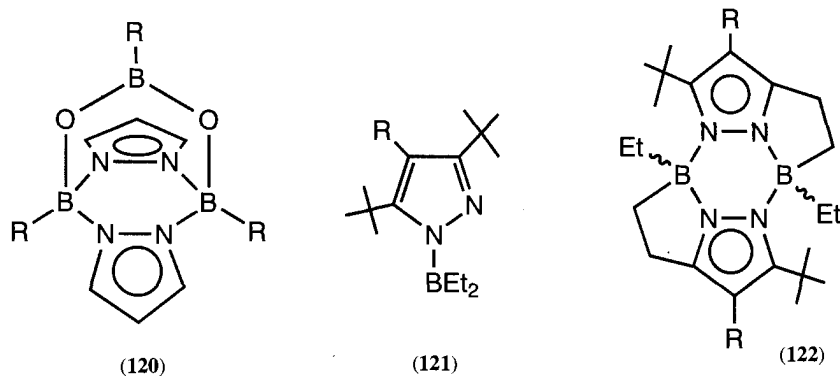
This is one of the fields that has developed considerably since CHEC-I <84CHEC-I(5)167>. The compounds containing metalloids on the nitrogen are described in the order of the periodic group of the element.

(i) Boron

Although not so important as pyrazolylborates (see Section 3.01.5.3.5), neutral derivatives of boron constitute a large group of pyrazole derivatives. The work of Niedenzu in connection with pyrazaboles (117) <84CHEC-I(5)167> should be quoted <86TCC(131)1>; this author has also prepared compounds (118) related to pyrazaboles <90IC538> as well as pyrazole derivatives of diborane such as $[(pz)_2B-B(pz)_2]_2$ (119) <88JA817>.

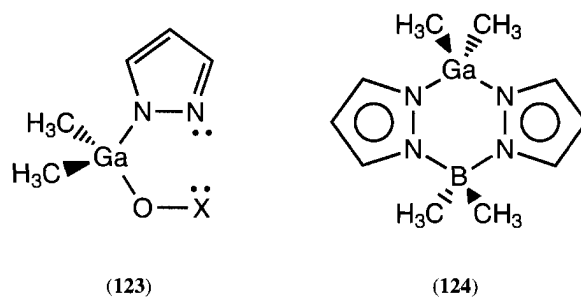


Yalpani has prepared other boron derivatives of azoles; compounds **(120)** resulted from the reaction of pyrazole with triorganylborrowins <88CB1553>, while compounds **(121)** and **(122)** are formed when crowded 3,5-di-*t*-butylpyrazoles-4-substituted ($R = H, Me, Et$) react with BEt_3 <91CB1699>.



(ii) Gallium

Storr and Trotter have developed considerably the chemistry of pyrazoles derivatives of gallium <84CHEC-I(5)167>. For instance they have prepared a series of ligands of type **(123)**, where X represents a group (picoline, aniline) with a lone pair on a nitrogen atom <87CJC2469, 88CJC355>. Another very interesting contribution of this group is the first synthesis of a pyrazagabole **(124)** <90CJC59>.



(iii) Indium

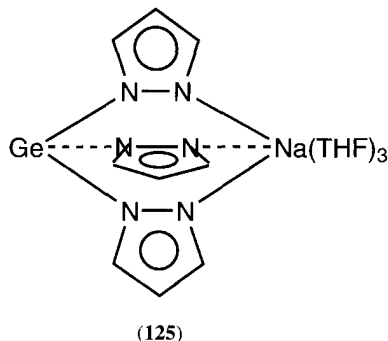
Dialkylindium derivatives of pyrazole, 3(5)-methylpyrazole and 3,5-dimethylpyrazole, $pz-InMe_2$ or $pz-InEt_2$ have been prepared: they are dimeric compounds with structures similar to **(124)** <91JOM(420)1>.

(iv) Silicon

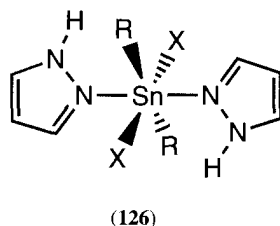
Begtrup <90ACS1050> has developed a general procedure for silylation of azoles including 1-(trimethylsilyl)pyrazole.

(v) Germanium

Sodium tris(pyrazol-1-yl)germanate (**125**) has been prepared and characterized by x-ray crystallography (the sodium atom is solvated by three tetrahydrofuran rings) <93CC1702>.

*(vi) Tin*

Pyrazoles *N*-linked to tin are quite common compounds. Amongst others, the x-ray structures of $\text{SnMe}_2\text{Cl}_2(\text{dmpzH})_2$ ($\text{dmpzH} = 3,5\text{-dimethyl-pyrazole}$) <82JCS(D)805> as well as those of $\text{SnEt}_2\text{Br}_2(\text{pzH})_2$ ($\text{pzH} = \text{pyrazole}$) <88JOM(353)169>, and $\text{Sn}(\text{CH}=\text{CH}_2)_2\text{Cl}_2(\text{pzH})_2$ <89JOM(375)167> (**126**) have been determined.

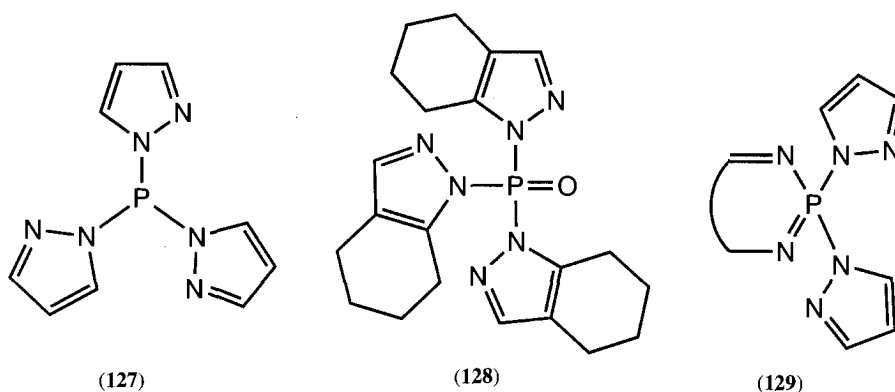
*(vii) Phosphorus*

Tris-(pyrazol-1-yl)phosphine (**127**) has been determined <75AX(B)2731>: the P atom lies on a crystallographic threefold axis (the authors report that the crystals are extremely sensitive to traces of water). This ligand (as well as those where one or two pyrazole rings were replaced by phenyl rings) have been used to prepare manganese(I) and rhenium(I) complexes <76CJC2967>. Campho[2,3-*c*]pyrazole (**221**) and the menthone derivative (**217**) were the chiral precursors (see Section 3.01.10.1.2.(ii)) used to prepare tris(pyrazol-1-yl)phosphine oxide ligands (**128**), where the cyclohexene rings is either a menthone or a camphor derivative <94OM2855>.

(Pyrazol-1-yl)phosphazenes (**129**) have been synthesized and used to prepare palladium(II) and platinum(II) complexes <82CJC521>.

3.01.5.4 Electrophilic Attack at Carbon**3.01.5.4.1 Reactivity and orientation**

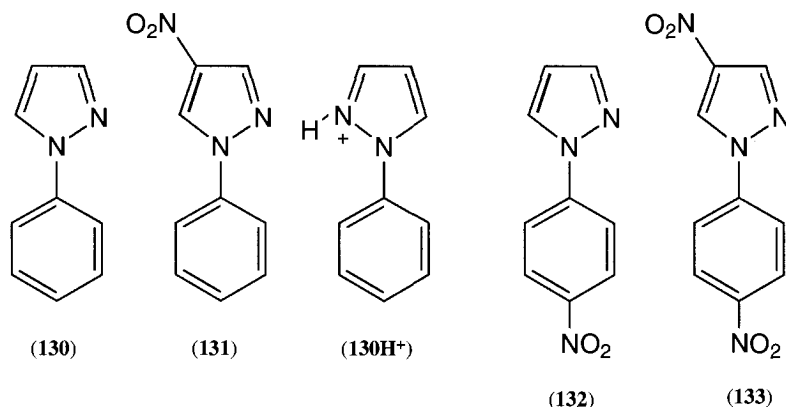
CHEC-I <84CHEC-I(5)167> described the known situation until the early 1990s when Begtrup put some order in the reactivity of heteroaromatic compounds <92H(33)1129>. His model is based on the donor-acceptor concept and contains many references and useful discussions concerning pyrazoles and pyrazole-*N*-oxides. The period between 1983 and 1989 has been covered by Katritzky and Taylor <90AHC(47)139>.



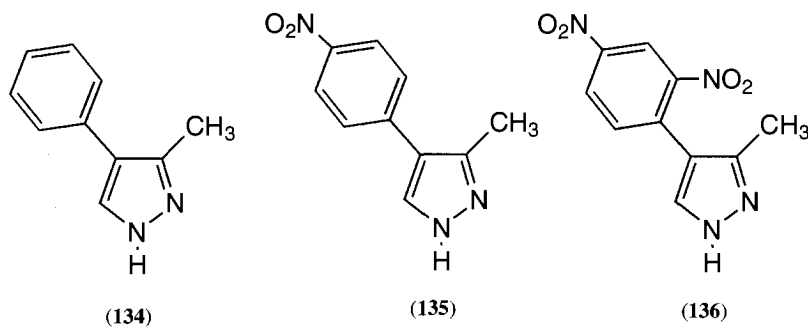
3.01.5.4.2 Nitration

The 1993 review by Hurst <93AHC(58)215>, "The Nitration of Phenyl-substituted Heterocycles," covers the case of pyrazoles and indazoles. Chapter references are up to 1991, but its most recent reference concerning nitration of 1-arylpyrazoles is <88CHE353>, which is a review on nitropyrazoles.

The free base of 1-phenylpyrazole (**130**) undergoes nitration at the 4-position to form (**131**), whereas the conjugate acid (**130H⁺**) undergoes nitration at the *para*-position of the phenyl ring to form (**132**). Both isomers can be further nitrated, as free bases, to afford 1-(4-nitrophenyl)-4-nitropyrazole (**133**)



Hurst <88H(27)371> confirmed that the nitration of 3-methyl-1-phenylpyrazole using nitric acid/sulfuric acid gives a mixture of mononitration (*p*-nitrophenyl derivative) and dinitration (1-(4-nitrophenyl)-3-methyl-4-nitropyrazole). On the other hand, 3-methyl-4-phenylpyrazole (**134**) gives the *p*-nitrophenyl product (**135**) initially with the second nitration also occurring in the phenyl ring to afford (**136**).



In summary <88CHE353, 93AHC(58)215>, three types of compounds are formed depending on the character of the substituents in the pyrazole ring and on the nitrating agent used: (i) 1-(4-nitrophenyl)-4-nitropyrazoles are usually found when a mixed acid nitrating combination is used

for 1-phenylpyrazoles containing substituents such as phenyl, methyl, chloro, and thienyl in the 3- and 5-positions of the pyrazole ring; (ii) 4-nitropyrazoles are formed exclusively in the case of nitration using nitric acid in acetic anhydride and nitronium tetrafluoroborate in sulfolane; (iii) 4-nitrophenylpyrazoles are initially formed in the case of nitration using nitric acid or nitrating mixtures under mild conditions, and the reaction goes further with an increase in temperature or in nitric acid to give 1-(4-nitrophenyl)-4-nitropyrazoles.

3.01.5.4.3 Sulfonation

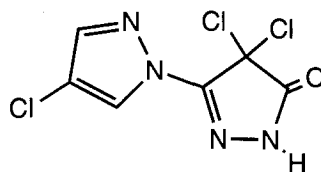
Formation of C-sulfonyl derivatives of pyrazoles and indazoles <84CHEC-I(5)167> has been updated <90AHC(47)139>. A significant example is the synthesis of the 4-sulfonyl chloride derivative by reacting 1,3-dimethyl-5-chloropyrazole with chlorosulfonic acid <86JCR(S)388>, subsequent treatment with ammonia affords the sulfonamide.

3.01.5.4.4 Acid-catalyzed hydrogen exchange

Proton–deuterium exchange in pyrazolium salts has been reported by Begtrup to take place at positions 3 and 5 <92ACS1096>. Older references were reported in <90AHC(47)139>.

3.01.5.4.5 Halogenation

Halogenation of pyrazoles and indazoles has been summarized by Katritzky and Taylor <90AHC(47)139> and by Grimmett <93AHC(57)291, 94AHC(59)245>. Chlorination of pyrazole (7) with chlorine affords a mixture of (106; R = Cl) and (137) <93BSB735>; the x-ray structure of (137) was determined as well as the fact that chlorination transforms (106; R = Cl) into (137). Other authors have used *N*-chlorosuccinimide to introduce a 4-Cl substituent in 3(5)-aryl-5(3)-methylpyrazole <86JHC459>, or even chloroperoxidase to chlorinate pyrazole (7), 1-methylpyrazole and 3(5)-methylpyrazole (11) <87JHC1313> in much better yields than using hypochlorous acid.



(137)

Iodination of 3,5-diaminopyrazole was only successful using [Ipy][BF₄] <93JCS(P1)2229> (in 3,5-diamino-4-iodopyrazole, the signal of C₄ appears at 29.5 ppm). Concerning indazoles, the most significant reference is <84JOC3401> where bromination of 2-phenylindazole is described (first 3-bromo, then bromine entered the 5- and the 7-positions).

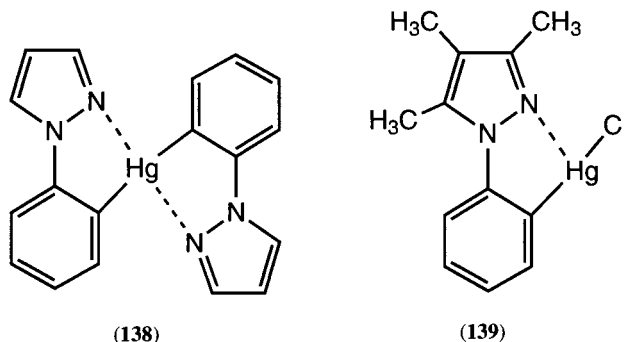
3.01.5.4.6 Acylation and alkylation

Treatment of pyrazole with 1-bromoadamantane affords either 4-(1-adamantyl)pyrazole (273) <94TL183, 94H(37)1623> or 3(5)-(1-adamantyl)pyrazole (271) <94CL2079> (see Section 3.01.12.1) depending on the experimental conditions (heating in a sealed tube or heating in a microwave oven). The x-ray structure of 4-(1-adamantyl)pyrazole was determined <94H(37)1623>.

Progress has been made in the experimental procedures for the formylation of pyrazoles (Vilsmeier–Haack reaction) at their 4 position <93JHC957, 94CPB237>. For instance, 4*H*-pyrazolo[1,5-*a*]indoles are formylated under milder conditions than pyrazoles <94CPB237>.

3.01.5.4.7 Mercuration

Mercuration of 1-phenylpyrazole and 1-phenyl-3,4,5-trimethylpyrazole affords organomercury derivatives (138) and (139) <93AJC1323>, the structures have been established using ^{199}Hg NMR spectroscopy.



3.01.5.4.8 Diazo coupling

Similarly to 5-hydroxypyrazoles which react with arenediazonium salts to afford 4-arylo-5-hydroxypyrazoles <84CHEC-1(5)167>, some 4-hydroxypyrazoles yield 1-aryl-3-phenylsulfonyl-4-hydroxy-5-arylazopyrazoles on reaction with arenediazonium chlorides using pyridine as solvent <92JHC543>.

3.01.5.4.9 Nitrosation

Both 1-methyl-3,5-diphenyl-4-nitrosopyrazole and 1,3-dimethyl-5-phenyl-4-nitrosopyrazole were prepared and used as spin traps: the ESR spectra of the radicals formed in the trapping ($\text{CH}_2\text{OH}\cdot$ and $\cdot\text{CH}_3$ radicals) were recorded <89ACS503>.

3.01.5.4.10 Reaction with aldehydes and ketones

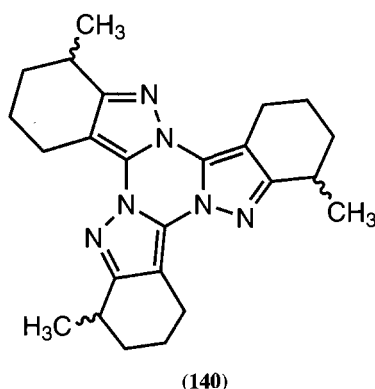
Bispyrazole (80) was prepared by the reaction of 3,5-dimethylpyrazole with formaldehyde (a 4- CH_2OH derivative is the probable intermediate) <84ICA99>. Pyrazolo[1,5-*a*]pyridines react similarly affording bis-derivatives with a $-\text{CH}(\text{R})-$ bridge between carbons corresponding to position 4 of pyrazoles <93JHC1045>; the nature of R depends on the aldehyde used ($\text{R} = \text{H}, \text{Me}, \text{Ph}, \text{Ar}$). When 3(5)-aminopyrazole reacts with methylisocyanate and acetone a dimer was isolated in which two 1-carbamoyl-5-aminopyrazole units are linked by a $-\text{C}(\text{CH}_3)_2-$ bridge between the positions 4,4' <91AP(324)257>.

3.01.5.4.11 Oxidation

Pyrazole (7) is oxidized by isolated rat liver microsomes to 4-hydroxypyrazole (see Section 3.01.7.5.4) <87MI 301-05>. Bromine oxidation of the silver salt of 7-methyl-4,5,6,7-tetrahydroindazole yields a C,N'-linked cyclic trimer (140) but not N,N'-linked dimers as reported in the literature <85H(23)2629>.

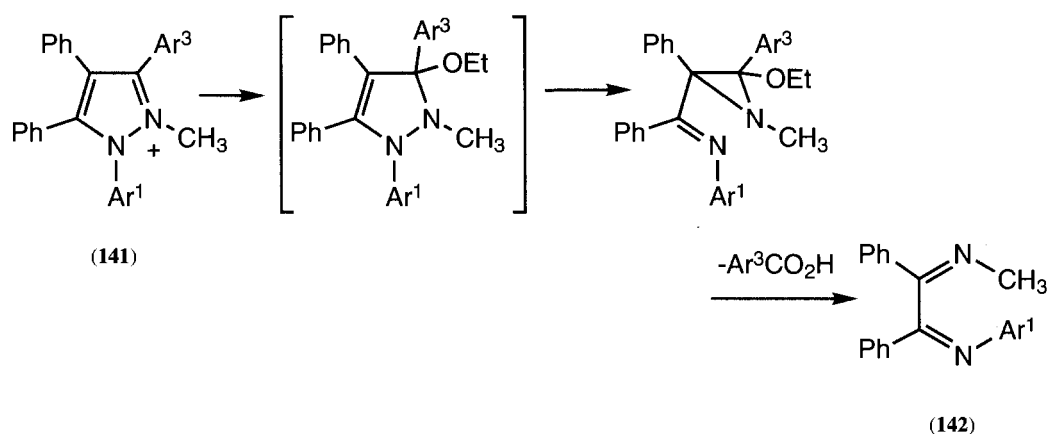
3.01.5.5 Nucleophilic Attack at Carbon

Here also, for a general theory of nucleophilic reactions of pyrazole-N-oxides in the framework of the donor-acceptor concept see <92H(33)1129>. The most relevant results in this field are those



obtained by Butler in the case of pyrazolium quaternary salts and by Begtrup in the case of pyrazole-*N*-oxides.

Butler has described that the treatment of 1-ethoxycarbonylmethyl-2,3,4,5-tetraarylpyrazolium salts with base in the presence of DMAD (dimethyl acetylenedicarboxylate) affords 1-(2'-amino-vinylpyrroles) and pyrrolo[1,2-*a*] pyrazines <93JCS(P1)883>; a mechanism has been proposed for this unexpected behavior. Reaction of 1,3,4,5-tetraaryl-2-methylpyrazolium salts (**141**) with ethoxide base produces the fragmentation of the pyrazole ring with formation of 1,2-bisimines (**142**): the mechanism is represented in Scheme 2 <94JCR(S)12>. In both cases the structures of the resulting products were supported by x-ray determinations.



Scheme 2

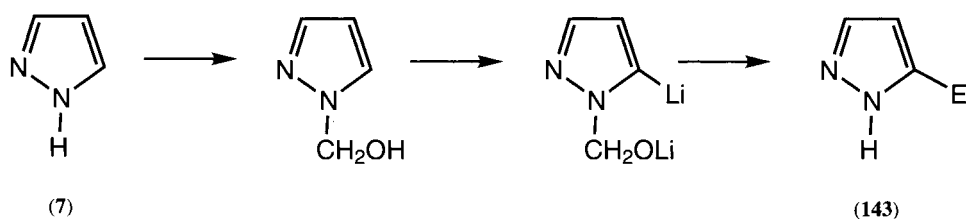
Begtrup <92ACS1096, 92H(33)1129, 92JCS(P1)2555, 93JCS(P1)625> has shown that azole-*N*-oxides after *O*-silylation can be used to activate the 3 and 5 ring positions.

3.01.5.6 Nucleophilic Attack at Hydrogen

3.01.5.6.1 Metallation at a ring carbon atom

This section has been reviewed by Grimmett and Iddon <94H(37)2087>. It has been shown that *N*-unsubstituted pyrazole (**7**) is readily converted into 3(5)-substituted derivatives (**143**) in a one-pot sequence, using formaldehyde both for *N*-protection and to mediate the lithiation at the 5-position <89T4253>; the transient *N*-(hydroxymethyl) unit is readily removed during workup. The regioselectivity is a consequence of heteroatom-directed metallation (electrophile, E = C₆H₅CH(OH), C₆H₅S, C₆H₅CH₂, (C₆H₅)₂C(OH), C₆H₅NHCO). Direct lithiation of 1-substituted pyrazoles provides an efficient entry to 1,5-disubstituted pyrazoles <91JHC1849, 92SL327>.

Another possibility to introduce a substituent E at position 5 (E = Me, TMS, CH₂Ph, CO₂Me, I) is to use the tosyl substituent as protecting group. For example, 1-arylpyrazoles can undergo *ortho*-lithiation on either the aryl substituent or the pyrazole 5 position <92CL357>.



3.01.5.6.2 Hydrogen exchange at ring carbon in neutral pyrazoles

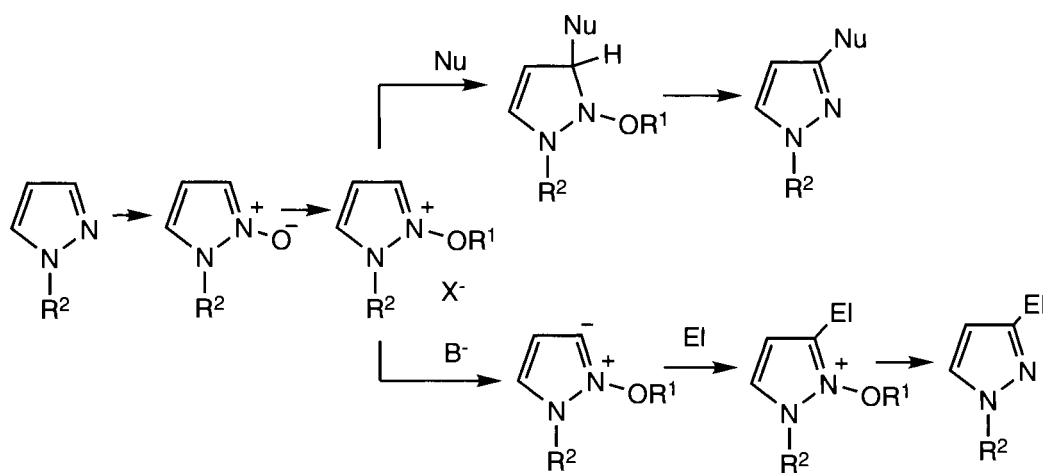
Progress has not been made on the base-catalyzed hydrogen exchange of pyrazoles since the early 1980s <84CHEC-1(5)167>. Begtrup <92ACS1096> reports that H₃ and H₅ are more acidic in 1-benzylpyrazole-2-oxide than in the parent 1-benzylpyrazole.

3.01.5.6.3 Hydrogen exchange at ring carbon in pyrazolium cations

The relative acidity of protons of 1-benzylpyrazole-2-oxide has been determined by exchange with deuterium oxide-tetraduteriomethanol/potassium hydroxyde <92ACS1096>: as a result 59% and 55% of exchange at H₃ and H₅ was measured.

3.01.5.6.4 C-substitution via deprotonation

Deprotonation of 1-substituted pyrazole-2-oxides followed by addition of dimethyl disulfide affords 3- and 5-methylthio as well as 3,5-bis(methylthio) pyrazoles <92ACS1096>. The general procedure developed by Begtrup <88BSB573, 92H(33)1129> to transform pyrazoles into 3-substituted derivatives via *N*-oxides is represented in Scheme 3, where Nu = nucleophile and El = electrophile.



Scheme 3

3.01.5.7 Reaction with Radicals and Electron-deficient Species

3.01.5.7.1 Carbenes and nitrenes

Irradiation of 1-(2-azidophenyl)-3,5-dimethylpyrazole affords the corresponding nitrene which cyclizes into the corresponding pyrazolo[1,2-*a*] benzotriazole <91JA6928> (compare with <84CHEC-1(5)167> formulae (341) and (342)).

3.01.5.7.2 Free radical attack at the ring carbon atoms

Pyrazolinones are oxidized by phenoxy radicals to the corresponding radicals which, in turn, dimerize or combine with the phenoxy radical <93JPR607>. Trichloromethyl radicals react to pyrazoles to afford ring-expansion products (see Section 3.01.5.2) <89PJS377>.

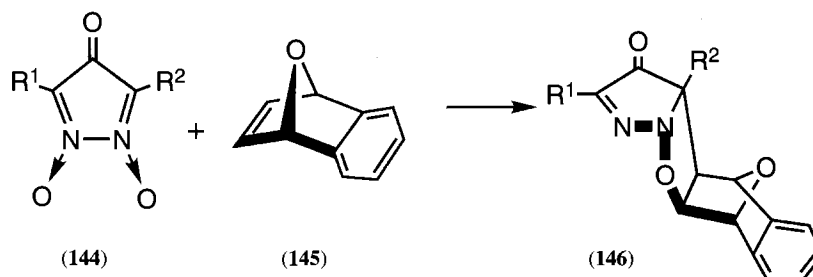
3.01.5.7.3 Electrochemical reactions and reactions with free electrons

Electrochemical reduction of 1-nitropyrazole (**18**) results in the cleavage of the N—N bond with formation of pyrazole and nitrous acid <92MI 301-02>. The electrochemical properties of Difenzoquat (1,2-dimethyl-3,5-diphenylpyrazolium cation) were examined <91JEC169>: the reduction gives pyrazolines and dimers.

3.01.5.8 Reactions with Cyclic Transitions States

3.01.5.8.1 Diels–Alder reactions and 1,3-dipolar cycloadditions

The cycloaddition of 3,5-disubstituted-4*H*-pyrazol-4-one *N,N*-dioxide (**144**) towards various unsaturated compounds like 1,4-epoxynaphthalene (**145**) was investigated <93JHC1557, 94JCS(P2)1337>; predominance of the *exo*-1,3-dipolar cycloadducts (**146**) was observed.



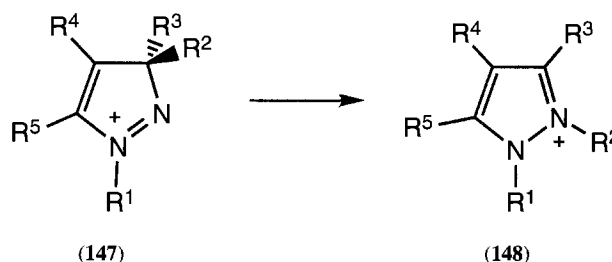
It is known that 4-benzal-1-phenyl- Δ^2 -pyrazolin-5-one reacts both like an heterodiene and an alkene in a Diels–Alder reaction towards 2,3-dimethylbutadiene <88T5229>. The 1,3-dipolar cycloaddition of nitrones to the *NH*-tautomer of 1-phenyl-3-methyl-3-pyrazolin-5-one yields a non-isolated cycloadduct which rearranges to a 4-substituted derivative of the starting material (4-substituent = CH(Ar)—N(Ph)—OH) <94JCR(S)154>.

3.01.6 REACTIONS OF NONAROMATIC COMPOUNDS

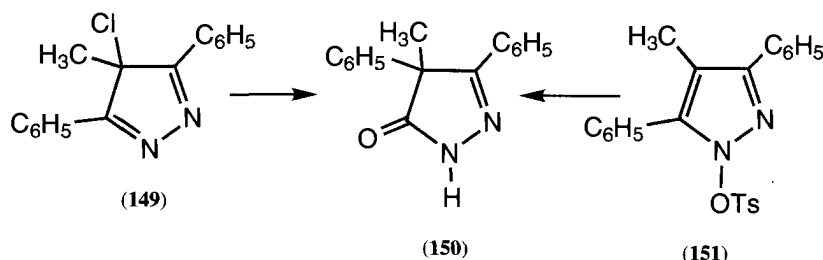
3.01.6.1 Isomers of Aromatic Derivatives

3.01.6.1.1 Compounds not in tautomeric equilibrium with aromatic derivatives

Nagai <93OPP403> has written an authoritative review of 3*H*-pyrazoles (pyrazolenines) which updated that of Katritzky (see Table 1). Jochims has extended the Van Alphen–Hüttel rearrangement to 3*H*-pyrazolium salts (**147**) into 1*H*-pyrazolium salts (**148**) <94CB541>; theoretical AM1 calculations were carried out to support the mechanism. Nevertheless, most studies regarding the rearrangement of 3*H*-pyrazoles are due to Warkentin <91CJC373, 92JA6318, 94JOC455>.



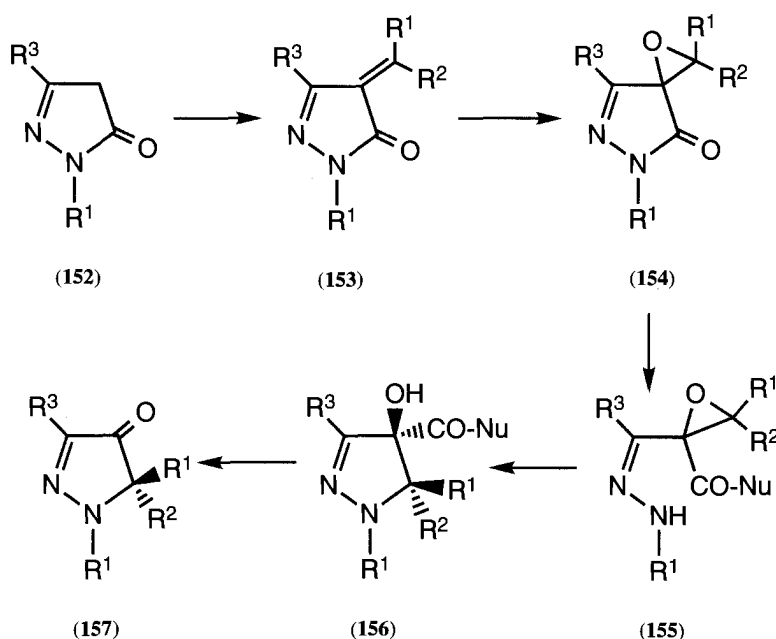
New lithium-selective chloroionophoric compounds with arylazobutenoic acid structure have been synthesized from 1-aryl-3-R-4,4-dichloro-2-pyrazolin-5-ones and alcohols (94LA265): this ring opening is somewhat related to Carpino's reaction (84CHEC-I(5)167). The fact that rearrangement of 4-chloro-4*H*-pyrazoles (isopyrazoles) (149) into 2-pyrazolin-5-ones (150) involves a cation related to (13) was supported by *ab initio* calculations (87JOC4058). The same pyrazolin-5-one (150) is formed in the hydrolysis of the *N*-(tosyloxy)-pyrazole (151). Grigg (94T895) has studied the reaction of 1-phenyl-3-methylpyrazolin-4,5-dione (1; $R^1 = \text{Ph}$, $R^3 = \text{Me}$) with α -amino acids.



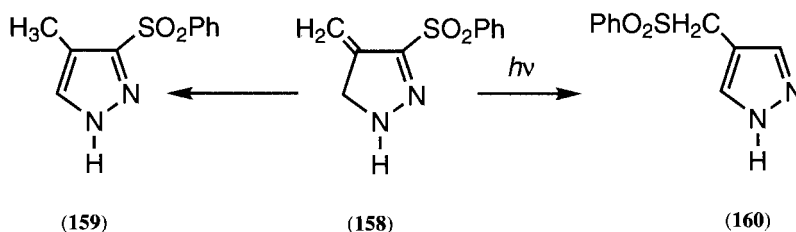
3.01.6.1.2 Compounds in tautomeric equilibrium with aromatic derivatives

The results obtained in the nitration of 1-phenyl-3-hydroxypyrazoles, 1-phenyl-3-methoxypyrazoles, 1-phenylpyrazolin-5-ones, and 1-phenyl-5-methoxypyrazoles have been summarized by Hurst (93AHC(58)215). Compared with 1-phenylpyrazoles (see Section 3.01.5.4.1), the OH or OMe group activates the 4-position of the pyrazole ring. The regioselectivity of allylation of pyrazolin-5-ones (C_4 , N_1 , and N_2 -positions) can be modified using the Pd(0)-catalyzed procedure of Moreno-Mañas (94T515). The reaction of 1-phenyl-3-methylpyrazolin-5-one with trithiazyltrichloride affords bis(pyrazolinone)-sulfides (see Section 3.01.7.6) amongst other bis(derivatives) (with bridges such as $=N-S-N=$ and $-N=$) (87ZC434).

Starting from 1-aryl-3-R-2-pyrazolin-5-ones (152; $R = \text{OC}_2\text{H}_5$, pyrrolidino, CH_3) the following sequence of reactions was supported by x-ray structure determinations (94LA159): Knoevenagel condensation with acetone or benzaldehyde (153), epoxidation with hydrogen peroxide (154), ring-opening by reaction with nucleophiles (155), ring closure (156), and oxidation into 2-pyrazolin-4-ones (157).



Padwa <88JOC2232> has described the aromatization of 4-methylene- Δ^2 -pyrazoline (**158**) into pyrazole (**159**) using a trace of acid or base and into pyrazole (**160**) on exposure to light.



Arán has studied the reactivity of 1,1-disubstituted indazol-3-ylidene oxides <93JCS(P1)1119>, for instance, treatment of these compounds with hydrochloric acid affords the corresponding 3-hydroxyindazoles; the Wawzonek rearrangement (formation of 1,2-disubstituted indazolinones) was also observed.

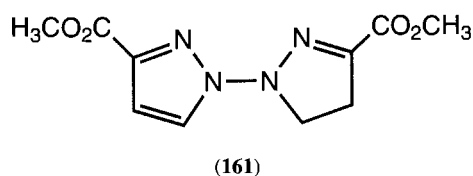
3.01.6.2 Dihydro Derivatives

3.01.6.2.1 Tautomerism and isomerization

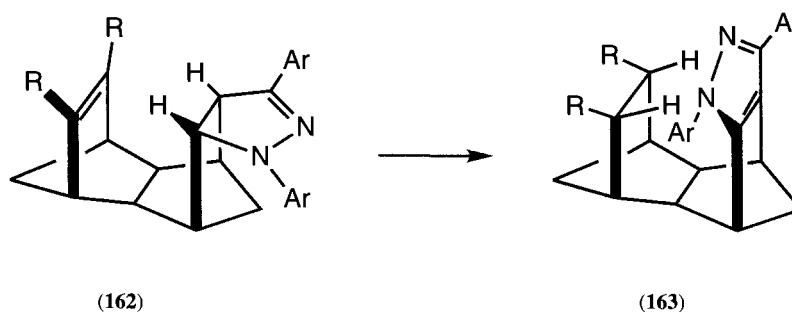
The fact that 3-amino- Δ^2 -pyrazolines exist as such <84CHEC-I(5)167> and not in other tautomeric forms (iminopyrazolidine, amino- Δ^3 -pyrazoline) has been established experimentally in the solid state by crystallography <88AX(C)909> for 1-phenyl-3-amino and 1-*m*-trifluoromethylphenyl-3-amino derivatives (BW755C: formula 719 in <84CHEC-I(5)167>). Rearrangement of 1-allyl-1-methyl-3-amino- Δ^2 -pyrazoliniums occurs to give 1-methyl-2-allyl-3-iminopyrazolidines <88JHC415>. The equilibrium between 3-trimethylsilyl- Δ^1 -pyrazoline and 1-trimethylsilyl- Δ^2 -pyrazoline (tautomerism with concomitant silylotropy) has been followed by ¹H NMR <85JOM(293)177>.

3.01.6.2.2 Aromatization

Oxidation of 3-methoxycarbonyl- Δ^2 -pyrazoline with lead tetraacetate yield a complex mixture of compounds amongst them the *N,N'*-derivative (**161**).



Pyrazolines have been used as models of intramolecular dyotropy by Mackenzie *et al.* <87T5981, 93JCS(P2)1211>. In a series of beautiful experiments, which combine primary deuterium kinetic isotope effects and x-ray crystallography, Mackenzie shows that in convenient polycyclic systems, like (**162**) there is a double proton transfer to (**163**) which take place by simple heating (for instance, melting).



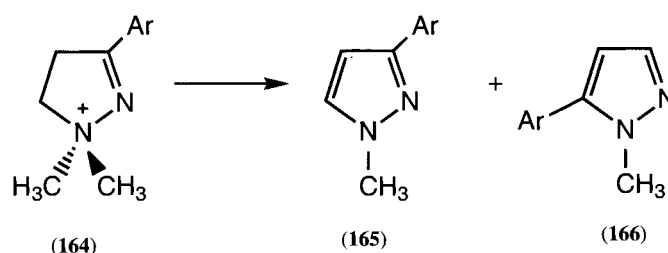
Transformation of Δ^1 -pyrazolines bearing a benzenesulfonyl group at position 3 occurs to give pyrazoles by reaction with KOH/MeOH with loss of the SO₂Ph group <92T8101>.

3.01.6.2.3 Reduction

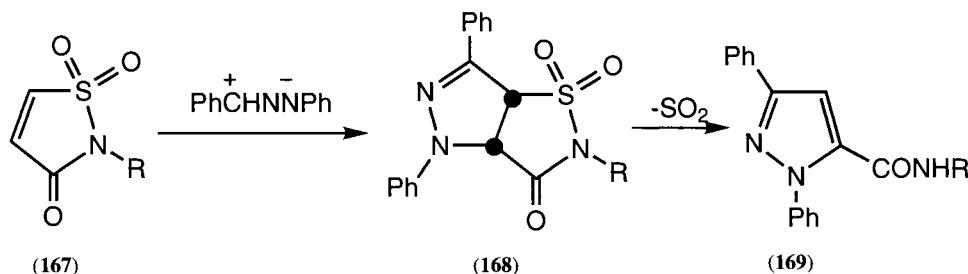
The reduction of Δ^2 -pyrazolines into pyrazolidines will be examined with these last compounds (see Section 3.01.6.3). There, the Grignard reaction will be used to transform pyrazolines (**171**) and (**174**) into 3-substituted pyrazolidines (**172**) and (**175**): a single racemic diastereomer (the *d,l*) is obtained $\langle 92\text{JOC}4563 \rangle$.

3.01.6.2.4 Thermolysis and pyrolysis

Thermolysis of 3-aryl-1,1-dimethyl- Δ^2 -pyrazolinium fluoroborates (**164**) gives an isomeric mixture of 1-methyl-3-arylpyrazole (**165**) and 1-methyl-5-arylpyrazole (**166**). The authors propose the “normal” compound (**165**) to be formed by demethylation followed by oxidation while isomer (**166**) results from transmethylation reactions $\langle 92\text{JCB}172 \rangle$. Some labeling experiments support this explanation.



Gas-phase thermolysis of 4-methylene- Δ^1 -pyrazolines $\langle 84\text{CHEC-I}(5)167 \rangle$ continues to arouse interest $\langle 90\text{CB}1161 \rangle$. A novel chelotropic process has been described by which pyrazolines (**168**) (prepared by 1,3-dipolar cycloaddition of diphenylnitrilimine over (**167**)) are transformed into pyrazoles (**169**) $\langle 92\text{C}335 \rangle$.

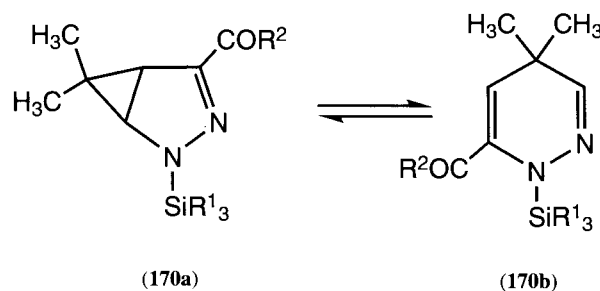


A new class of localized biradicals, the cyclobutanediyls, have been synthesized from suitable Δ^1 -pyrazolines and observed by matrix isolation EPR spectroscopy $\langle 88\text{JA}1356 \rangle$. These pyrazolines have a methylene bridge between positions 3 and 5 (diazabicyclo[2.1.1]hex-2-enes). The reactivity of bicyclic Δ^1 -pyrazolines has been explored by Adam $\langle 93\text{JA}12571, 94\text{JA}7049 \rangle$.

3.01.6.2.5 Other reactions

An unusual rearrangement converts 3-benzoyl- Δ^2 -pyrazolines into phenylpyridazinones $\langle 83\text{H}(20)2385 \rangle$. The azido/tetrazole tautomerism of 3-azido- Δ^2 -pyrazolines has been studied by ¹H and ¹³C NMR $\langle 84\text{CS}195 \rangle$. Maas $\langle 92\text{CB}1227 \rangle$ has described the so-called homopyrazoles (2,3-diazabicyclo[3.1.0]hex-3-enes) (**170a**) which exist in equilibrium with 1,4-dihydropyrazines (**170b**).

Hurst $\langle 93\text{AHC}(58)215 \rangle$ has summarized the results of nitration of 1-phenyl- Δ^2 -pyrazolines; for instance, 1,5-diphenyl-3-aryl-2-pyrazolines are nitrated by potassium nitrate in sulfuric acid to afford the 1-*p*-nitrophenyl derivative in quantitative yield. Thermal ring opening of Δ^2 -pyrazolin-3-carboxylic acids has been used as a method of preparation of β -aminonitriles $\langle 94\text{T}7543 \rangle$, while base-promoted ring opening of 1,1-disubstituted-3-amino- Δ^2 -pyrazolinium salts affords either *N,N*-disubstituted hydrazines or α,β -unsaturated amidrazones $\langle 86\text{SC}585 \rangle$.



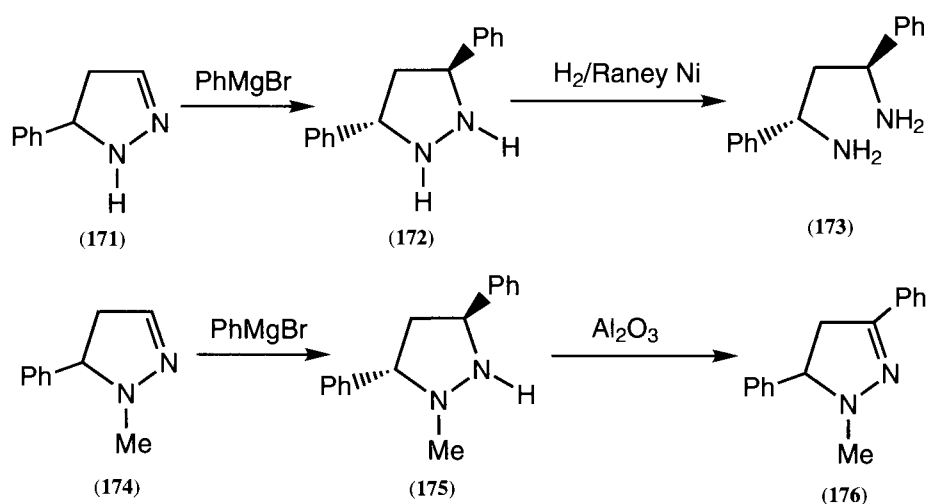
3.01.6.2.6 Stereochemistry

Acid-catalyzed experiments, monitored by proton NMR, show that optically active 5-substituted Δ^2 -pyrazolines exchange their protons on C_4 faster than the C_5 substituent (a phenyl group) epimerizes. Resolution of 1,3-dimethyl-5-phenyl- Δ^2 -pyrazoline was achieved using liquid chromatography on triacetylcellulose. Proton-deuterium exchange in deuterioacetic or deutero-trifluoroacetic acids shows that the C_4 -proton *trans* to the phenyl group exchanges faster than the other C_4 -proton. The epimerization of the C_5 substituent was determined by ^1H NMR in the presence of chiral lanthanide shift reagents $\langle 87\text{CS}283 \rangle$. The resolution of 1,3-dimethyl-5-phenyl- Δ^2 -pyrazoline was achieved by formation of an inclusion compound with a chiral host $\langle 95\text{CC}1453 \rangle$.

These experiments demonstrate that two mechanisms of *cis-trans* isomerization concurrently work in Δ^2 -pyrazolines: the C_4 epimerization and the C_5 epimerization, the first one being the most efficient. The different rates of exchange of protons on C_4 correspond to the protonation of the intermediate Δ^3 -pyrazoline by the less hindered face. Tóth $\langle 89\text{JCS(P}2)319, 93\text{T}863 \rangle$ has devoted a great effort to the conformational analysis and stereochemistry of Δ^2 -pyrazolines.

3.01.6.3 Tetrahydro Compounds

As indicated in Table 1, a review on these compounds has appeared $\langle 92\text{KGS}829 \rangle$. There is a paper by Alexakis *et al.* $\langle 92\text{JOC}4563 \rangle$ where most significant reactions of pyrazolidines are described; Scheme 4 summarizes their results.



Scheme 4

3.01.6.3.1 Oxidation

Pyrazolidines (175) are oxidized to pyrazolines (176) on simple attempt to purify the pyrazolidine on Al_2O_3 .

3.01.6.3.2 Ring fission

Pyrazolidines (**172**) can be transformed into diamines (**173**) by Raney Ni; the *d,l* stereochemistry is preserved.

3.01.6.3.3 Other reactions

Nitration of 1-phenylpyrazolidines takes place first on the *para* position of the phenyl ring and then at the *ortho-para*-positions <93AHC(58)215>. By searching for antiarrhythmic agents related to procainamide, the whole chemistry of pyrazolidines was developed <93JHC109>. The electron impact mass spectrometry of some pyrazolidines has been reported <93JHC1641>.

3.01.6.3.4 Stereochemistry

The *trans* stereochemistry of (**175**) was also found to be dominant in a previous work <87JOC2277>.

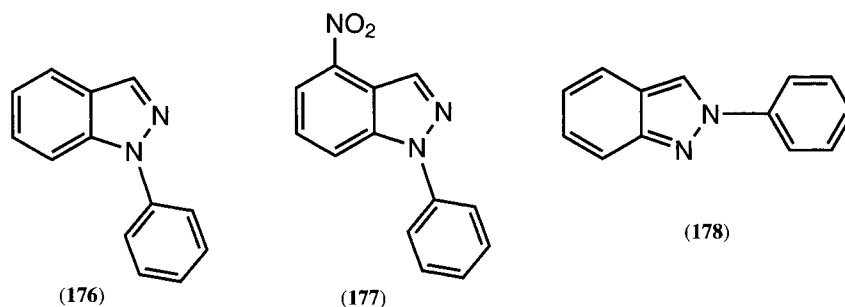
3.01.7 REACTIONS OF SUBSTITUENTS ATTACHED TO RING CARBON ATOMS

3.01.7.1 General Survey of Substituents on Carbon

Begtrup <92H(33)1129, 92JCS(P1)2555> has provided this field with a comprehensive theory, in particular for reactions at the α -position of side chains. Regarding the Boulton–Katritzky rearrangement involving pyrazoles or pyrazolines <84CHEC-I(5)167>, the main contribution has been made by Korbonits <86JCS(P1)9, 86JST(136)215, 88CB723>, although other authors have also contributed <93H(35)453>.

3.01.7.2 Indazoles

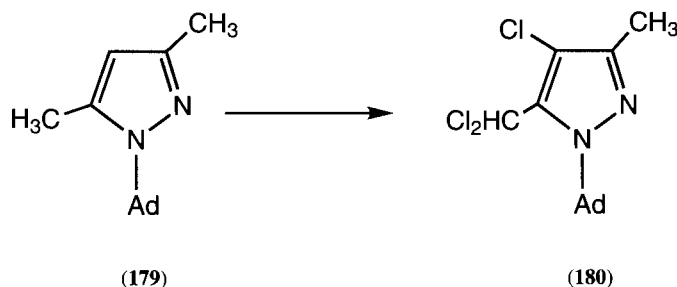
Nitration of 1-phenylindazole (**176**) in 86% nitric acid gives 1-phenyl-4-nitroindazole (**177**); when 2-phenylindazole (**178**) is nitrated in the cold, two mononitro compounds (m.p. 170°C and 184°C) were isolated but not identified <93AHC(58)215>. Preparation of 2-*p*-nitrophenylindazole (m.p. 224–226°C) can be achieved by reaction of indazole with *p*-fluoronitrobenzene in PTC conditions without solvent <93SC1947>, thus the unknown mononitro derivatives of 2-phenylindazole are probably nitrated on the indazole ring.



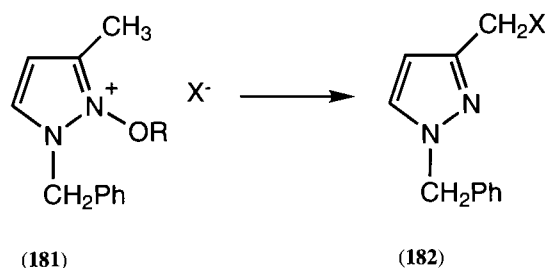
3.01.7.3 Other C-linked substituents

3.01.7.3.1 Alkyl groups

When trying to prepare the 4-chloro derivative of 1-adamantyl-3,5-dimethylpyrazole (**179**; Ad = 1-adamantyl) the trichloro derivative (**180**) was obtained <86JHC1045>.



Transformation of 4-methylpyrazoles into 4-carboxylic acids takes place readily by cobalt-manganese bromide mediated oxidation <91CL585>. Begtrup <92JCS(P1)2555> has developed a method to activate methyl groups at positions 3 and 5 using 2-alkoxy-pyrazolium derivatives (**181**); in this way pyrazoles (**182**) were prepared (X = D, I, OMe).



3.01.7.3.2 Aryl groups

Nitration at the *para* position of *C*-phenylpyrazoles has been already reported (see Section 3.01.5.4.2).

3.01.7.3.3 Other carbon-linked functionality

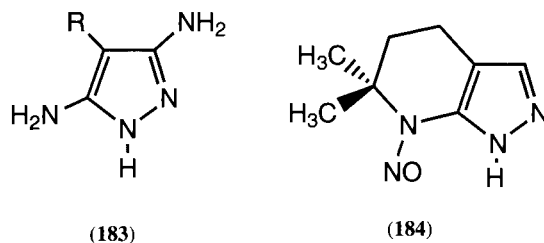
The x-ray structure of the monosodium salt of 4-nitro-3,5-dicarboxylic acid shows that it is the 3-CO₂H group which is ionized in the solid state <94MI 301-06>. It has been demonstrated that Δ²-pyrazolin-3-carboxylic acids can be decarboxylated thermally <94T7543>. Regioselective lipase-catalyzed transesterification of pyrazole-3,5-diester have been achieved <94BMC2523>. The normal reactivity of aromatic aldehydes is demonstrated by, for instance, the corresponding hydrazones, semicarbazones, oximes, and azines have been prepared <90M837, 93JHC957>. Becher has transformed the 4-formyl group into a carbothioaldehyde group <91S609> and has studied the rearrangement, produced by sodium azide, of 4-formyl-5-chloropyrazole into 4-cyanopyrazoles <92JOC2127>. The dienic reactivity of 4-vinylpyrazoles has been summarized by its discoverers <93FES195>.

3.01.7.4 N-linked Substituents

3.01.7.4.1 Amino-pyrazoles and -indazoles

The basicity and the protonation site of 3-amino, 4-amino, 5-amino 1-methyl-, and 1-phenyl-pyrazoles has been determined: most protonate on the pyrazole N₂ ring nitrogen (only 4-amino-pyrazoles protonate on the amino group) <85JHC997, 85MRC367, 89JCS(P2)1941>.

Acylation, alkylation, and the reaction with carbon disulfide of 3(5)-aminopyrazoles was studied by Graubau $\langle 93JPR88, 93JPR585 \rangle$; for instance, the reaction of 3(5)-aminopyrazole with methyl-isocyanate yields mixtures of mono-, di-, and triacylation derivatives $\langle 93JPR(335)585 \rangle$. Deamination of monoaminopyrazoles has been reported $\langle 91JHC1545 \rangle$; even the double deamination of 3,5-diaminopyrazoles (**183**) can be carried out affording 4-R pyrazoles $\langle 93SC925, 93JCS(P1)2229 \rangle$. In some cases, this last reaction leads to bicyclic systems like (**184**) when R = isopentyl $\langle 93G529 \rangle$.



Transformation of 5-aminopyrazoles into 5-(pyrrol-1-yl)pyrazoles has been achieved by means of 2,5-dimethoxytetrahydrofuran $\langle 94EJM233 \rangle$ which is the first step for the synthesis of pyrazolo-[4.3-*f*]pyrrolo[1,2-*a*]diazepines, a new class of anxiolytics (see Section 3.01.13.2). Pyrazole 5-iminophosphoranes have been used by Wamhoff $\langle 94JOC3985 \rangle$ as starting materials for the synthesis of zwitterionic heteropolycyclic pyrazoles.

3.01.7.4.2 Aminopyrazolium ions

Rearrangement of 1-aminopyrazole and 1-alkylaminopyrazoles into the corresponding 5-aminopyrazoles has been achieved in 48% aqueous hydrobromic acid; the reaction proceeds by protonation followed by ring opening/ring cyclization $\langle 90JCS(P1)809 \rangle$. The 1-alkylaminoindazoles rearrange into 2-alkyl-3-aminoindazoles $\langle 92JOC1563 \rangle$. The site of protonation of *C*-aminopyrazoles was determined by ¹⁵N NMR spectroscopy (see Section 3.01.7.4.1) $\langle 89JCS(P2)1941 \rangle$. The site of protonation of 1-aminopyrazole, 1- and 2-aminoindazoles occurs on the azole nitrogen atom and not on the amino group (¹³C and ¹⁵N NMR spectroscopy and theoretical studies) $\langle 93JCS(P2)1687 \rangle$.

3.01.7.4.3 Imines

The results of the electrooxidation of 1-aminopyrazoles in the presence of lithium perchlorate depends on the reaction medium employed: 1,2,3-triazines, *NH*-pyrazoles are formed $\langle 90CPB1524 \rangle$. In the presence of water *N,N'*-dipyrazolyl-1,3-propanediimine (pz—N=CH—CH₂—CH=N—pz) is formed.

3.01.7.4.4 Nitro and nitroso groups

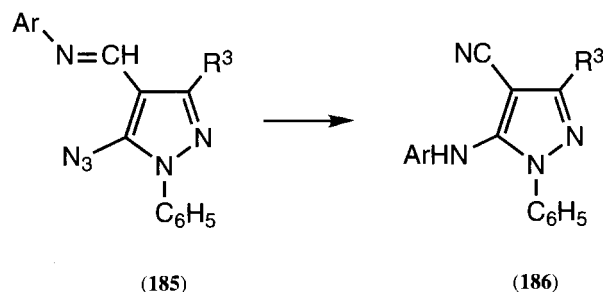
The *cine*-substitution of 1,4-dinitropyrazoles affords 4-nitro-3(5)-substituted pyrazoles including the antibiotics formycin and pyrazofurin $\langle 91JCS(P1)1077 \rangle$. Makosza $\langle 89LA545 \rangle$ has illustrated his vicarious nucleophilic substitution of hydrogen by examples of 4-nitropyrazole derivatives. The reduction of 1-nitropyrazole into 1-aminopyrazole was achieved by lithium aluminum hydride $\langle 92AQ724 \rangle$.

3.01.7.4.5 Azo-, diazo-, and azido-pyrazoles

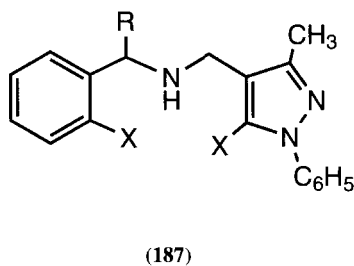
The rates of cyclization of 3(5)-azidopyrazolate anions into pyrazolo[1,5-*a*]tetrazolates have been measured $\langle 83AQ248 \rangle$ and the equilibrium between 3-azido-Δ²-pyrazolines and the corresponding bicyclic tetrazoles has been studied $\langle 84CS195 \rangle$. The factors affecting rates of thermal decomposition of 5-azidopyrazoles have been explored $\langle 94JCS(P2)2401 \rangle$. Rearrangement of *in situ* generated 5-azido-1-(substituted)-pyrazole-4-carboxaldehydes to 1-substituted-4-cyano-5-hydroxypyrazoles occurs efficiently $\langle 92JOC2127 \rangle$. The 3,5-dimethylpyrazole-4-diazonium cation and 2,3-dimethyl-1-phenyl-3-

pyrazolin-5-one-4-diazonium cation (antipyrene-4-diazonium cation) have been used to prepare Mo^{II} complexes (see Section 3.01.5.3.5) <86JCS(D)103>.

Becher has discovered that 5-azido-4-iminomethylpyrazoles (**185**) isomerize into 5-amino-4-cyanopyrazoles (**186**) via ring opening/ring closure and has succeeded in isolating the open-chain intermediate (a diazadiene) <91TL3565>.



Molina has used the double azide (**187**; $\text{X} = \text{N}_3$) to prepare rigid bicyclic guanidines through the double iminophosphorane (**187**; $\text{X} = \text{N}=\text{PPh}_3$) <93JOC1687>. Pyrazole-5-diazonium chloride has been transformed into the corresponding chlorosulfonyl derivative <94JHC93>.



3.01.7.5 O-linked Substituents

3.01.7.5.1 Interconversion and modes of reaction of tautomeric forms

The most important contribution to pyrazolinone tautomerism is the inclusion of solvent effects on the theoretical calculations <90JCS(P2)195, 93JA2352>. Theoretical calculations of the relative stabilities of the four tautomers of pyrazolinone (3-hydroxypyrazole **A** (OH form), 3-pyrazolin-5-one **B** (NH form), 5-hydroxypyrazole **C** (OH-form), and 2-pyrazolin-5-one **D** (CH form)) have been considered a challenge to theory <93JA2352>; theory predicts the order $\text{D} < \text{A} < \text{C} < \text{B}$ in the gas phase, which is different from the experimental results in solution <84CHEC-I(5)167>.

3.01.7.5.2 3-Hydroxy-pyrazoles and -indazoles

Boulton <86JCS(P1)1249> has described the synthesis of 3-methoxyindazole from indazolinone and Arán <93JCS(P1)1119> has reported the transformation of *spiro*-indazolylio oxides into dimeric macrocycles (1-alkyl-3-alkyloxy-bisindazoles).

3.01.7.5.3 5-Hydroxypyrazoles

The problem of protecting the OH group in pyrazolinones unsubstituted at the nitrogen atoms is a difficult one. In the case of 3-ethoxycarbonyl-pyrazolin-5-one, this has been achieved by reaction with dihydropyran <93JHC1097>: two compounds were isolated, a major one, which is the *O*-protected 3(5)-ethoxycarbonyl-5(3)-*O*-tetrahydropyranylpurazole, and a minor one, which is the *N*-tetrahydropyranylpurazolin-5-one. Oxidation of 1,3-disubstituted pyrazolinones gave a 4,4'-dimer with an OH group at position 4 <94JPR70>.

3.01.7.5.4 4-Hydroxypyrazoles

The 4-hydroxypyrazoles are the metabolites of pyrazole oxidation (see Section 3.01.5.4.11). Costero <93AHC(58)171> reported the oxidation of 3,5-diphenyl-4-hydroxypyrazole into 2,5-diphenyl-3,4-diaza-2,4-cyclopentadienone (**4**; $R^3 = R^5 = \text{Ph}$) as well as the chemistry of 1,4-dihydroxypyrazoles.

3.01.7.6 S-linked Substituents

Relatively little progress has been made in this area <84CHEC-I(5)167>. Bis(pyrazolin-5-one)sulfides have been prepared by reaction of pyrazolin-5-ones with trithiazyltrichloride ($\text{ClSN})_3$ (see Section 3.01.6.1.2) <87ZC434>. The IR and Raman spectra of thioantipyrine have been reported <89MI 301-03>. Pyrazolium quaternary salts bearing SCH_3 or SO_2CH_3 substituents at positions 3 and 5 react with sodium cyclopentadienid to afford 2,3-diazafulvenes (Δ^3 -pyrazolines with an exocyclic double bond) <94AP(327)385>.

3.01.7.7 Halogen Atoms

3.01.7.7.1 Nucleophilic substitution reactions: neutral pyrazoles and indazoles

When 4-formyl-5-chloropyrazoles were treated with potassium hydrogen sulfide the corresponding thiolaldehydes were obtained <89CC1349> (for an overview see <94JCS(P1)2553>). This method has been used by Becher to prepare a new type of binucleating macrocycle <90JA3709>. The transformation of 3-bromoindazole into a variety of 3-substituted indazoles (for instance, 3-methylindazole) has been achieved via the 1,3-dianion <92S937>; it is not necessary to protect position 1. Similarly, 4-bromopyrazole is transformed by butyllithium into 1,4-dilithiopyrazole <91JHC1189>, the double anion is a useful source of 4-acyl and 4-carbinolpyrazoles. Other examples are reported in <94H(37)2087>.

3.01.7.7.2 Other reactions

The transformation of 1-methyl-4-bromopyrazole into 1-methyl-4-trimethylsilylpyrazole by an “*in situ* Grignard” synthesis has been described <84JOC4687>.

3.01.7.8 Metal and Metalloid-linked Substituents

Reaction of 1-trimethylsulfonyl-5-trimethylsilylpyrazole with electrophiles affords 1-trimethylsulfonyl-5-substituted pyrazoles (for instance, $R^5 = \text{CH}(\text{OH})\text{R}$) <91CB1639>. The synthetic utility of 5-trimethylsilylpyrazoles to prepare the corresponding bromo, iodo, carbinols, and ketones has been examined <84JOC4687, 91CB1639>. Preparation of 4 (or 5) substituted pyrazoles (iodo, acyl, or aryl substituents) has been achieved from 1-phenyl-4- or 5-stannylpyrazoles <92H(33)813>.

3.01.7.9 Fused Heterocyclic Rings

Even excluding the [5,6] bicyclic derivatives, which constitute a chapter in themselves <84CHEC-I(5)305>, there are many fused ring systems containing pyrazoles; for instance fused sulfones (**246**) have been prepared <92T8101> (see Section 3.01.10.1.2(ii)). A beautiful example are the polycycles related to dimethanopyrazolo[3,4-*b*]pyrazoloazepino[2,3-*f*]azocine <89JCS(P2)137>; these compounds are formed when 5-methylaminopyrazoles react with hexane-2,5-dione.

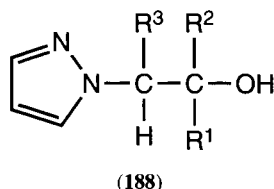
3.01.8 REACTIVITY OF SUBSTITUENTS ATTACHED TO RING NITROGEN ATOMS

3.01.8.1 Aryl Groups

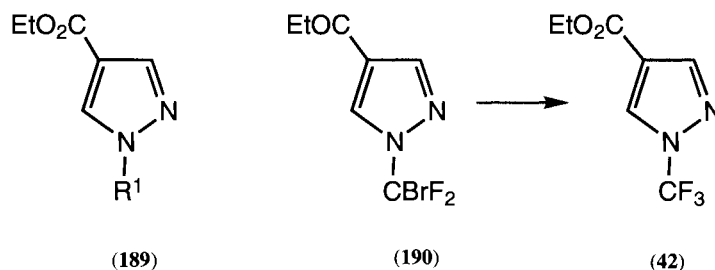
The σ_m and σ_p coefficients of 3-methylpyrazole (0.161 and 0.083, respectively) have been determined by alkaline hydrolysis of the *p*-methoxycarbonyl esters <86CB1627>.

3.01.8.2 Alkyl Groups

The lithiation of bispyrazolymethane (**88**; R = H) takes place on the CH₂ group and at 5-position of the pyrazole ring. The resulting carbanions react with a variety of electrophiles <83T4133>. Phenylthio, methylthio, and methoxy-substituted silylmethylpyrazoles act as *N*-pyrazolymethyl anion equivalents <89CJC1144, 89T637>. In this way, a large variety of compounds of general formula (**188**) have been prepared (R¹ = Ar, R² = H, Me, Ph, R³ = H, OMe, SMe).



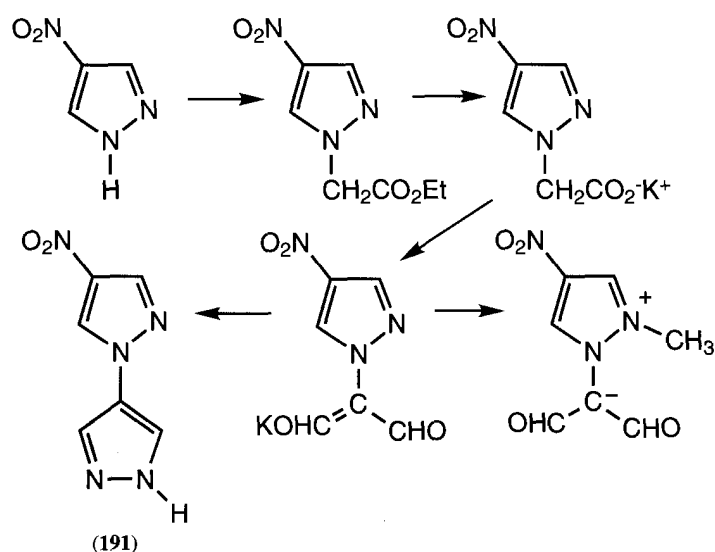
The only *N*-trifluoromethylpyrazole (**42**) (and one of the few representatives of an azole carrying a CF₃ group on the nitrogen <95OPP33>) has been prepared by a sequence of reactions that involves the transformation of the *N*-CBrF₂ derivative (**190**) into (**42**) <90JHC807>. The *N*-fluoroalkyl derivatives (**189**; R¹ = CH₂F, CHF₂) were also prepared. The *N*-*t*-butyl group can be removed by simple heating with formic acid, thus *t*-butyl group can be used as a protecting group for *NH*-pyrazoles <93H(36)2291>.



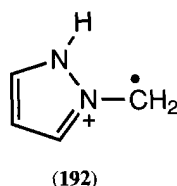
An interesting sequence of reactions, involving 4-nitropyrazolylacetic acids has been described (Scheme 5): it affords 4-(4-nitropyrazol-1-yl)pyrazole (**191**) <88CCC1519, 88CCC1529>.

3.01.8.3 Acyl Groups

The *N*-acylpyrazoles can be used as synthons due to their controlled alcoholysis <94S61>; the stability constants of their charge-transfer complexes with iodine and iodine bromide have been measured by Garnovskii <88ZOB194>. Flash vacuum pyrolysis of 1-alkynoyl-3-methylpyrazoles yield pyrazolo[1,5-*a*]pyridin-5-ols <94AJC991>; the reaction proceeds through 3-(*N*-pyrazolyl)-propanedienones. 1-Bromocarbonylindazoles ($\nu_{C=O}$ at 1750 cm⁻¹) react with methanol to afford 1-carbomethoxyindazoles (with water, the COBr group is hydrolyzed) <93TL239>. Decarbonylation of 1-acetylpyrazole in a mass spectrometer produces a nonclassical methylenepyrazolium radical-ion (**192**) <84BSB1057>. Isomerism of 3- and 5-methyl-1-carboxamidopyrazoles has been studied due to their industrial importance <87ZC435>.



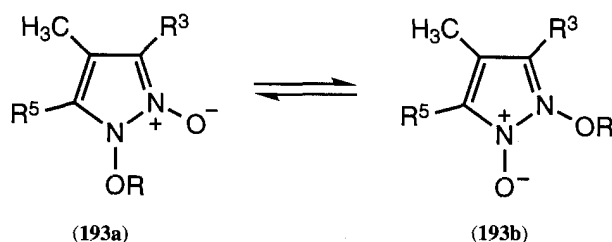
Scheme 5



It has been shown that 1*H*-pyrazole-1-carboxamide hydrochloride is a useful reagent for guanylation of amines and for preparation of guanidines $\langle 92\text{JOC}2497, 93\text{TL}3389 \rangle$.

3.01.8.4 *N*-oxides

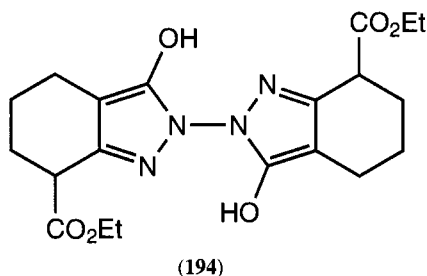
The rearrangement of *N*-(tosyloxy)pyrazole (**151**) involves a pyrazole cation (pz^+) similar to (**13**) $\langle 87\text{JOC}4058 \rangle$. Begtrup has described the *O*-silylation of pyrazole-*N*-oxides $\langle 93\text{JCS}(\text{P}1)625 \rangle$. Reversible [1,7] *O,O'*-alkylotropy of 1-alkoxy-2-oxi-pyrazoles (**193**) has been observed and the kinetic data determined $\langle 91\text{DOK}(321)530 \rangle$. The 2-hydroxy/1*H*-2-oxide tautomerism of indazoles has been studied by NMR spectroscopy (see Section 3.01.4.4.2) $\langle 87\text{MRC}721 \rangle$.



3.01.8.5 *N*-amino Groups

The structure of *N*-aminoazoles has been determined by x-ray crystallography, ^{15}N NMR spectroscopy, and INDO calculations $\langle 90\text{JCS}(\text{P}2)237 \rangle$. Among the 153 different *N,N'*-linked dimers of azoles, the 1,1'-bipyrazole (**14**) proved to be one of the most difficult to obtain. Some old references

were found to be false (the compounds are dimers but they are not *N,N'*-linked) <85H(23)2629> and other more recent references, correspond in fact to much more complex reactions than described <85H(23)2619>. The dimerization of ethoxycarbonyl derivatives of 4,5,6,7-tetrahydroindazolone with iodine affords not the *N,N'*-linked derivative (**194**) but *N,C* or *C,C'*-dimers <86T2377>.

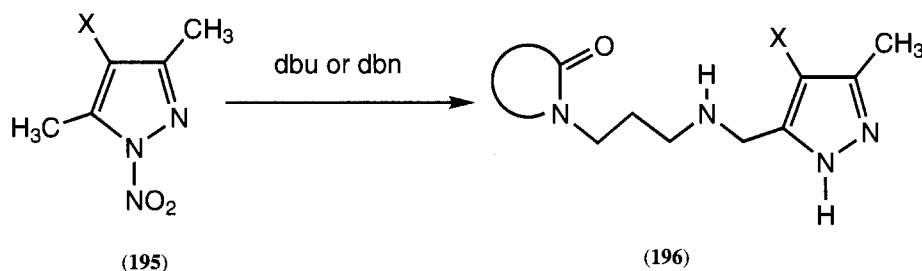


Pozharskii's interest for *N*-aminoazoles <92AHC(53)85> continues; he described the Schiff bases derived from 1- and 2-aminoindazole <93ZOR1896>. It has been shown that *N*-aminopyrazole reacts with nitrofurfural to afford the Schiff base (**28**), which has interesting antitrypanosomal activity <87AP(320)115> (see Section 3.01.13.2). Other imines derived from *N*-aminopyrazoles and *N*-aminopyrazolinones have been reduced by hydrogenation into *N*-alkylamino derivatives <92JHC321>.

The most used reaction of *N*-aminopyrazoles is their oxidation to 1,2,3-triazines <93LA367>. The mechanism of this reaction has been studied by Boulton <86JCS(P1)1249> using ¹⁵N labeling on the amino group; one of the examples described is the rearrangement of 1-amino-3-methoxyindazole into 4-methoxy-1,2,3-benzotriazine.

3.01.8.6 *N*-nitro Groups

Reduction of *N*-nitropyrzazole into *N*-aminopyrazole has been successfully achieved by lithium aluminum hydride <92AQ724>. Reactions of 1-nitro-3,5-dimethyl-4-halopyrazoles (**195**) with dbu and dbn affords derivatives (**196**) <94T865>. Reaction of 5-chloro-2-nitroindazole with amines affords 3-amino-5-chloroindazoles <85PHA105>, while 2,5-dinitroindazole on treatment with *N*-methylpiperazine affords 3,5-dinitroindazole and 3-(*N*-methylpiperazino)-5-nitroindazole <94PHA319>.



3.01.8.7 Halogens

No significant progress has been made since CHEC-I <85CHEC-I(5)167>.

3.01.8.8 *N*-metallic Derivatives

3.01.8.8.1 Boron

Tetrakispyrazolylborate salts (see Section 3.01.5.3.5) present an interesting problem concerning their protonation since the resulting molecule is neutral; actually the x-ray structures of (dmpz)₄BH

and (pz)₄BH have been determined <84CC188, 94RRC795> (dmpz = 3,5-dimethylpyrazole, pz = pyrazole) and correspond to zwitterions B[−]/pzH⁺. It is possible to replace the B—H bonds of pyrazabole (**117**; R = H) (see Section 3.01.5.3.15) by B—F bonds <88IC3085>.

3.01.8.8.2 Silicium

Reaction of 1-(trimethylsilyl)pyrazole with chlorocarbonyl isocyanate gives 1-oxo-1*H*-pyrazolo[1,2-*a*][1,2,4]triazol-4-ium-3-olates <88CB895>. Another interesting reaction of the same compound is with *N*-fluoropyridinium fluoride to afford 2-(pyrazol-1-yl)pyridine (**24**), a useful chelating agent (see Section 3.01.5.3.4(v)) <93JOC4476>.

3.01.8.8.3 Chromium

Chromium trioxide-3,5-dimethylpyrazole is a mild and selective reagent for oxidation of α -methylenecyclopropanes into cyclopropylketones <93CC954>.

3.01.9 PYRAZOLES, INDAZOLES, AND THEIR DERIVATIVES AS STARTING MATERIALS FOR THE SYNTHESSES OF FUSED RING SYSTEMS

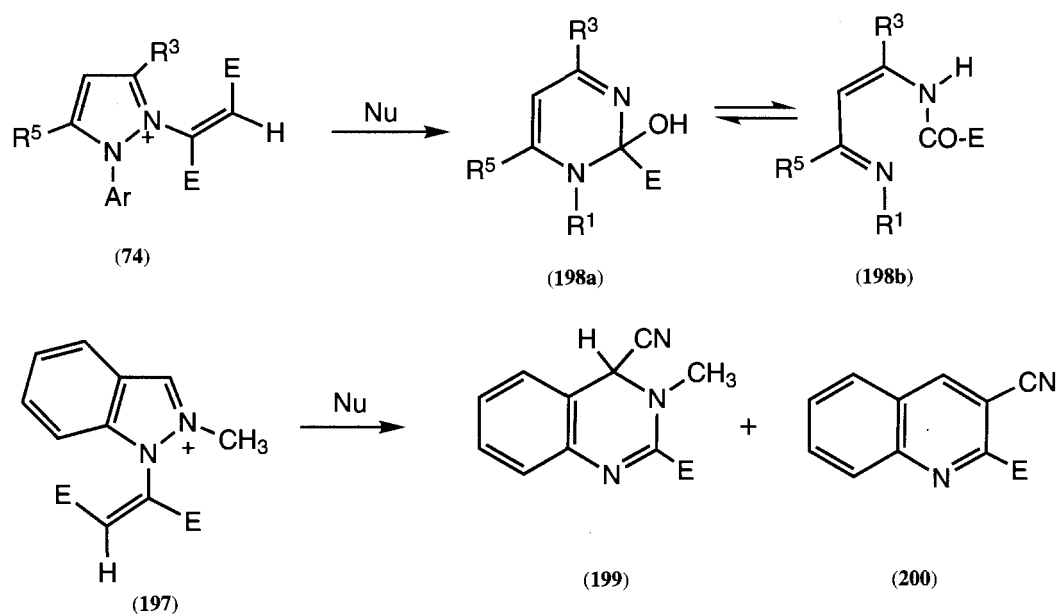
Without doubt, the most useful pyrazole synthons for building fused heterocyclic systems are aminopyrazoles. For instance, 1-methyl-4-cyano-5-aminopyrazole is the starting material for the synthesis of pyrazolo [4,3-*f*]pyrrolo[1,2-*a*][1,4]diazepines which possess anxiolytic activity <94EJM233>; 1-phenyl-3-methyl-4-nitroso-5-aminopyrazole has been used to prepare imidazo[4,5-*c*]pyrazoles and pyrazolo[3,4-*d*]thiazoles <90T5777, 93H(36)857>. An important nucleoside, 1-(2-deoxy- β -D-ribofuranosyl)-3-methyl-5-amino-1*H*-pyrazolo[4,3-*d*]pyrimidin-7-one, has been prepared from 3(5)-methyl-4-amino-5(3)-ethoxycarbonylpyrazole <92JA1470>. To prepare pyrazolo[*a*]acridin-9(10*H*)-ones 5-amino- and 6-aminoindazoles have been used <90JCR(S)350>. On the other hand, 1-ethyl-5-iminophosphoranepyrazole has been used to prepare several zwitterionic polycyclic heterocycles <94JOC3985>.

The two most important photographic couplers of modern times are both [5,5]-fused pyrazole derivatives (see Section 3.01.13.3); the one discovered by Bailey is a derivative of 1*H*-pyrazolo[5,1-*c*][1,2,4]triazole <91JCS(P2)1363, 91JCS(F1)3479> and that discovered by Sato derived from 1*H*-pyrazolo[1,5-*b*][1,2,4]triazole <94JCS(P2)531>. Due to their potential CNS-activity, imidazo[1,2-*b*]pyrazoles continue to be prepared <94JHC737>.

Reaction of 4-acetyl-5-chloropyrazoles with phenylhydrazine yield pyrazolo[3,4-*b*]quinoleines <86JHC999>. The reaction of *N*-vinylpyrazolium (**74**) and *N*-vinylindazolium salts (**197**) with cyanide ion affords 1,2-dihydropyrimidines (**198**), 3,4-dihydroquinazolines (**199**), and quinolines (**200**) <92JOC4151, 93T11305> (see Section 3.01.5.2).

3.01.10 SYNTHESSES CLASSIFIED BY NUMBER OF RING ATOMS IN EACH COMPOUND

The same classification as in CHEC-I <84CHEC-I(5)167> is followed. It is clear that two methods of preparing pyrazoles and their derivatives continue to dominate all other methods, in both the two nitrogen atoms come from one of the reagents, either hydrazine (see Section 3.01.10.1.2(ii) (CCC + NN)) or a 1,3-dipole, diazoalkane, nitrilimine, etc. (see Section 3.01.10.1.2(ii) (CNV + CC)). The other methods are curiosities mostly discovered by hazard or variations of these two great principles.

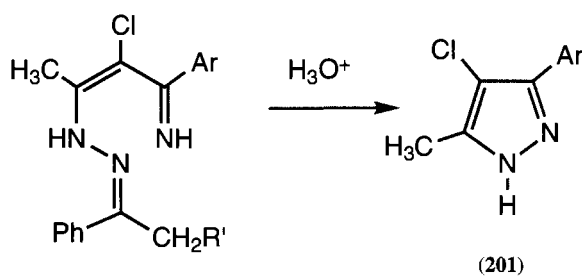


3.01.10.1 Ring Synthesis from Nonheterocycles

3.01.10.1.1 Formation of one bond

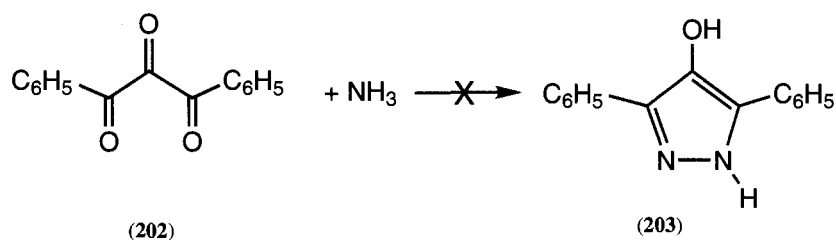
(i) Between two heteroatoms

One clear example of synthesis of pyrazoles by formation of the $\text{N}_1\text{—N}_2$ bond <84CHEC-I(5)167> is the ring closure of iminohydrazone (1-azadienes) to *NH*-pyrazoles (**201**) <86JHC459>.

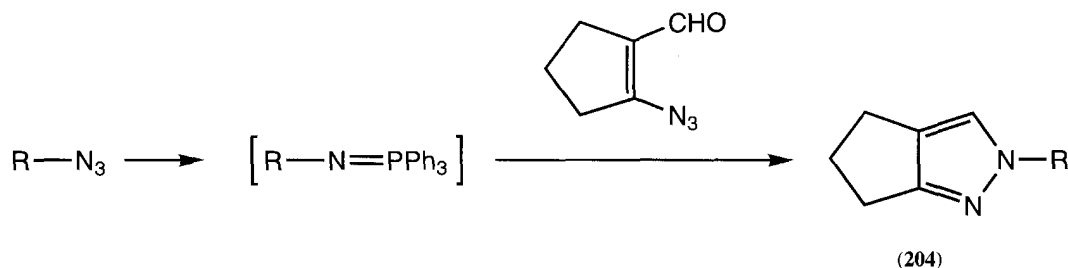


A new synthetic way, found by a computer-assisted organic synthesis program, to prepare 3,5-diphenyl-4-hydroxypyrazole (**203**) from diphenylpropanetrione (**202**) and ammonia failed <88AQ285>. A rationale for the failure is provided by MNDO calculations.

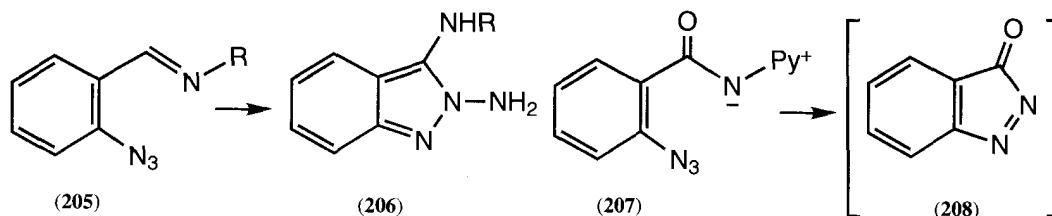
An original synthesis of *N*-substituted-3,4-trimethylenepyrazoles (**204**) from iminophosphoranes



and 2-azido-1-cyclopentene-1-carboxaldehyde has been described ($R = \text{Ph}, \text{CH}_2\text{Ph}, \text{CH}_2\text{CO}_2\text{Et}$) <88S742>.

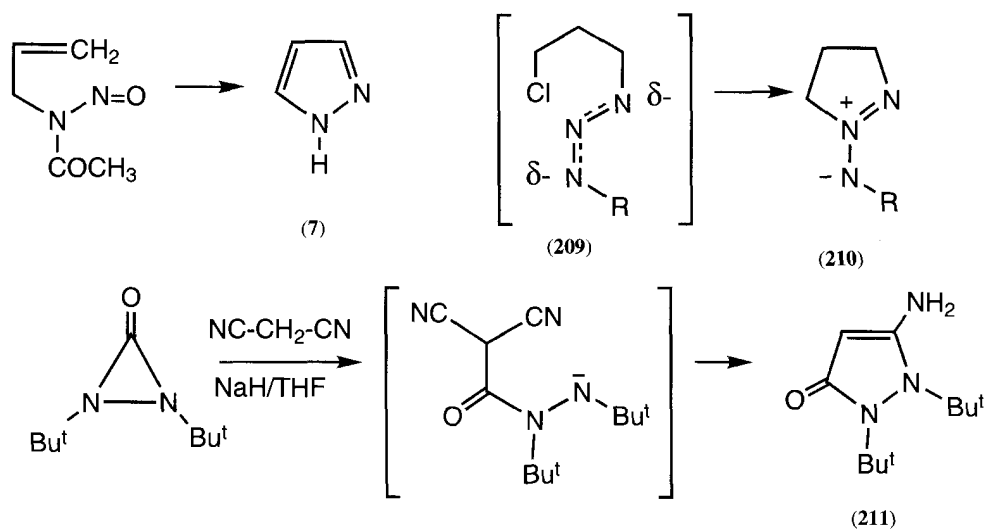


A new synthesis of *N,C*-diaminoindazoles (**206**) involves the treatment of *o*-azidobenzaldimines (**205**) with tertiary phosphine via the Staudinger reaction followed by hydrolysis ($R = \text{Ph}, \text{Pr}^n$) <89TL6237>. Related to this reaction is the preparation of 3*H*-indazol-3-one (**208**) from *N*-(*o*-azidobenzoyl)-iminopyridinium ylide (**207**) <85TL5707>. Compound (**208**) is unstable (it is a Structure (3)-like derivative) and has to be trapped by dienes.



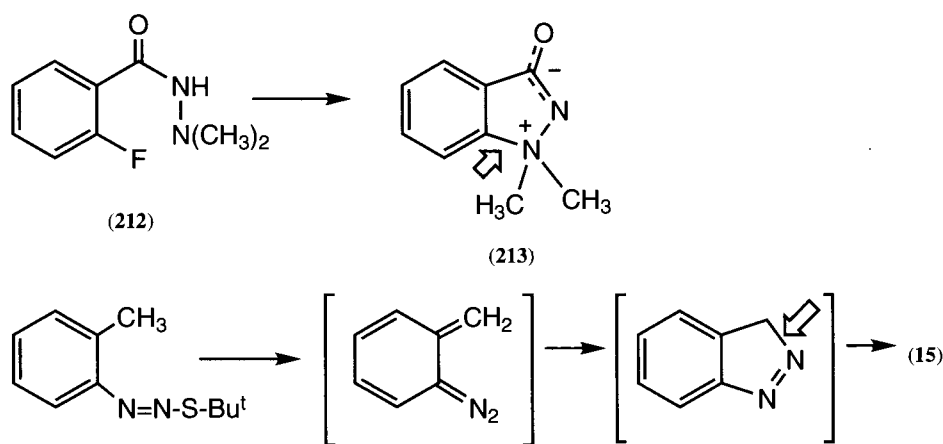
(ii) *Adjacent to an heteroatom*

In this section, all the reactions have in common the formation of an N—C bond as the last step in the synthesis of pyrazoles and indazoles. First, pyrazoles and then indazoles are discussed. Pyrazole itself and many other *NH*-pyrazoles have been obtained from *N*-allyl-*N*-nitrosamides <90H(30)789>; to illustrate the reaction, Scheme 6 represents the case of pyrazole (**7**). The reaction of 1-azido-3-chloropropane with various Grignard reagents, affords an intermediate (**209**) which cyclizes into a new class of azimines derived from Δ^1 -pyrazolines (**210**) <92TL4683>. Ring enlargement of diaziridinone by reaction with bifunctional carbanions lead to pyrazolinones <92JOC7359>; in Scheme 6 is represented the case of malononitrile which affords 1,2-bis-*t*-butyl-3-aminopyrazolin-5-one (**211**).



Scheme 6

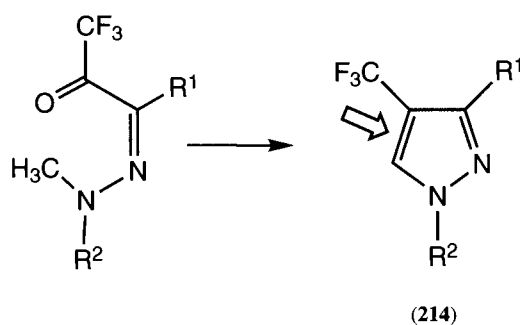
Concerning indazoles, first of all, the report by Barton of a new method to prepare indazolinone (67) (Scheme 51, <84CHEC-I(5)167>) was an error <83CC1376>. The 3-substituted-2-acylaminoindazoles have been prepared via lead tetraacetate oxidative cyclization of *N*-carbonylhydrazones of *o*-aminoarylketones <94H(37)1541>. Examples of each of the possibilities to form an indazole derivative by closing an N—C bond are represented in Scheme 7. The first example concerns the N₁—C_{7a} bond <93JCR(S)218> and the second the N₂—C₃ bond <94T3529>. Cyclization of *N,N'*-disubstituted 2-halogenobenzohydrazides (212) give 1,1-disubstituted indazol-3-ylidene oxides (213). On the other hand, treatment of arylazosulfides affords indazoles, for instance, indazole itself (15).



Scheme 7

(iii) β to a Heteroatom

The very interesting synthesis of 3-R-4-trifluoromethylpyrazoles (214) from hydrazones has the limitation that position 5 has to remain unsubstituted <88JOC519, 88TL5281>.



3.01.10.1.2 Formation of two bonds

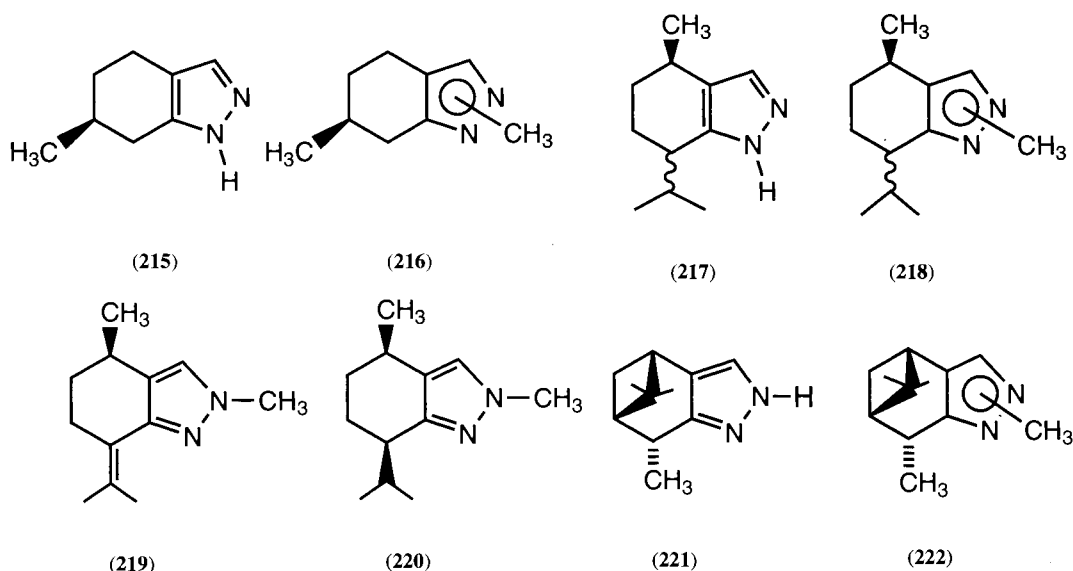
(i) From 4 + 1 atom fragments

The synthesis of pyrazolines and pyrazoles by a [CCNN + C] process has not made significant advances since <84CHEC-I(5)167>. A new method to prepare 1-hydroxypyrazole 2-oxides by nitrosation of acrylophenone oxime, [CCCN + N] has been reported <93JHC1163>.

(ii) From 3 + 2 atom fragments

(a) [CCC + NN]. The use of hydrazines and β -dicarbonyl compounds continues to be the method of choice for the synthesis of pyrazoles. For instance $^{15}\text{NH}_2\text{—}^{15}\text{NH}_2$ and $^{15}\text{NH}_2\text{—}^{14}\text{NH}_2$ have been used for preparing double-labeled and mono-labeled pyrazoles (see Section 3.01.12.3).

A series of papers by Shimizu <88AQ176, 88AQ183, 88AQ191, 88AQ198> were devoted to the synthesis of pyrazoles from optically active natural carbonyl compounds: this series of papers constitutes the major effort to prepare chiral pyrazoles. In this way were prepared (215) and (216) <88AQ176>, (217)–(220) <88AQ183, 88AQ198>, (221) (campho[c]pyrazole, see Section 3.01.4.4.1), and (222) <88AQ191>.

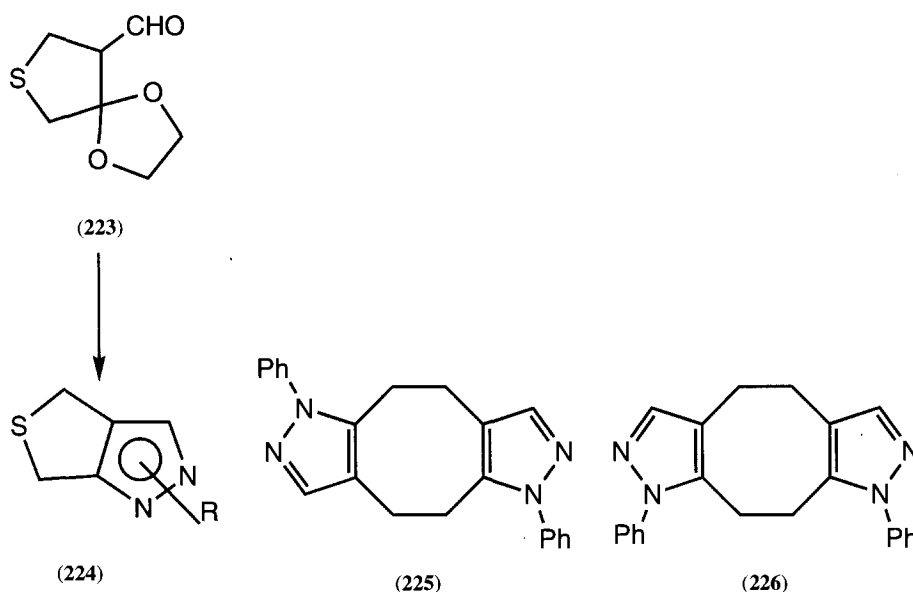


Reaction of phenylhydrazine with 2-fluoro-1,3-diketones affords 1-phenyl-4-fluoropyrazoles <92JFC(56)141> while 1-adamantylhydrazine has been used to prepare *N*-adamantylpyrazoles <84JHC249, 86JHC1045>. There is much interest on regioselectivity, for instance, ethoxymethyl-enketonitriles when reacted with hydrazines afford either 4-cyanopyrazoles or 4-acyl-5-aminopyrazoles <91AJC1263>. Bis(alkylthio)acrylaldehydes react with arylhydrazines to afford only the 5-thiomethyl isomer of 1-arylpyrazoles <86JPR321>. It has been shown that α,β -ethynylketones can be used instead of β -diketones <93JHC755> to regioselectively direct the reaction to one or the other isomer.

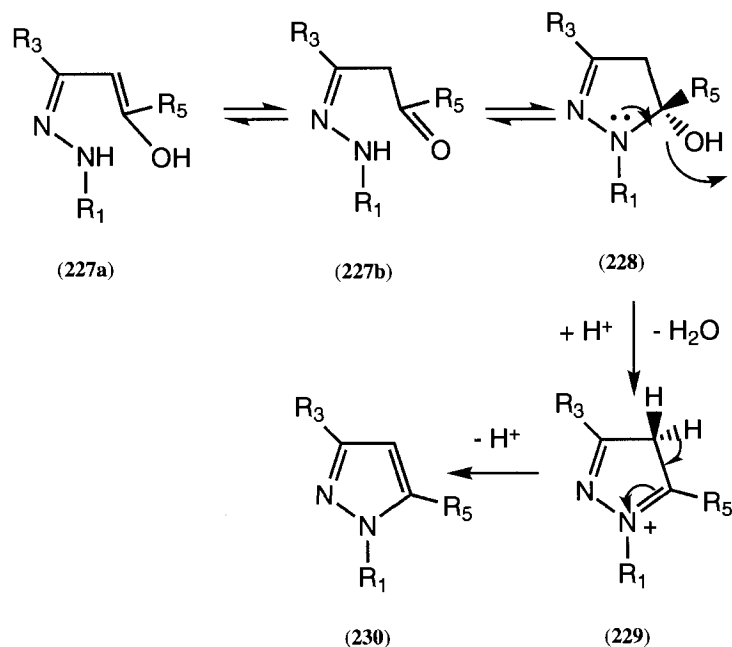
The reaction of hydrazines with dehydroacetic acid affords 3,4-linked pyrazolopyrazolinones <87BCJ4425, 90JHC865>. Reaction of hydrazine hydrate with 6-acetyl-7-(2-dimethylaminovinyl)-pyrazolo[1,5-*a*]pyrimidines affords a 6-(pyrazol-3-yl) derivative and not a diazepine as was formerly claimed by the same authors <94JCS(P2)1657>. When 1,1-dimethylhydrazine is used, one *N*-methyl group is eliminated and *N*-methylpyrazoles are obtained <92SC3081>; in this way 1,3,5-trimethyl-4-arylpyrazoles have been synthesized. Peet has explored the chemistry of 1,5,6,7-tetrahydroindazol-4-ones <87JOC4384, 91H(32)41>; these systems are prepared by reacting hydrazines with cyclohexanetriones.

Reichardt has found a very general method to prepare 4-substituted pyrazoles from *C*-substituted malondialdehydes <84LA649, 85LA1969>. With this method all derivatives from 4-cyclopropyl- to 4-cycloheptyl-pyrazoles <84LA649>, 1-*p*-nitrophenyl-4-(2,4,6-cycloheptatrien-1-yl)pyrazole and 1,2-dimethyl-pyrazolium cation have been prepared <85LA1969>. Another useful precursor is triformylmethane, with which it is easy to prepare 4-formylpyrazoles <90BSF660>. With convenient β -dicarbonyl compounds and hydrazines a series of 1,3,5-trisubstitutedpyrazole mevalonolactones were prepared to be evaluated as inhibitors of cholesterol biosynthesis <90JMC31> and a novel amino protection-deprotection procedure uses a tetrahydroindazole as leaving group <93CC776>.

To modify the regioselectivity in the reaction of 2,4-diketoesters towards arylhydrazines, the carbonyl groups were protected as methoxyimino derivatives <93JHC307>, thus, the ratio of the 1-phenyl-3-ethoxycarbonyl pyrazole over the 1-phenyl-5-ethoxycarbonylpyrazole was reversed. Pyrazoles fused with a tetrahydrothiophene ring, like (224), were prepared from a masked β -ketoaldehyde (223) <93JOC493>; in the same publication are described two interesting analogues of dibenzocyclooctene (225) and (226).



Preparation of 3(5)-trifluoromethylpyrazoles was done using the same methods as with conventional pyrazoles $\langle 84\text{CHEC-I(5)167} \rangle$, the main difference being that the intermediate 5-hydroxypyrazolines **(228)** are usually isolated (Scheme 8). According to the mechanism proposed for the formation of pyrazoles by reaction of β -dicarbonyl compounds with hydrazines $\langle 90\text{JCR(S)120} \rangle$, the presence of a strong electron-withdrawing substituent at position 5 hinders the formation of the intermediate immonium salt **(229)**. Other authors have also isolated the 5-hydroxy-5- R_F - Δ^2 -pyrazolines **(228)** $\langle 89\text{TL2049, 90JHC919, 92ZOR1380, 93JHC1159} \rangle$ (the last authors reported that for $R_1 = \text{C}_6\text{H}_5$, the dehydration of **(228)** to **(230)** using sulfuric acid failed).



Scheme 8

Spectroscopic results prove that in the case $R_5 = \text{CF}_3$, the 5-hydroxypyrazoline exists as **(228)** and not in the open-chain tautomer **(227)** (the monohydrazone of the β -diketone). In the synthesis of 3-hydroxy-5-trifluoromethylpyrazoles the intermediate 5-hydroxy-5-trifluoromethylpyrazolidinones have also been isolated $\langle 90\text{JHC243} \rangle$. The reaction summarized in Scheme 8 has been used by

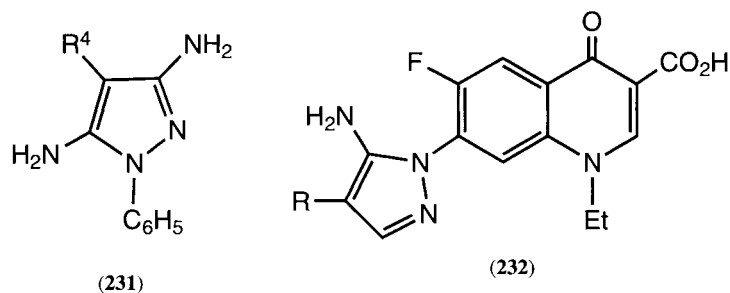
Jorgensen as a test for the program CAMEO (Computer-Assisted Mechanistic Evaluation of Organic Reactions) <88JOC2504>.

The synthesis of trifluoromethylpyrazoles from hexafluoroacetylacetone and hydrazines $R-NH-NH_2$ ($R = H$, benzyl, phenyl, *p*-nitrophenyl, 2,4-dinitrophenyl) <91JFC(51)283> has been questioned (see below). In the case of $R = p$ -chlorophenyl, the pyrazole structure of the resulting products was established by x-ray crystallography <87JHC739>. The use of heterocyclic hydrazines has been studied and it has been found that they behave like aromatic hydrazines <88JHC1641, 92IJC(B)233>. The problem of establishing the structure of the products obtained ((228) or (230)) has been clarified definitely by Threadgill *et al.* <93JFC(65)21> and by Singh *et al.* <93JCR(S)163> thanks to the combined use of ^1H , ^{13}C , and ^{19}F NMR spectroscopy (see Section 3.01.3.4.2). Regioselective synthesis of trifluoromethylpyrazoles by selective protection of trifluoromethyl- β -diketones has been achieved <90JHC919, 92IJC(B)233, 92H(34)791>.

Other authors have successfully used the reaction of hydrazines with trifluoroacetylthyenes and with alkynic esters to prepare trifluoromethylpyrazoles and pyrazolinones <89TL2049, 90JFC(48)123>. Reaction of copper(II) polyfluorinated β -diketones and β -keto-esters with hydrazines yields the corresponding trifluoromethylpyrazoles and -pyrazolinones <93JHC49, 90IZV640>. The same kind of compounds can be prepared from β -trifluoroacetylactams <93TL5075>. Other functional derivatives of β -diketones have been used to prepare 3(5)-fluoroalkyl-ethoxycarbonylpyrazoles <88IZV1367>.

Other synthesis of trifluoromethylpyrazoles which also use hydrazine or substituted hydrazines can be summarized as follows. The synthesis of trifluoromethyl-substituted pyrazoles from 1,1,1-trifluoro-3-phenylsulfonyl-2,2-propanediol has been reported <90SL353>. A novel and practical method for preparing 3-trifluoromethylpyrazoles uses as starting material perfluoroiodopropane and acetylenic compounds <94CC631>; in general, 3(5)-perfluoroalkylpyrazoles have been obtained from perfluoroalkylaldehydes and hydrazine (the reaction involves the formation of a hydrazone intermediate followed by elimination of hydrogen halide and intramolecular nucleophilic addition) <94JCS(P1)2161>. The preparation of 1-methyl-3-perfluoroalkyl-4-fluoro-5-phenylpyrazoles from 1-phenyl-1-trimethylsilyl perfluoroalkanols <94TL409>, is a rather complex reaction but one which proceeds in excellent yields (the same compounds can also be obtained from enol phosphates derivatives from perfluoroalkyl ketones) <88CL819>. The reaction of α,α,α -trifluorotoluene, hydrazine and ozone was reported to give a mixture of several products, amongst them 3(5)-trifluoromethylpyrazole (32) and 4-trifluoromethylpyrazole but without any structural proof <90RTC577>. Other less general syntheses of 4-trifluoromethylpyrazoles had been reported previously <90JFC(47)45>, as well as formation of 3-dialkylamino-4-trifluoromethylpyrazoles from trifluoropyruvichthioamides <90BSB941, 90BSF843>.

A series of interesting aminopyrazoles have been prepared using the general procedure: 3,5-diaminopyrazoles (231) <88S813> and a 5-aminopyrazole derivative related to antibacterial quinolones (232) <88JHC1543>.



Preparation of 3- and 5-dimethylaminopyrazoles can be achieved from α -chlorodienamines, $Me_2N-C(Cl)=C(R^1)-C(R^2)=C(CN)_2$, and hydrazine or phenylhydrazine <93BSB129>. Other 5-aminopyrazoles were prepared using as precursors hydrazines and ketene dithioacetals or *N,N*-bis(methylthio)-methylene-*p*-toluenesulfonamide <90JHC775, 90JHC1245>. Thus were prepared multifunctionalized pyrazoles like (233) and (234). Dipyrazolo[3,4-*b*;4',3'-*f*]azepines (236) were prepared from azepines (235) and phenylhydrazine <89JCS(P1)2095>.

Benzoylhydrazones of 2,2-dimethyl-4,4-diphenylbut-3-enal undergo a novel photochemical cyclization to afford Δ^2 -pyrazolines (1-benzoyl-4,4-dimethyl-5-diphenylmethyl) <93CC721>. Prinzbach has described an interesting series of reactions <93CB429>; starting from the bicyclic dione (237), the addition of hydrazine yields the double-Michael adduct (238) (and not the bishydrazone) which is cyclized into the double- Δ^2 -pyrazoline (239) for, finally, obtaining the desired double- Δ^1 -pyrazoline (240) (to prepare iron-tricarbonyl complexes).



Reaction of α -trifluoromethylthiocinnamides with hydrazine yields a mixture of *trans*- and *cis*- Δ^2 -pyrazolines (**241**) and (**242**) (<90BSF843>; the *cis*-isomers are predominant, probably due to the protonation of the intermediate Δ^3 -pyrazoline by the less hindered face, these pyrazolines are readily oxidized to the corresponding pyrazoles. The x-ray structure of the *trans* pyrazoline (**241**) is reported in the same paper.



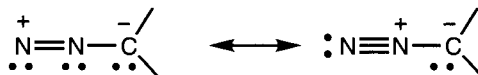
(b) **[CNN + CC]**. This is the second method in importance for the synthesis of pyrazole derivatives. Concerning pyrazoles and according to Huisgen classification (Scheme 9) three main classes of 1,3-dipoles can be distinguished. The first method of synthesis uses diazoalkanes as a source of the **[CNN]** fragment, the second one uses nitrilimines or their precursors, the third one, the less common, uses azomethine imines, the **[CC]** fragment coming from alkenes or alkynic compounds.

Hetarylpyrazoles have been prepared by intramolecular cyclization of diazovinyl compounds $\langle 88M1037 \rangle$. The 1,3-dipolar cycloaddition of diazomethane to trifluoromethyl-substituted alkenes

Octet-stabilized 1,3-dipoles with double bond

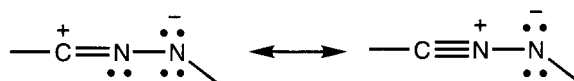
1) Diazonium betaines:

Diazoalkanes

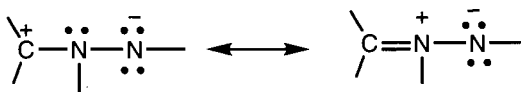


2) Nitrilium betaines

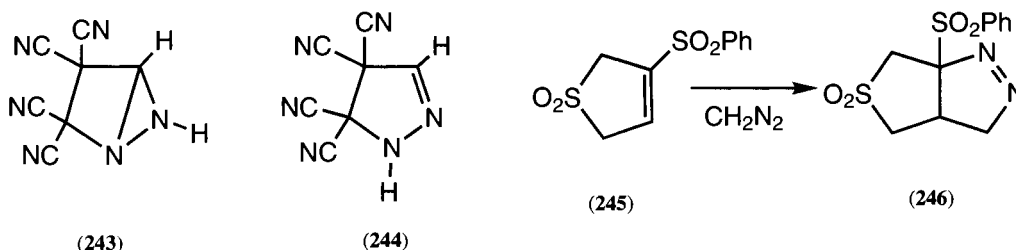
Nitrilimines

**Octet-stabilized 1,3-dipoles without double bond**

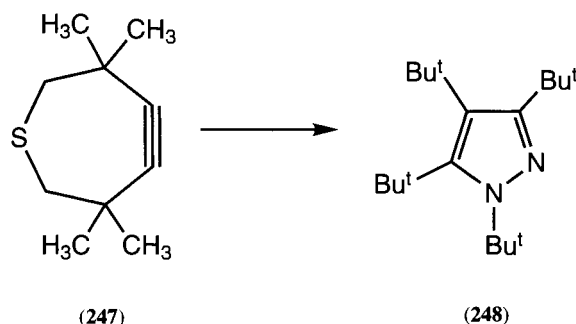
3) Azomethine imines



Scheme 9



allows the synthesis of trifluoromethyl Δ^1 - and Δ^2 -pyrazolines <92JCR(S)40>. Nagai has systematically explored <89JOC1135, 89JOC5912> the reactions between disubstituted diazomethanes and chlorinated alkenes. To prepare 3(5)-trifluoromethyl-5(3)-phenylpyrazole α -trifluorodiazomethane compounds have been used <90JFC(46)173>. Trifluoromethylacetyl-ethynes are reported to give 4-trifluoromethylpyrazoles in good yields <93JFC(62)39>. The most crowded pyrazole ever described (**248**) was prepared by Krebs <92TL5947> by the addition of di-*t*-butyldiazomethane on the thiacycloalkyne (**247**). A little different are the additions to ethynylphenyl-iodonium triflate to afford either 3-iodo or 4-iodopyrazoles <92T3527>.

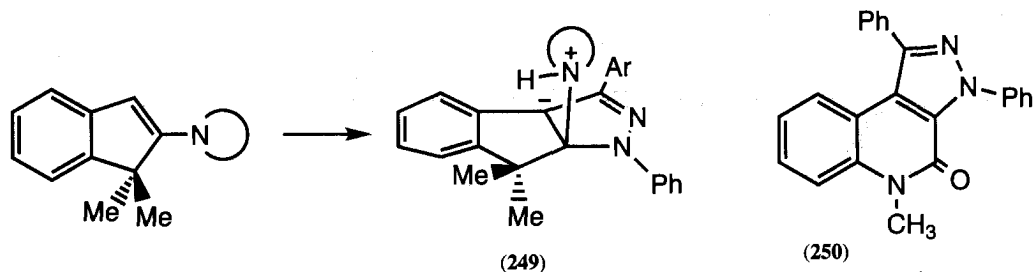


The reaction of nitro alkenes attached to sugar residues with diazomethane gave 3-methyl-3-nitro-4-gly- Δ^1 -pyrazolines <88JOC5648>. In a similar way was prepared an intermediate for the synthesis of 2',3'-dideoxyformycin B (a pyrazolopyrimidine) <92TL2921>.

Concerning the use of nitrilimines (Scheme 9), Huisgen himself has reported new examples <84CHEC-I(5)167>. Thus, in a series of papers <83CB3027, 83CB3039, 83CB3062, 83CB3438> he has explored the reaction of nitrilimines of general structure $\text{R}-\text{C} \equiv \text{N}^+ - \text{N}^- - \text{Ph}$, where $\text{R} = \text{H}$, Me , or Ph (this is the most common one); the synthesis, ^1H NMR spectra and mechanism of a large family of Δ^2 -pyrazolines and pyrazoles have been described.

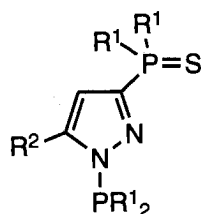
Laude has published a very complete series of studies concerning the 1,3-dipolar cycloaddition

of diarylnitrilimines towards alkenes which are part of a polycyclic system. For instance in <89CC632> he reports the isolation of the first example of a stable zwitterionic nitrilimine-enamine cycloadduct (249). In <91CR(B)1129> he discusses the regiochemistry of the reaction of diphenylnitrilimine with carbostyryl and indole derivatives where compounds like (250) were isolated.



An "alkene" which has been made to react with diphenyl nitrilimine is C_{60} fullerene: the diadduct has been characterized by FAB MS <94TL1763>. Hydrazidoyl chlorides are useful precursors of nitrilimines; for instance, Δ^2 -pyrazolin-3-carboxylic acids have been prepared with this method <94T7543>. The dipolar cycloaddition of *in situ* generated nitrile imines with the enolates of β -diketones affords 4-acyl-5-R-pyrazoles ($R = CF_3$) <94T8827>. Grünanger has studied the regioselectivity of the reaction between diphenyl- nitrilimine and, on the one hand, cycloheptatriene and, on the other hand, (cycloheptatriene)tricarboxyliron <93G209>; Δ^2 -pyrazolines and pyrazoles are isolated. Reaction of 2-phenyl-4-arylideneoxazol-5(4*H*)-ones with nitrileimines affords spiro- Δ^2 -pyrazolines and, by ring opening of the azaspirane ring, a mixture of Δ^2 -pyrazolines and pyrazole-5-carboxylic acids <90JCR(S)202>.

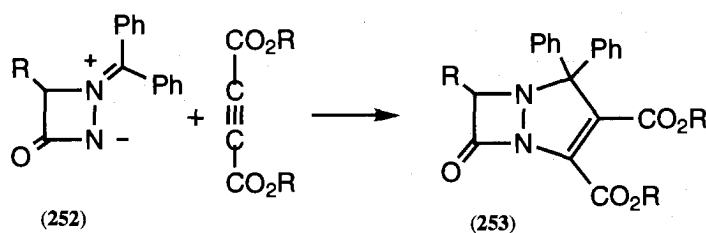
Bis(trimethylstannyl)diazomethane reacts with trityl chloride to afford bis(triphenylmethyl)-nitrilimine which is the precursor (through reaction with olefins and acetylenic compounds) of 1,3-bis(trityl)- Δ^2 -pyrazolines and pyrazoles <92AG(E)439>. Intramolecular nitrilimine cycloadditions have been explored <94JCS(P1)433>: the reaction affords pyrazolo[1,5-*a*]benzoxazepines. Alkoxy-carbonylazoalkenes ($R^1-N=N-C(Me)=CH-CO_2R^2$) on reaction with triphenylphosphine afford betaine intermediates which undergo thermolysis to afford either 5-alkoxypyrazoles or 4-(triphenylphosphoranylidene)-pyrazolin-5-ones <92T1707, 94JCR(S)192>. Bertrand <90AG(E)1123> using *N*-phosphino *C*-thiophosphinoyl nitrilimine has prepared pyrazoles (251).



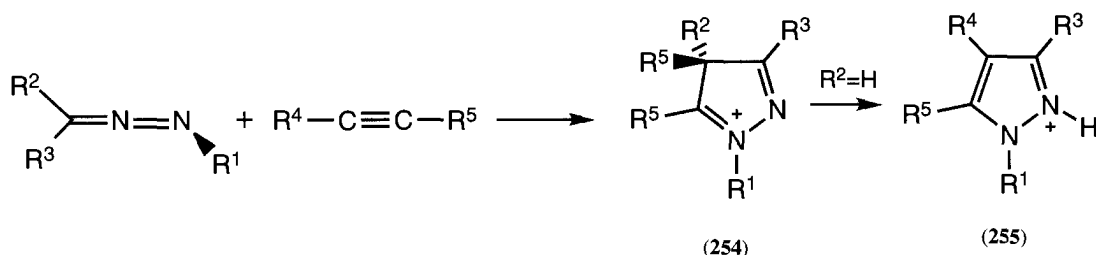
(251)

Concerning the use of azomethine imines (Scheme 9), the synthesis by Taylor of aza- β -lactams (253) from azomethine imine (252) must be quoted <91T9599>. Related to these syntheses are the $[3^+ + 2]$ cycloadditions of hydrazine hydrochlorides <87JOC2277>; using this methodology introduced by Grigg <87T5873> a variety of pyrazolidines and pyrazolines have been prepared, including various [5,5] fused ring systems with two ring junction nitrogen atoms.

Finally, 1-aza-2-azonia cations, prepared *in situ* from geminal chloro(alkylazo) compounds, react



with ethynes to give either 1*H*-pyrazolium salts (**255**) or 4*H*-pyrazolium salts (**254**) <94CB541>. Subsequently, AM1 calculations were carried out on this 1,3-dipolar cycloaddition with reverse electron demand.



3.01.11 RING SYNTHESIS BY TRANSFORMATION OF ANOTHER RING

3.01.11.1 Ring Opening

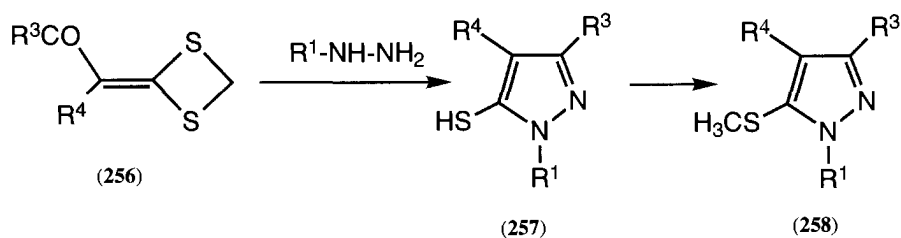
For the sake of similarity this section has been kept <84CHEC-I(5)167> as it corresponds to the ring opening of bicyclic systems already containing the pyrazole nucleus.

3.01.11.2 Ring Transformations

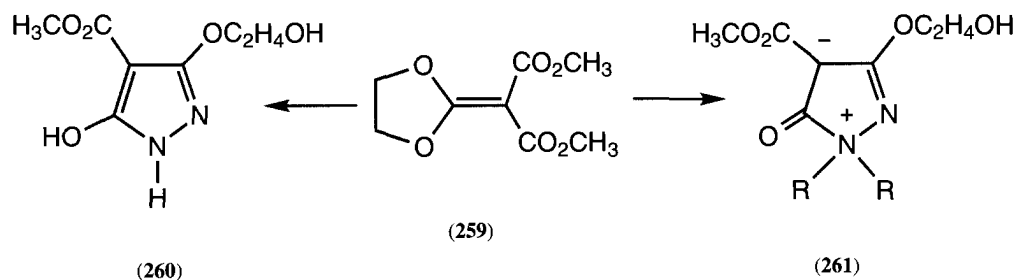
3.01.11.2.1 Masked β -difunctional compounds

(i) One functional group

Reaction of 2-methylene-1,3-dithietanes (**256**) with hydrazines affords 5-thiopyrazoles (**257**) <90JHC567>. These last products were converted into 5-*S*-methyl pyrazoles (**258**) by methyl iodide. Other authors <87JCS(P1)1945> have used α -aroyl- α -bromoketenedithioacetals to prepare 3(5),4-bis(alkylthio)pyrazoles.

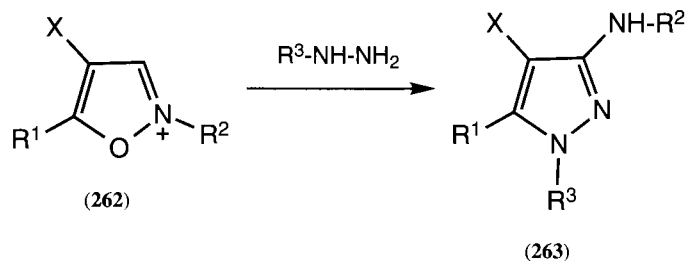


Transformation of (1,3-dioxolan-2-ylidene)methylphosphonates (or phosphinates) to 5-amino-*N*-substituted-3-(2-hydroxyethoxy)-4-phosphono (or phosphino)pyrazoles occurs by reaction with hydrazines, $R^1-NH-NH_2$ ($R^1 = CH_3, C_6H_5, OEt$) <92HCA124>. Similarly, dioxolanes (**259**) are transformed into 5-hydroxypyrazoles (**260**) by reaction with hydrazine and into pyrazolium betaines (**261**) by reaction with 1,1-disubstituted hydrazines <92HCA1039>.

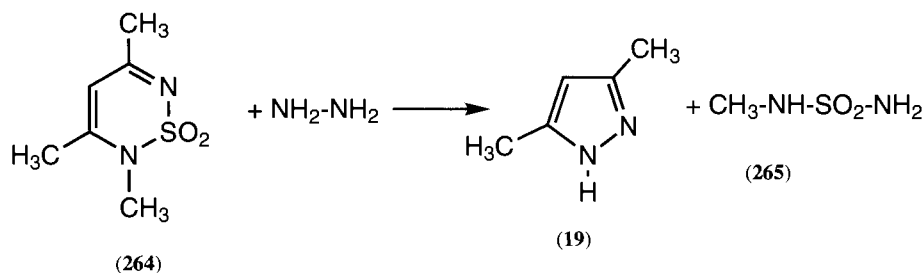


(ii) Both functional groups

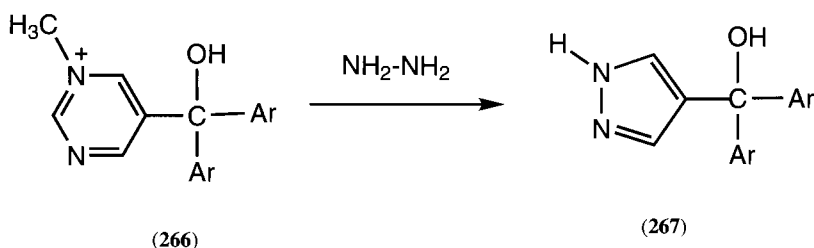
Reaction of hydrazines with 3-unsubstituted isoxazolium salts (**262**) yield 3-aminopyrazoles (**263**; $X = \text{H}, \text{NO}_2, \text{Cl}, \text{Br}, \text{COMe}, \text{CO}_2\text{Et}, \text{R}^3 = \text{H}, \text{Me}, \text{Ph}, \text{CONH}_2$) <88S203>.



The 1,2,6-thiadiazine-1,1-dioxides, for instance (**264**), also react as masked β -dicarbonyl compounds to afford pyrazoles <89H(29)245>. Interestingly enough, the secondary products formed in the reaction (sulfamides) can be recovered and, in the case of *N*-methylsulfamide (**265**), this can be a useful procedure to obtain this simple but rather difficult to prepare compound. Extrusion of SO_2 by flow vacuum pyrolysis (550–700°C) in (**264**) affords 3,5-dimethylpyrazole (**19**) <93CJC410>. A wide variety of 3(5)-substituted pyrazoles ($\text{R} = \text{NH}_2, \text{NHNH}_2, \text{NHMe}, \text{NHBu}^t, \text{NHPh}, \text{NMe}_2, \text{Ph}, \text{SMe}$) were prepared in very good yields by ultrasonic desulfuration or deselenylation-ring contraction of 1,3,4-thiadiazines or 1,3,4-selenodiazines <87ZC296>.



In order to study estrogen synthetase inhibitors, it was necessary to prepare the carbinol (**267**). This compound was obtained from the corresponding *N*-methylpyrimidininium salt (**266**; $\text{Ar} = p$ -chlorophenyl) <90JMC416>.

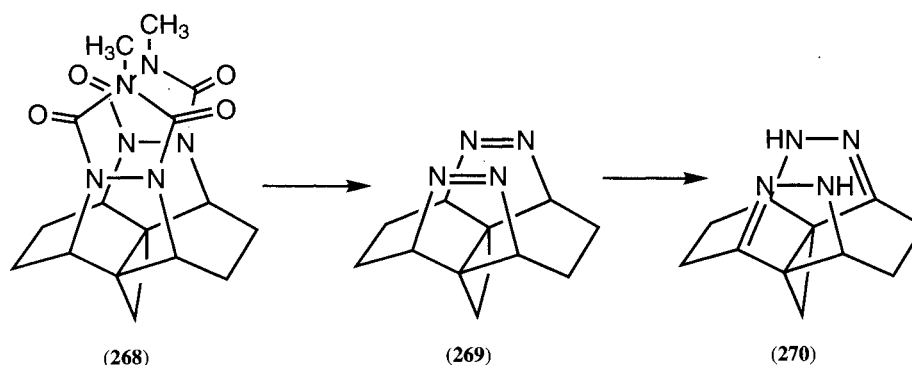


3.01.11.2.2 Bimolecular reactions

The most important method of this group of syntheses <84CHEC-I(5)167> is that using sydnone. The problem of the synthesis of 4-trifluoromethyl derivatives of pyrazoles has been thoroughly discussed by Meazza *et al.* <93JHC365> and a new and general method has been described which consists in 1,3-dipolar cycloaddition from sydnone with 1-aryl-3,3,3-trifluoropropynes. Cycloaddition of β -substituted enones to a bicyclic sydnone affords tetrahydropyrazolo[1,5-*a*]pyridines <89TL4625>. Treatment of 4-bromo-3-arylsydnone containing an *ortho*-carbonyl substituent with HBr gas affords 1-bromocarbonylindazoles <93TL239>.

3.01.11.2.3 Monomolecular rearrangements

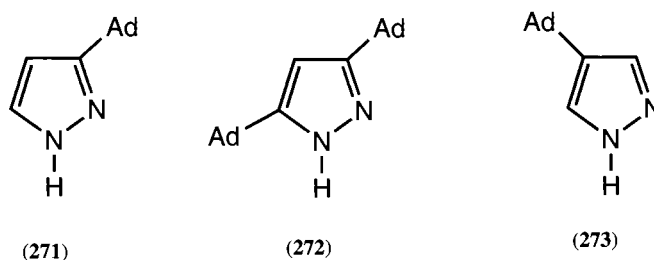
The [4 + 1] cycloaddition of 3,6-bis(trifluoromethyl)-1,2,4,5-tetrazine with isocyanides yields, in two steps, the interesting 3,5-bis(trifluoromethyl)-4-aminopyrazole <82AG(E)284>. Dihydroindazoles have been prepared by the same authors from 3,6-bis(trifluoromethyl)-1,2,4,5-tetrazine by a Diels–Alder reaction with inverse electron demand <91CB171>. Heinisch has described a novel ring contraction, the formation of pyrazoles from pyridazines <94H(38)2081> while Baccolini <93HAC497> described the use of chlorodiazaphospholines to 2-alkenyl- Δ^3 -pyrazolinones. The photochemical or thermal rearrangement of 2-alkenyl-5-substituted tetrazoles affords 3-substituted pyrazoles <91JCS(P1)329, 91MI 301-01>. Prinzbach <93CB429> has described a synthesis of pyrazolines (**269**) and (**270**) which involves the degradation of a bis-urazole (**268**).



3.01.12 SYNTHESIS OF A PARTICULAR CLASS OF COMPOUNDS AND A CRITICAL COMPARISON OF THE VARIOUS ROUTES AVAILABLE

3.01.12.1 General Methods

Pyrazoles bearing tertiary bulky substituents like Bu^t and (1-adamantyl) can be prepared easily from pyrazole. In this way 3(5)-adamantylpyrazole (**271**), 3,5-bisadamantylpyrazole (**272**), and 4-adamantylpyrazole (**273**) have been prepared (see Section 3.01.5.4.6) <94TL183, 94H(37)1623, 94CL2079>.

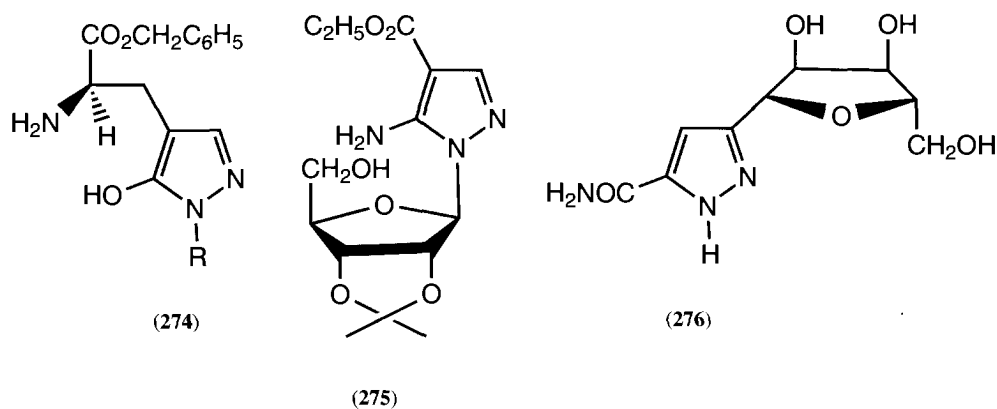


The best method for preparing large quantities of very pure 1-methylpyrazole uses PTC without solvent (yield of methylation with methyl iodide: 90%) <90SC2849>. For 1-arylpyrazoles where the aryl is not activated by a nitro group, the best procedure uses aryl-lead triacetates <92TL659> (with indazole, a mixture of isomers is obtained, the 1*H*-derivative being the most abundant one).

3.01.12.2 Nucleosides and Aminoacids

Starting from convenient precursors and hydrazines (see Section 3.01.10.1.2(ii)), aminoacids (**274**; R = H, Me, Ar) (glutamate agonist probes) <91CC314> and nucleosides (**275**) <91MI 301-02> were

prepared. Preparation of 4-deoxypyrazofurin (**276**) was achieved by cycloaddition of a glycosyl-diazoalkane to propiolic ester <91S747>. Giese has prepared glycosylpyrazole from pyrazole and the glycosyl bromide in the presence of tributyltin <93JOC1083>.



3.01.12.3 Labeled Compounds

The synthesis of 3,5-bis(trideuteriomethyl)pyrazole was achieved by reaction of perdeuterated acetylacetone with perdeuterated hydrazine hydrate <90MI 301-02>. Preparation of [$^{15}\text{N}_2$]pyrazoles was achieved from commercial $^{15}\text{NH}_2$ - $^{15}\text{NH}_2$ and β -dicarbonyl compounds or the corresponding acetals <89JA7304, 92JA9657, 92JCS(P2)1737>.

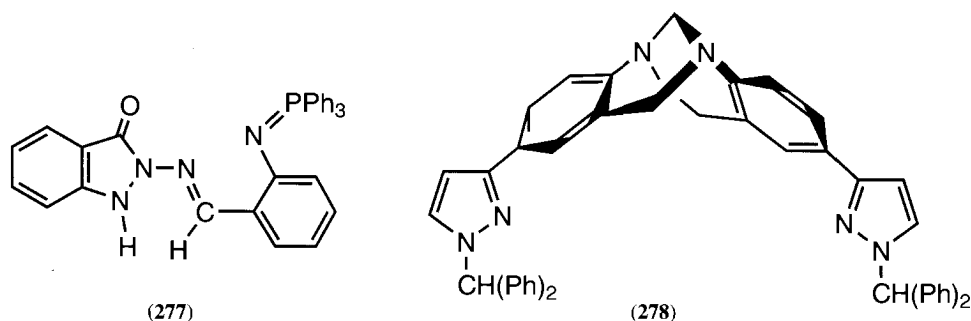
3.01.12.4 Chiral Derivatives

The interest in chiral derivatives of pyrazoles is increasing partly due to the demand of chiral ligands in coordination chemistry. Some of these compounds have already been described: (**111**), (**128**), (**215**)–(**222**). Several others have been prepared: chiral derivatives of 4-pyrazolol starting from D-glucose <92RTC427>, (2*S*)-2-(3,5-dimethyl-4-pyrazolyl)glycine hydrochloride <93TL7119>, Δ^1 -pyrazolines obtained by reaction of diazomethane to 7-oxanorbornene derivatives <93H(35)63>, and new chiral pyrazoles derived from (+)-3-carene <94TA479>.

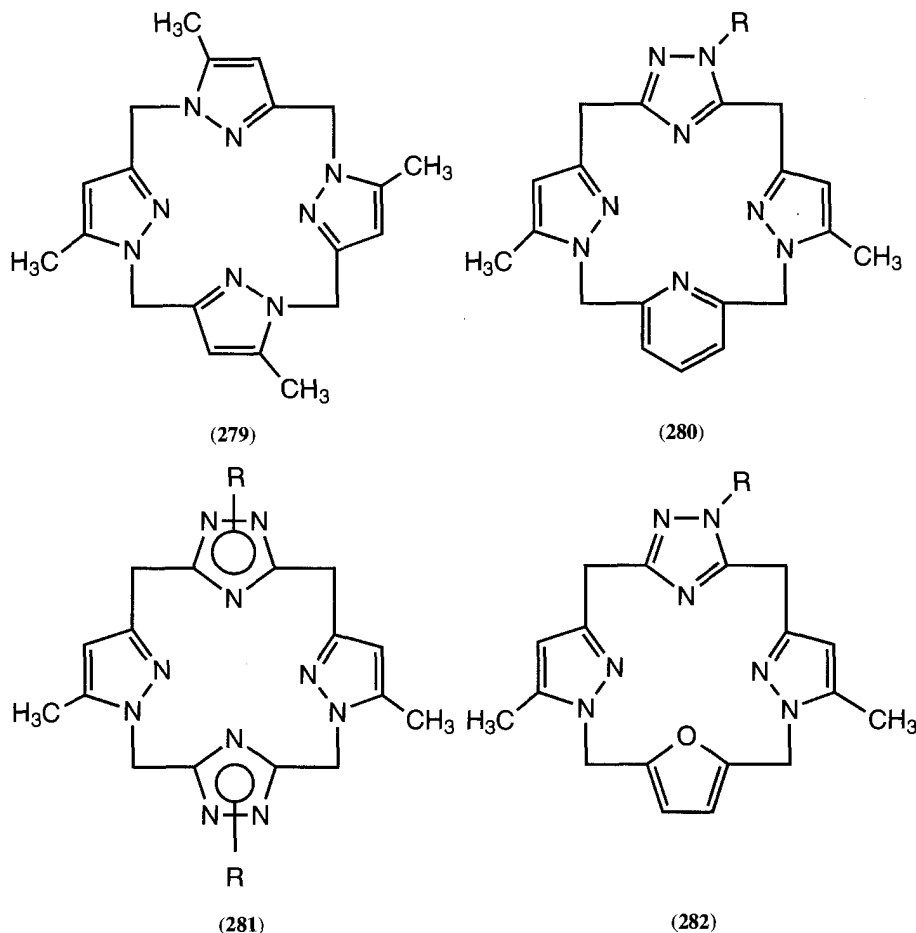
3.01.13 IMPORTANT COMPOUNDS AND APPLICATIONS

3.01.13.1 Pyrazoles in Supramolecular Chemistry

In host–guest chemistry, the indazolone derivative (**277**) has proved very efficient for alcohols and amines <92JPO507, 93MI 301-03>. Tröger's bases, when conveniently modified, are interesting hosts; one of such modifications (**278**) involves pyrazolyl substitutions <93JCS(CC)1713>; the benzhydryl group can be removed.

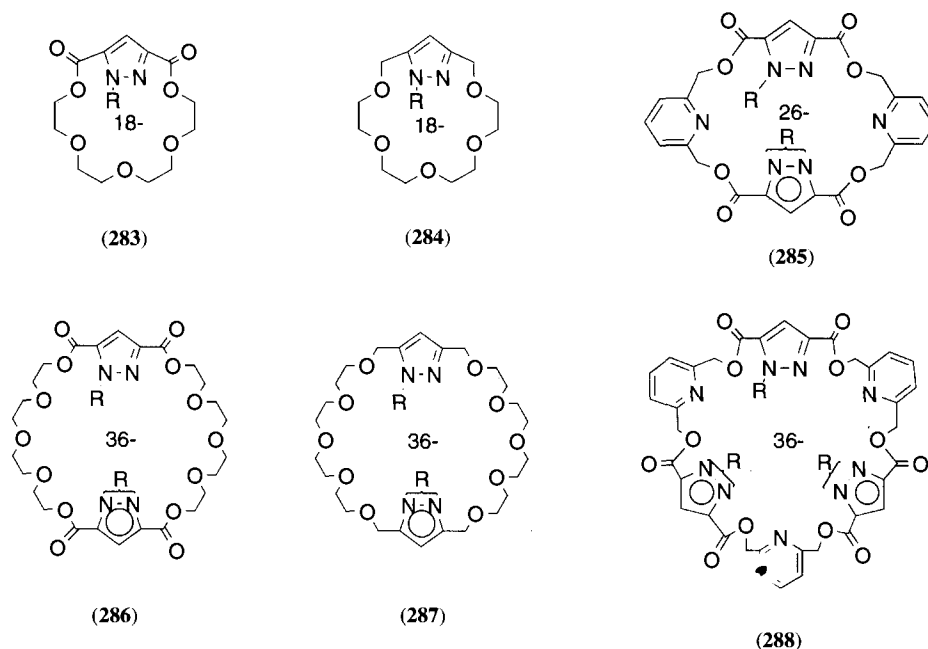


A series of papers by Tarrago and Marzin have further developed this important field <84CHEC-1(5)167>. For instance, they have described the synthesis and cation (Li^+ , Na^+ , K^+ , Cs^+ , NH_4^+) binding properties of macrocycles (279)–(282) <90JOC420, 91NJC677>, as well as the synthesis of chiral macrocycles and their enantioselective transport of carboxylic acids <93MI 301-04, 93MI 301-05>. These and other related ligands have been used for preparing ruthenium(II) complexes <86IC1775, 86IC1778, 93MI 301-06, 94IC4054>.

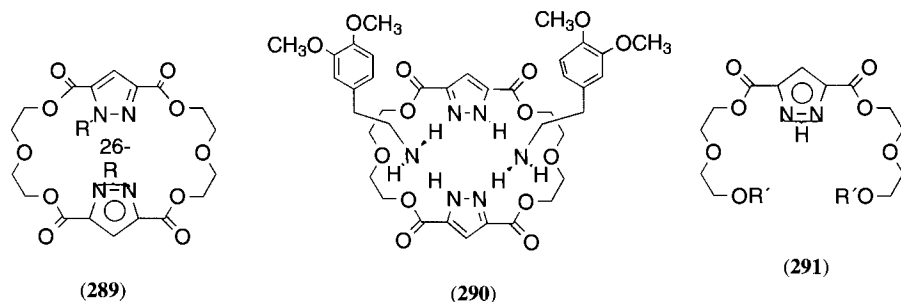


Navarro *et al.* have reported a series of ester-polyether and polyether crowns derived from 1-methyl and 1*H*-3,5-disubstitutedpyrazoles containing both one ((283), (284)) and two ((285)–(287)) pyrazole units <88CC1365, 89JOC1391, B-93MI 301-07>. All the structures were established on the basis of their FAB, ^1H , and ^{13}C NMR data (when both isomers are present the *N*-*R* substituent is situated between two nitrogen atoms). The x-ray structure of the smaller asymmetric crowns (283; $\text{R} = \text{CH}_3$) and (284; $\text{R} = \text{CH}_3$) allows the influence of either two rigid carbonyl bridges, or two flexible methylene ones on the shape and size of the cavity to be evaluated. Shift reagents $\text{Eu}(\text{fod})_3$ and $\text{Pr}(\text{fod})_3$ have been used as NMR probes, for determining the different binding sites involved in the complexation with spherical cations.

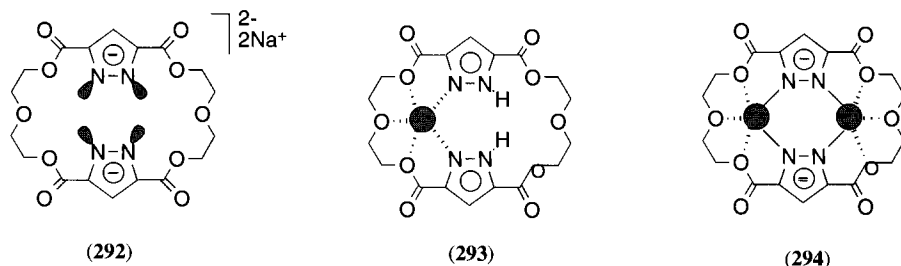
The selective transport ability of the above ligands toward NH_4^+ and alkaline cations through a bulk liquid membrane of chloroform has been evaluated. In general, the larger receptors of size similar to Valinomycin (36-membered) are much more effective carriers than their analogues with half the ring size (18-membered). The tetraester crown (286; $\text{R} = \text{H}$) is a selective and efficient carrier of K^+ ions, while the two polyether analogues (287; $\text{R} = \text{H}$ or CH_3) are selective carriers of NH_4^+ ions. Furthermore, symmetric ligands ($\text{R} = \text{H}$) are better carriers than their asymmetric analogues ($\text{R} = \text{CH}_3$). In particular, (287; $\text{R} = \text{H}$) transports NH_4^+ ions with higher efficiency than DB18C6 and shows excellent $\text{NH}_4^+/\text{Na}^+$ and NH_4^+/K^+ selectivities. Pyrazolopyridophanes (285) and (288) 24- and 36-membered rings, have been synthesized <90T2917>. In this case the hexaester receptor (288) is an efficient complexing agent that selectively transports NH_4^+ in relation to Na^+ , K^+ , and Ca^{2+} ions.



The synthesis of the 26-membered proton ionizable tetraester crown (**289**; $R = H$) has been performed either by Lewis acid catalyzed debenzoylation of its 1-benzyl substituted precursor (**289**; $R = \text{benzyl}$) <91JCR(S)126> and by direct cyclization of pyrazole 3,5-dicarbonyl dichloride with the acyclic diol (**291**; $R^1 = H$) <94T4765>. This symmetric receptor (**289**; $R = H$) strongly interacts with the amino group of homoveratrylamine affording a solid dinuclear complex (**290**) <93TL7299>.

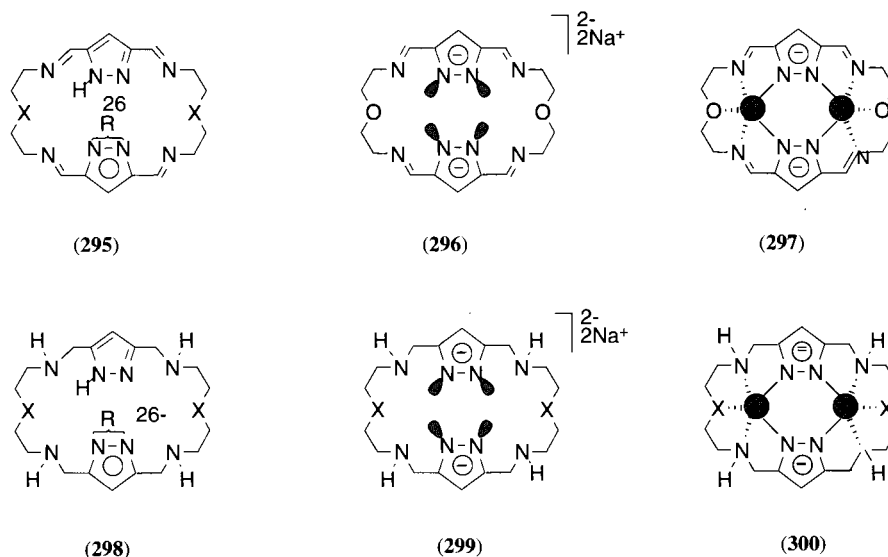


The macrocyclic effect of (**289**; $R = H$) on the proton ionizable character of pyrazole rings has been evaluated by comparing their deprotonation pK_a values (MeOH—H₂O at 25°C: pK_{a1} 9.1; pK_{a2} 10.9) with that of its acyclic analogue (**291**; $R^1 = \text{CH}_3$, pK_a 9.1). The disodium dipyrazolate salt (**292**) was isolated as a crystalline solid and from (**289**; $R = H$) and (**292**) mono- and dinuclear Zn^{II} complexes (**293**) and (**294**) were obtained <94T4765>.

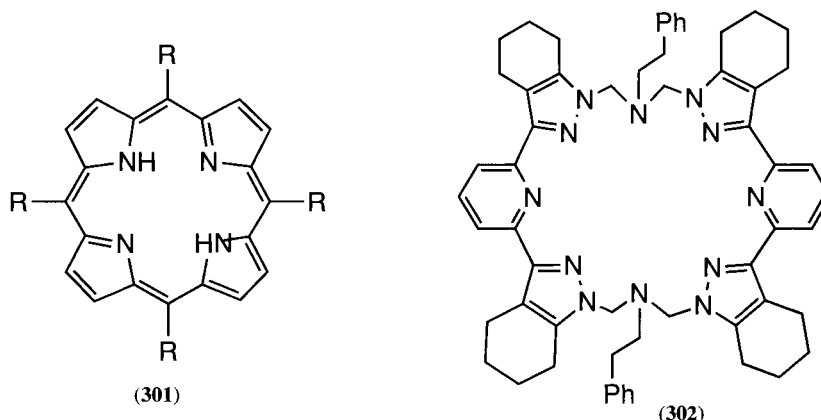


The same group has also prepared 26-membered polyazamacrocycles (**298**; $X = O, \text{NH}$), by condensation of 1*H*-pyrazole-3,5-dicarbaldehyde with 1,5-diamino-3-oxapentane and diethylene-triamine followed by hydrogenation of the resulting Schiff bases (**295**; $X = O, \text{NH}$) <93TL3159>.

Dipyrazolate salts (**299**; X = O, NH) and dinuclear Zn^{II} complexes (**300**; X = O, NH) were studied by ¹³C NMR. Besides, from (**296**) and (**299**; X = NH), dinuclear Cu^{II} complexes (**297**) and (**300**; X = NH) have been isolated as crystalline solids. The x-ray crystallographic analysis of (**300**; X = NH) demonstrates that inside the macrocyclic cavity, the two pyrazole rings are simultaneously acting as exobidentate ligands linking both metal cations, the Cu–Cu separation being 3.9 Å <94TL5723>.



The synthesis of *meso*-tetrapyrazolylporphyrins (**301**; R = pyrazol-3-yl residue) has been described, their atropisomerism (four isomers) studied by ¹H NMR at high field (600 MHz) <92JCR(S)370>, and the FAB and electrospray ionization MS recorded <92RCM540>. Potvin <92CJC2249> has reported the synthesis of macrocycle (**302**) an interesting complexing agent.



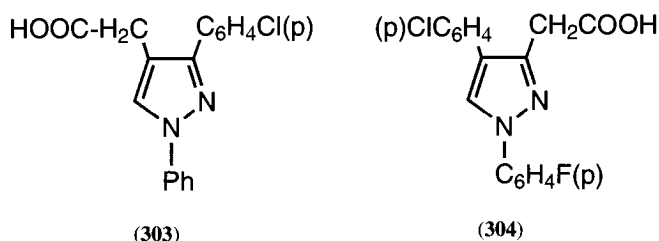
Becher <90JA3709> has studied by californium-252 plasma desorption mass spectrometry the alkali metal ion complexation of a crown ether containing two pyrazole subunits. Rebek <93RTC330> prepared one of his famous molecular clefts with two 3-*t*-butylpyrazol-1-yl substituents.

3.01.13.2 Pharmaceuticals and Agrochemicals

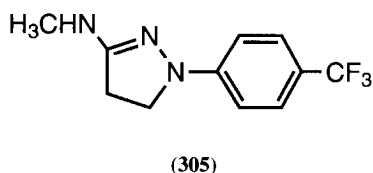
Pyrazole derivatives are widely used in agrochemistry as insecticides, herbicides, or fungicides. For instance, a powerful fungicidal composition for the protection of plants from phytopathogenic fungi, containing 4-chloro-3-(3,5-dichlorophenyl)-1*H*-pyrazole, has been patented <93EUP538156>. A use of 3(5)-methylpyrazole is as a nitrification inhibitor of soil <89MI 301-04>. Figaron, 5-chloro-

1*H*-3-indazoleacetic acid ethyl ester, is a citrus fruit-ripening stimulator <86MI 301-03>. By spraying trees with Figaron, treated fruits reach maturity a week before non-treated fruits.

Lonazolac (**303**) is a new nonsteroidal antiinflammatory drug <85MI 301-02, 86MI 301-04>. A close structure of Lonazolac, Pyrazolac (**304**) has shown to be efficient in rheumatoid athritis treatment <87MI 301-06>.



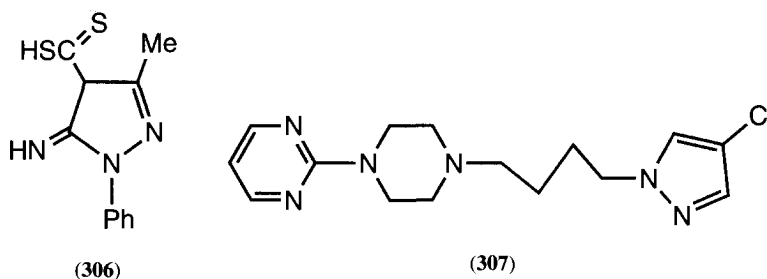
It has been shown that 1-(2-aminopropyl)- and 1-(3-amino-2-hydroxypropyl)-3,5-diphenyl-1*H*-pyrazoles are very active antiinflammatory products in rats <92FES1235>. Both *N*-substituted 4-carboxy-1-phenyl-1*H*-pyrazole-5-propanamides <93FES539> and 4-phenyl-5-(3,5-diphenyl-1*H*-pyrazol-1-yl)pyrimidines <92FES171> present platelet antiaggregating activity *in vitro* superior to that of acetylsalicylic acid, as well as moderate antihypertensive, local anesthetic, analgesic, and antiinflammatory properties. The antiinflammatory agent BW-540C (**305**) has been selected for evaluation in the treatment of psoriasis <84BP339>.



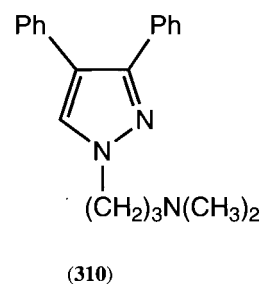
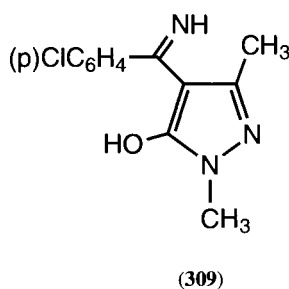
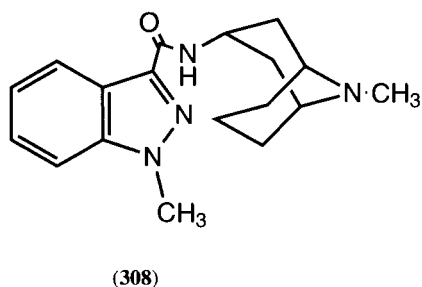
Studies of structure-activity relationships (QSAR) of 1-phenyl-3-aminopyrazolines as inhibitors of immune complex-induced inflammation have been reported <90JPS609>. Other related compounds have been described as inhibitors of cyclooxygenase, lipoxygenase, and thromboxane synthetase <89EJM435>.

Trans-indazolium bisindazoletrichlororuthenate(III) deserves special attention for its remarkable activity in a highly resistant type of tumor at negligible toxicity in rats <89MI 301-05>. The therapeutic efficiency of Pyrazofurin, 4-hydroxy-3- β -D-ribofuranosyl-1*H*-pyrazole, as pyrimidine antagonist, has been examined in cultured human leukemic cell lines <87MI 301-07>. Besides, Pyrazofurin has been studied for its antiviral activity and shown to be a potent inhibitor of respiratory syncytial virus <87AAC1225> and inhibits arenavirus replication <90MI 301-03>.

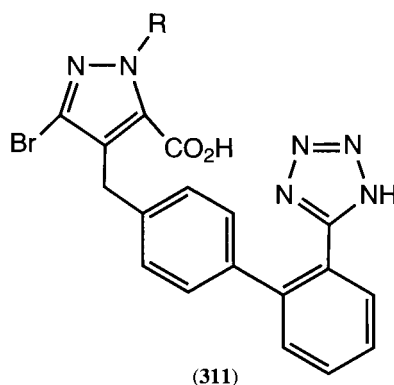
Nitropyrazole derivatives such as 4-nitropyrazole, 1-methyl-4-nitropyrazole and 4,4'-dinitro-1,1'-methylene dipyrazole are known as antiparasitic agents <88MI 301-02>. It has been shown that 3,4-bis(2,4-dinitrobenzoyl-hydroxymethyl) pyrazole has remarkable antimicrobial activity; it is more efficient than penicillin, levomycetin, and polymyxin <92MI 301-03>. The synthesis of Δ^2 -pyrazoline-4-dithiocarbamic acid (**306**) and the dipyrazolo-4,4'-dithiocarbamate derivatives has been accomplished and they were screened *in vitro* as antibacterial and antifungicidal agents <93MI 301-08>. Lesopitron (**307**) is a new nonbenzodiazepine anxiolytic, without side effects, which is currently in phase II trials <94MI 301-05>.



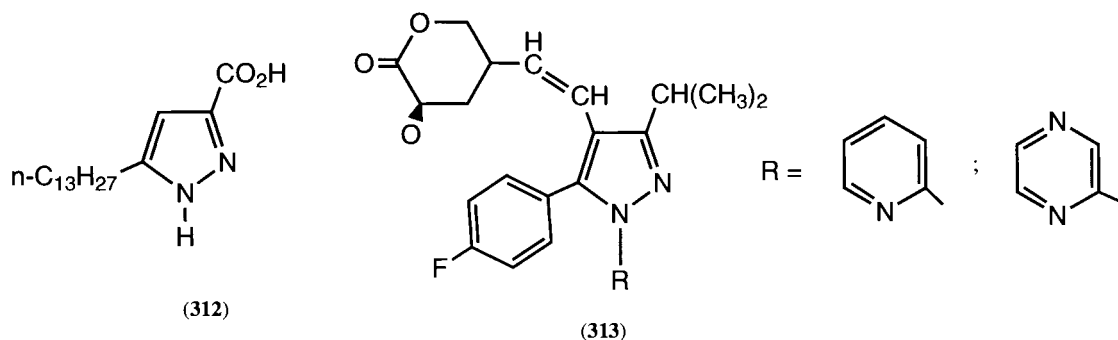
Granisoton (**308**) has been described as a novel receptor antagonist of serotonergic system in the central nervous system and is in evaluation in clinical trials <89MI 301-06, 90MI 301-04, 91MI 301-03>. The antipsychotic properties of the pyrazole (**309**) have been studied and showed an activity in the Sidman avoidance and self-stimulation test in rats <87JMC1807>. Fezolamine (**310**) has been reported as antidepressant and has the advantage, over tricyclic antidepressants, to be devoid of anticholinergic effects <85JMC256>.



The synthesis of 1*H*- and 2*H*- pyrazolo[3,4-*c*][2,1]benzothiazepines has been accomplished in view to develop new derivatives with potential psychotropic activity <94JHC93>. Pyrazolemethylenetriaryl-tetrazoles (**311**) are highly potent antagonists of angiotensin II and their pharmacokinetic parameters in the rat have been reported <94BMC151, 94CPB1617>.

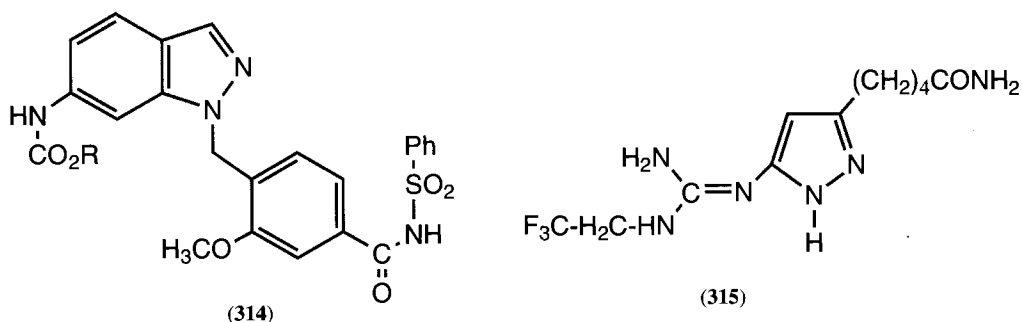


Fomepizole, 4-methylpyrazole, a potent inhibitor of liver alcohol dehydrogenase (LADH) <91IJQ269> may be an alternative to ethanol therapy for ethylene glycol intoxication <87MI 301-08>. Other 4-alkylpyrazoles have been theoretically studied as LADH inhibitors <94MI 301-06>. Pyrazolecarboxylic acid (**312**) and pyrazole mevalonolactones (**313**) have been reported for their hypocholesterolemic effects <88CPB1117, 92JMC2095>.

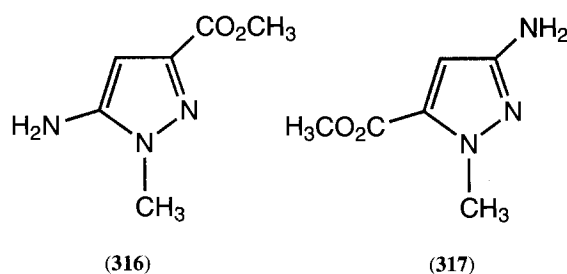


Various new indazole nucleosides, haloindazole-1-*D*-ribofuranosides, have been prepared to examine their biological activity <89MI 301-07>. Lonidamine, indazole-3-carboxylic acid, is of interest

for its biochemical and pharmacological properties <84MI 301-01>. The indazole derivative (314), whose generic name is ICI 198,615, is a leukotriene receptor antagonist and an antiallergic agent <86MI 301-05>. The fluorinated derivative (315) ICI 162,846, is effective at low doses for treatment of peptic ulcer disease <86MI 301-06>.

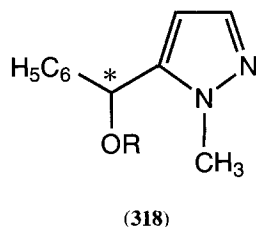


In the search for simpler analogues of netropsine and distamycin A, which are DNA minor groove binding antibiotics, pyrazoles (316) and (317) have been synthesized <89JOC428>. The x-ray structure of (316) was reported.



Some bis-pyrazoles (see (79) and (80) in Section 3.01.5.3.5) present cytotoxic activity <85CPB2535>. The *N*-adamantyl pyrazoles and indazoles, formally related to amantadine, have less antiviral activity than amantadine <85EJM359>. The *N,N'*-bis-azolyarylmethanes (90) and (91), structurally related to Chlortrimazol, were tested as antifungal agents but showed minimum inhibitory concentrations higher than the reference compound <88CPB2036>, while bispyrazolylmethanes (88) and ethanes (99) (see Section 3.01.5.3.5) are carbonic anhydrase activators <93MI 301-09>.

Both enantiomers of E-3710 (318), a novel analgesic, were prepared and their absolute stereochemistries assigned; their pharmacological properties were compared with those of the racemic and no significant difference was observed <93BMC269>.



Amongst the various biological activities described for perfluoroalkylpyrazoles are: growth inhibitory activity of derivatives of *N*-trifluoromethylpyrazoles (42) and (43) <90JHC807>, high biological activity as herbicides <93JHC49>, and as analgesic, antipyretic, antiinflammatory, and hyperglycemic agents <93JHC365>. Pyrazole HMGCoA inhibitors have been described <92JMC2095>.

A series of derivatives structurally related to Nifurtimox were prepared and tested against *Trypanosoma cruzi* <87AP(320)115>. Some of them, for instance (28), showed interesting activity <91CPB1990>. The x-ray structure of (28) and that of the corresponding thenylidene derivative have been determined <88BSB1055>: they show an E-sZ conformation along the N=C—C moiety. Betaines related to (5) were tested as antiprotozoal agents <90EJM309>.

The important applications of pyrazolinones, especially their analogy with β -lactams as antibiotics, have been summarized in <91OPP273>.

With the aim to prepare compounds with special flavors for use in food chemistry and in perfums, natural ketones such as (+)-3-methylcyclohexanone, (–)-menthone, (+)-isomenthone, (+)-isopinacampnone, (+)-camphor, and (+)-pulegone were transformed into pyrazoles and pyrazolinones (see Section 3.01.10.1.2.(ii)) <88AQ176, 88AQ183, 88AQ191, 88AQ198>.

3.01.13.3 Other Applications

Tartrazine, 4,5-dihydro-5-oxo-1-(4-sulfonyl)-4-[4-sulfonyl]azo]-1*H*-pyrazole-3-carboxylic acid trisodium salt, has been widely used for many years as food, drug, and cosmetic coloring. More recently, its biological effects on living organisms have been investigated <90MI 301-05> and its lack of carcinogenicity has been shown <87MI 301-09>. New dyes, prepared from *N*-(3- and 5-aminosubstituted triazinyl)-3-methyl-5-amine pyrazoles, present improved spectral absorption properties over the corresponding 5-amino-1-phenylpyrazole and 5-pyrazolinone dyes <86MI 301-07>.

Many pyrazole and indazole derivatives are of interest in photography. Among them amino-indazole compounds exhibit excellent charge transport properties in sensitized electrophotography layers <88C137>. Insoluble silver salts are formed by 5-nitroindazole, which is commonly used in photography developers to obtain high-contrast <84MI 301-02>. Important photographic couplers are 1*H*-pyrazolo[5,1-*c*][1,2,4]triazole and 1*H*-pyrazolo[1,5-*b*][1,2,4]triazole derivatives <94JCS(P2)531> (see Section 3.01.8.1).

Liquid crystal properties, investigated by optical microscopy, DSC and x-ray diffraction, have been described by Serrano *et al.* for pyrazole derivatives. The series of 3,5-bis(*n*-decyloxyphenyl)-pyrazole shows smectic A as well as smectic C phases <92LC887>. Dimerization of these (alkoxyphenyl) pyrazoles through BH₂ bridges yields pyrazaboles, which show hexagonal columnar mesomorphism at low temperatures <94AM(6)470>. Other authors have also reported liquid crystals based on pyrazole sub-units <92MCLC(A)67> or on trispyrazolylborates <94POL2107>. Judging from the number of patents, 3,5-dimethyl-1-*p*-nitrophenyl-pyrazole, known as DMNP, is one of the leading compounds in nonlinear optical (NLO) materials and second harmonic generation (SHG) devices <93JHC755>.

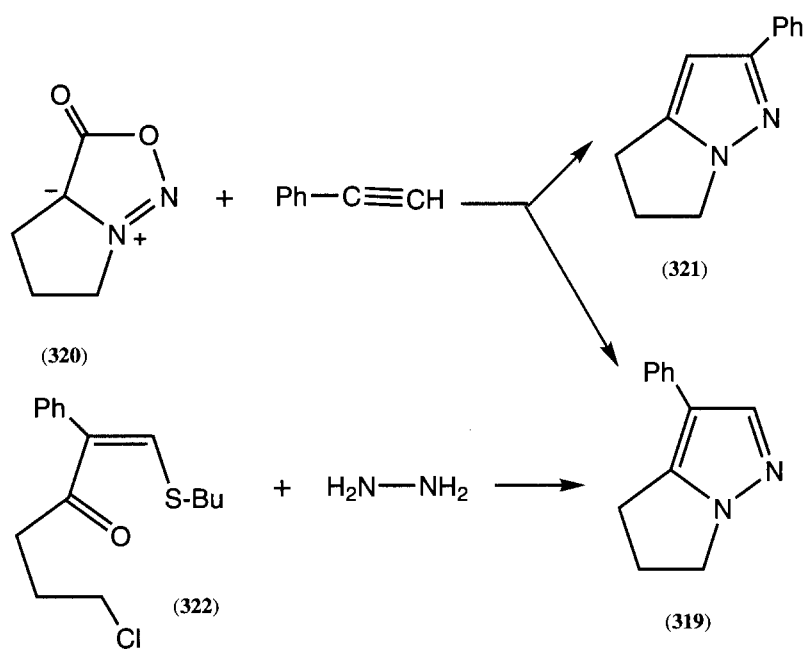
The major use of 3(5)-methylpyrazole is in the polymer field. As a bioactive agent, it has been linked to acrylic acid-divinylbenzene and 4-vinylbenzoic acid co-polymers to form polymeric inhibitors of soil nitrification <88MI 301-03>. In the early 1990s 3(5)-methylpyrazole has been used as chain-length regulator in the synthesis of poly(urethane)ureas, it modifies the molecular weight, mechanical properties, and viscosity of these polymers <93MI 301-10>. New plastic scintillators, polyvinyltoluene or polystyrenes doped with single wavelength shifters like 1-phenyl-3-mesityl- Δ^2 -pyrazoline or 1,3-diphenyl- Δ^2 -pyrazoline, have been developed with the characteristic of highly localized light emission <89MI 301-08>. Polymers bearing pyrazole groups have been prepared <94MI 301-07>.

Rhodium complexes with pyrazole or pyrazolate-type ligands have been studied as catalysts for hydrogenation of alkenes under ambient conditions in propan-2-ol <87JMOC341>. Hydroquinones (114)–(116) were studied as UV stabilizers, some of them exhibit excellent stability to light <90JA747>.

3.01.13.4 Natural Products

Withasomnina (319), one of the rare natural compounds containing a pyrazole ring, has been prepared by several ways. In the CHEC-I (formula (754) <84CHEC-I(5)302>) the method used was based on a 3(5)-allylation of 1-phenylsulfonyl-4-phenylpyrazole lithium derivative (see Section 3.01.5.6.1). Two other methods have been published, the first one (Scheme 10) uses the sydnone approach (see Section 3.01.11.2.2) and leads to a mixture of Withasomnina (319) and the unnatural isomer, iso-Withasomnina (321) by reacting the bicyclic sydnone (320) with phenylethyne <85SC259>; the second method (Scheme 10) uses the hydrazine way (see Section 3.01.10.1.2.(ii)) and,

in one-pot reaction, Withasomnina is obtained from a rather elaborate precursor (322) which is a masked β -diketone with an alkylating arm <91SC1667>.



Scheme 10

3.02

Imidazoles

M. ROSS GRIMMETT

University of Otago, Dunedin, New Zealand

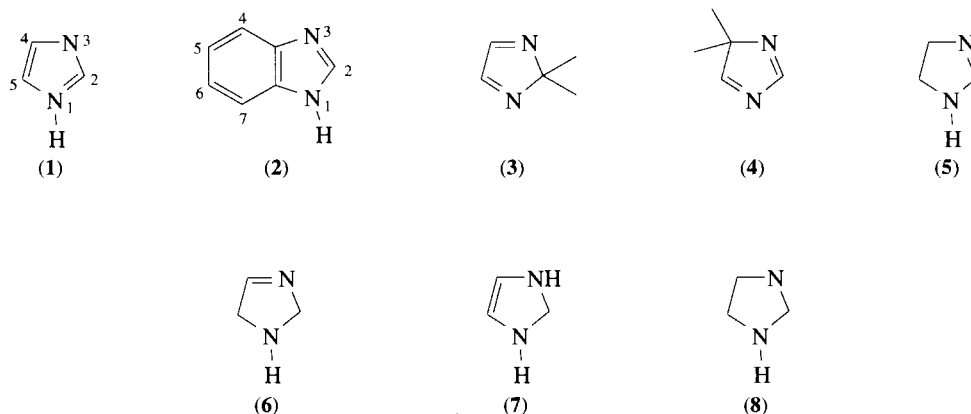
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3.02.1 INTRODUCTION

As described in the first edition of *Comprehensive Heterocyclic Chemistry* (CHEC-I) $\langle 84\text{CHEC-1}(5)345 \rangle$ imidazole (**1**) is an aromatic molecule with a pyrrole-type and a pyridine-type annular nitrogen. Its properties then can be envisaged as those of overlapping pyrrole and pyridine. Historically, the molecule has been named “glyoxaline” and “iminazole”, but imidazole is now used universally. The systematic name, 1,3-diazole, is seldom used. This chapter covers the aromatic systems, imidazole (**1**) and benzimidazole (**2**), 2*H*- (**3**) and 4*H*-imidazoles (**4**), the imidazolines (**5**)–(**7**), and imidazolidine (**8**).



Review material since 1982 has been confined to specific aspects of the chemistry of the compounds: *N*-oxides $\langle 93\text{CHE127} \rangle$, electrophilic substitution $\langle 90\text{AHC}(47)139 \rangle$, halogenation $\langle 93\text{AHC}(57)291 \rangle$, *N*-alkylation $\langle \text{B-94MI } 302\text{-}01 \rangle$, acidity $\langle 86\text{RCR411}, 87\text{AHC}(41)187, 88\text{CHE469} \rangle$, tautomerism $\langle 91\text{H}(32)329 \rangle$, metallation $\langle 85\text{H}(23)417, 94\text{H}(38)2487 \rangle$, aromaticity $\langle 85\text{CHE717}, 91\text{H}(32)127, 92\text{CHE241} \rangle$, linear free energy studies $\langle 86\text{RCR411} \rangle$, 2*H*-imidazoles $\langle 84\text{AHC}(35)375 \rangle$, 4*H*-imidazoles $\langle 84\text{AHC}(35)413 \rangle$, and synthesis of imidazole *N*-oxides $\langle 93\text{CHE127} \rangle$.

3.02.2 THEORETICAL METHODS

A survey of the applications of theoretical methods to azoles appeared in the *Handbook of Heterocyclic Chemistry* $\langle \text{B-85MI } 302\text{-}01 \rangle$. Since the publication of CHEC-I there has been growing interest in the application of such studies to imidazole structure, aromatic character, tautomerism, acidity and basicity, and general reactivity.

Molecular orbital calculations, both *ab initio* and semiempirical, have greatly increased in importance, with the latter seeming to provide useful results with fewer computational problems. Certainly the greatest concentration of effort has been applied to semiempirical studies of intrinsic basicity and tautomerism $\langle 81\text{JHC1189}, 83\text{AG}(E)323, 83\text{JCS}(P2)1869, 84\text{JHC1781}, 86\text{BSF}(2)429, 86\text{JOC1105}, 87\text{CHE44}, 87\text{JGU2471}, 87\text{JOC1713}, 89\text{CHE423}, 89\text{CHE1321}, 90\text{JA1303}, 90\text{JA4133}, 90\text{JCS}(P2)195, 91\text{JMC2056}, 94\text{T2405} \rangle$, and

frontier molecular orbital calculations <86CJC1240, 87JGU2471, 87JOC1713, 89CHE1321, 92JCS(P1)2779, 92JCS(P1)2789>. Calculations of HOMO energies can provide information about the polarizability of a molecule and gives a measure of the relative softness of imidazoles as bases <87JOC1713>. As well, FMO analysis of electrophilic reagents involved in addition-elimination reactions with amino-imidazoles has been used to account for preferred attack at nitrogen or carbon sites <92JCS(P1)2779>, and further applications of FMO theory to nitro- and amino-imidazoles <92JCS(P1)2789> are discussed (see Section 3.02.7.1.6).

Of the semi-empirical methods used in proton affinity (PA) studies, AM1 fails to treat the electrostatic proximity effects correctly <86JA3237>, and INDO was found to be qualitatively better in spite of large deviations. Experimental PA values for azoles can be reproduced by high level *ab initio* calculations <86JOC1105>, but the approach is limited by the enormous computational efforts needed. Although both MNDO and STO-3G approaches poorly predict the absolute values of proton affinities, there is good correlation between PA values calculated by STO-3G and experimental values of PA and pK_a for imidazoles. The *ab initio* method overestimates PA, while the semiempirical approach underestimates it because of underestimation of the enthalpy of proton formation <89CHE423>. Both methods show that pyrazole is less basic than imidazole although the absolute values do not correspond with the experimental ones (Table 1).

Table 1 Proton affinities (kcal mol⁻¹) and pK_a values of imidazoles.

	PA (MNDO)	PA (STO-3G)	PA (experimental)	pK_a (calc. from PA)	pK_a (experimental)
Imidazole	173.2	283.8	221.1	6.76	7.30
5-Methylimidazole	173.7	287.9	224.8	7.88	7.72 ^a
4-Methylimidazole	175.1	288.6	224.8	8.07	7.95 ^a
1-Methylimidazole	175.3	287.9	228.0	7.88	7.88

^a pK_a for 4(5)-methylimidazole 7.52; individual pK_a s computed using $K_T = 0.66$.

Density functional (DF) approaches to obtaining protonation enthalpies, geometric parameters, and dipole moments provide a computationally efficient alternative method <94T2405>. The use of STO-3G also underestimates the energy difference (ΔH_f) between imidazole and pyrrole by a factor of almost two ($\Delta H_f(\text{exp.}) = 53.2$; $\Delta H_f(\text{STO-3G}) = 33.1$; $\Delta H_f(\text{MNDO}) = 51.1$ kJ mol⁻¹) <89CHE1321>. Calculations of heats of formation continue to give useful data on the stabilities of individual imidazoles, for example, nitroimidazoles (see Section 3.02.7.1.7), fluoroimidazoles <88H(27)1803>, carbon anions of alkylimidazoles <89CHE874>, methylimidazoles <90JA1303> (see Section 3.02.4.3.1), and aminoimidazoles (see Section 3.02.4.3.1). The applications of nitroimidazoles as sensitizers in radiation therapy, and the particular selective toxicity of 2-nitroimidazole towards hypoxic tumour cells has stimulated studies of the geometry, electron affinities, and stabilities of nitroimidazoles. From *ab initio* computations made at the split-valence 3-21G basis level, the stabilities of the parent nitroimidazoles were shown to lie in the order 5-NO₂ $\approx$ 4-NO₂ > 2-NO₂, with the 4-nitro tautomer calculated to be more stable in solution, probably because of solvation. Electron affinities follow the order 2-NO₂ > 5-NO₂ $\gg$ 4-NO₂, closely paralleling the order of biological effectiveness, and consistent with suggestions that the "nitro-nitro radical anion" redox cycle is a possible determinant of radiosensitizer activity <89CJC1666>. A study of PA values of methyldiazoles has suggested that STO-3G fully optimized geometries of the neutral molecules and corresponding cations are necessary for the proper quantitative evaluation of the effects of the methyl substituents on intrinsic basicities <90JA1303>.

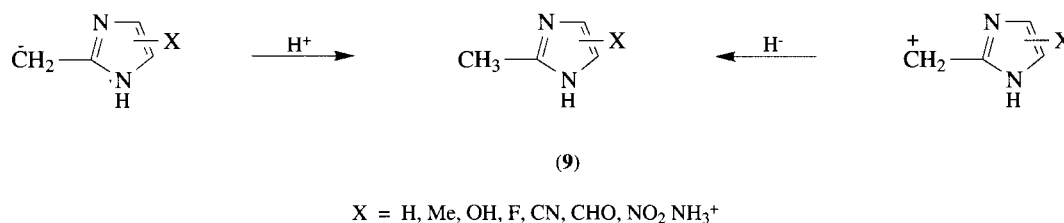
Both non-empirical <85JMR262> and semiempirical methods <83OMR(21)501> have been applied successfully to the interpretation of NMR spectra, particularly to the effects of solvent on chemical shifts.

Applications of MO calculations to studies of reaction mechanisms are of limited value because of the considerable demands placed on the computational method to guarantee reliable results. It is not always easy to formulate the task properly <89CHE1321>. Nevertheless, efforts to elucidate the diazo coupling reaction of imidazole have been assisted by MNDO calculations of the heats of formation of the possible Wheland intermediates <89JCS(P2)2055> (see Section 3.02.5.3.7), and an FMO analysis of the effects of methyl- and benzo-substitution on the facility of proton transfer from C-2 of imidazole, benzimidazole, and their 1-methyl derivatives has thrown light on the mechanism <86CJC1240>.

The application of a combination of quantum mechanical calculations of vacuum PA values, and a new method of calculation of hydration energies based on a continuum representation of the solvent, to the determination of pK_a differences between imidazolium congeners has proved reasonably successful for hydrogen- and methyl-substituted species, and molecules with differing substituent regiochemistry. Large deviations, however, were found with chloro and nitro substituents, indicating that the calculated proton affinities have errors which do not cancel when the substituents have very different properties. This restricts the method to narrow classes of compounds <90JA4133>.

The AM1 and PM3 semiempirical parameterizations devised by Dewar <85JA3902> and Stewart <89MI 302-01> seem satisfactory for describing tautomeric equilibria of isolated molecules <91H(32)329>. It is, however, crucial to account for solvent effects in the theoretical calculations of tautomeric equilibria even though there may not be much difference between the specific solvation energies of the tautomeric forms. Nevertheless, the electron distribution in the ring may be changed significantly from one tautomer to the other, leading to large differences in non-specific polar solvation terms. It has been shown that a SCRF-MO theory in combination with Dewar's AM1 parameterization gives a quantitative prediction of the tautomeric equilibrium constants in solvation (see Section 3.02.4.3) <89JOC6030>.

Use of the AM1 method to calculate proton and hydride ion affinities for 4- and 5-substituted 2-methylimidazoles (9) and attempting to relate these to model benzyl systems has demonstrated excellent correlations between 4-substituted compounds and *m*-toluenes and the 5-isomers and *p*-toluenes. The substituents appear to exert only minimal effects on the change in charges on the annular nitrogens as the anionic or cationic species are formed (Scheme 1) <93JOC7336>.



Scheme 1

The applications of MO calculations to aromaticity studies are discussed later (see Section 3.02.4.2.1).

Calculated π -density values appeared in CHEC-I. Some values are shown in Figure 1 <90JA1303>.

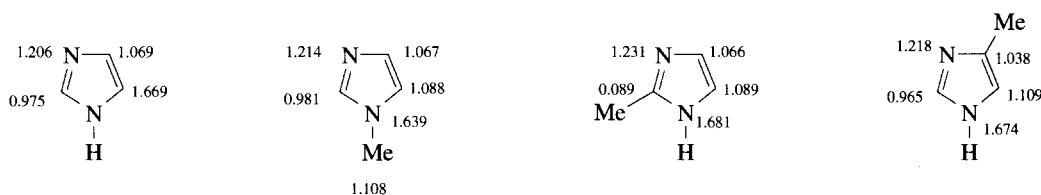


Figure 1 π -Charge distributions for imidazole and its 1-, 2-, and 4-methyl derivatives.

Molecular mechanics applications are proving more and more useful. The calculations have allowed potential blood-pressure reducers to be designed based on analogues of imidazole angiotensin II antagonists <92JMC877, 92JMC3858>. Quantum chemical model (AM1) calculations for simple amino- and nitro-imidazoles show that the amino groups are pyramidal while the nitro groups are essentially flat and coplanar with the heterorings <92JCS(P1)2779>. Molecular geometries, fully optimized using the INDO method for methylimidazoles <83JCS(P2)1869>, are in good agreement with microwave data <82ZN(A)1378>. The *syn-anti* energy differences in conformations of some imidazoline-2-thiones are satisfactorily reproduced by MM2/MMP2 calculations; the more crowded *syn*-conformer is preferred <87JOC5177>.

A quantitative modeling study of geometrical prerequisites and charge distribution in SYBYL supports the formation of a chelation complex between potassium ion, the nitro group, and a

nitrogen anion in the cyclization of (3-nitrophenyl)guanidines to 7-nitrobenzimidazoles <92S596>. Application of molecular mechanics to a study of the photochemical properties of 1-aryl-4-nitroimidazoles showed that whereas most had the aryl and imidazole rings coplanar, 2-methyl-4-nitro-1-phenylimidazole had its most stable conformer with a dihedral angle of 21.1° between the rings. In this non-planar compound a different oxidation process involving singlet oxygen must occur, as a radical anion cannot be stabilized to the same extent as in the other analogues <93T3899>.

Studies of the way in which acyl transfers occur during acylimidazole hydrolysis and nucleophilic attack by imidazole on esters have been assisted by calculation of the free energy surface for a three-dimensional reaction coordinate diagram, using the energy levels of the tetrahedral intermediate and the acylium ion, and intrinsic barriers for the edge reactions <87CJC1951>. The MM3 force field has been developed to improve the accuracy of the generality of molecular mechanics calculations. This allows one to obtain good geometries and energies, but rather unsatisfactory spectroscopic data, for example, the bond lengths and angles, dipole moments, and resonance energies for imidazole and benzimidazole correlate well with experimental values <93JA11906>.

Studies of linear free energy correlations have continued in the areas summarized in CHEC-I. There, the problems in choosing suitable σ values for the different types of annular nitrogen, and the complications of tautomerism were discussed. It was possible to correlate pK_a values of 1-, 2- and 4-substituted imidazoles with σ_m and σ_1 constants, and Taft σ^* values were found to give a measure of steric effects in *N*-acyl-imidazole hydrolysis and other imidazole-catalyzed ester hydrolyses in aqueous solution. Other aspects have been reviewed <86RCR411, 86UK769>, and much effort has been applied to investigations of acid-base properties of imidazoles and benzimidazoles, with correlations of chemical shifts, ionization energies, half-wave oxidation potentials of arylimidazoles, and solvolyses of acylimidazoles also receiving attention <86RCR411>.

From the pK_a values of 1-(3-aminopropyl)- and 1-(2-aminoethyl)-imidazoles the σ^* value for the imidazolyl substituent (2.63) has been determined (cf. $\sigma^* = 3.84$ for imidazolium). A linear free energy relationship exists between the free energy change for the replacement of an hydroxyl group in a carbonyl hydrate by imidazolyl, and the sum of the σ^* values for other substituents. The implications of these results are that a concerted rather than a stepwise mechanism is likely for the reactions of imidazole with aryl acetate <87CJC1951>.

Attempted correlations of half-wave reduction potentials of 2-substituted 5(6)-nitrobenzimidazoles with σ_1 , σ_R , and σ^O suggest that almost equal contributions of resonance and inductive effects of the substituent are involved <84CHE1021, 85CHE688>. The analogous substituent effects on pK_a values are around 80% inductive, indicating that there are differences in the natures and positions of the centres involved in reduction and dissociation <84CHE1021>. The positions of the substituents in benzimidazoles are also important in charge transmission. There is more resonance transmission from the 4- and 7-positions than from the 5- and 6-positions. In the anions, where the negative charge is probably highly delocalized, the resonance contribution becomes much more dominant <81OMR(15)219, 81OMR(17)1, 82OMR(20)212, 86RCR411>. The question of the roles of each of the annular nitrogens in electronic transmission of substituent effects is uncertain <86RCR411>. When a number of 2-methyl-5- and -6-substituted benzazoles were subjected to correlations of basic deuterium exchange at the methyl groups with chemical shifts, no set of σ values fitted the 2-methylbenzimidazole results (benzoxazoles and benzothiazoles could be correlated using σ_p), perhaps because of disturbance of the linear free energy (LFE) principle in the transition state for the exchange reaction because of the saturation effect <84CHE1011>.

Most applications of Hammett approaches to tautomerism studies are based on Charton's equation [$\log K_T = pK_B - pK_A = (\rho_B - \rho_A)\sigma_m$] (A and B are 1-methyl-4- and 1-methyl-5-substituted imidazoles). The value of 3.2 used by Charton for $\Delta\rho$ should probably be larger <76AHC(S)1> since it does not give very good correspondence with measured values, but the experimental values based on pK_a values for the *N*-substituted imidazole "models" almost certainly contain large errors. Nevertheless the approach has been used for determining tautomeric equilibrium constants for 4-substituted imidazoles, for example, histidine analogues (see Section 3.02.4.3.1) <86JHC921, 94H(37)735>.

In a study of the 4-nitration of a cobalt-coordinated imidazole, the $\text{Co}(\text{NH}_3)_5^{3+}$ group was given an electron-donating substituent constant, $\sigma_1 = -0.30$; it is a more powerful donor than a 1-methyl group ($\sigma_1 = -0.04$) <83IC678>.

Recent AM1 MO studies agree with earlier results (based on pK_a determinations and rates of solvolysis of imidazolyl-2-carboxylates) that 5-substituent effects follow σ_p^+ and 4-substituent effects follow σ_m^+ . The substituent effects are not readily transmitted through the $-\text{NH}-$ system and the resonance effects of a 5-substituent are more important than those of the same group at C-4 <93JOC7336, 94UP 302-02>.

3.02.3 EXPERIMENTAL STRUCTURAL METHODS

3.02.3.1 X-ray Diffraction

The numbers of x-ray structures reported in the literature have burgeoned since the publication of CHEC-I. Dimensions of some representative molecules are shown in Figure 2. Both imidazole-2-thione and its 1,3-dimethyl derivative (**10**) are planar molecules with C—S bond lengths longer than the usual C=S (161 pm). The C-2—N bonds have partial double bond character, implying a strong mesomeric shift of electron density from nitrogen to sulfur. Bond order calculations also give a C—S bond order of less than 2. The dipolar form (**13**) is likely to be a major contributor to the resonance hybrid <88CHE1309, 88JA2586> (see Section 3.02.4.3.2). The hydrobromide salt of (**10**) has an even longer C—S bond (173.0 pm) while other ring bonds are closer to aromatic lengths. Molecular units are linked through long zig-zag chains in which bromide forms a link between sulfur atoms <86MI 302-01>. Benzimidazole-2-thione has around 80% double bond character in its C—S bond <88CHE1309>. When (**10**) forms charge transfer complexes with iodine the C—S bond is lengthened to 172.4 pm, while the C-2—N bond is shortened (134.3 pm) <88JA2586>.

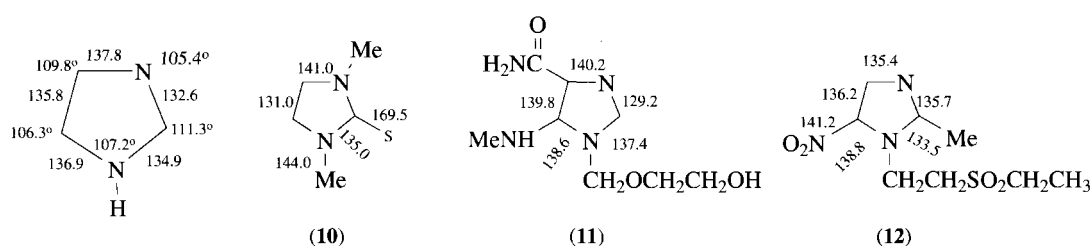
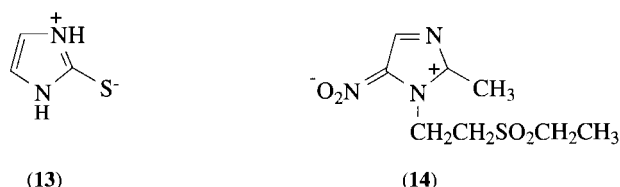


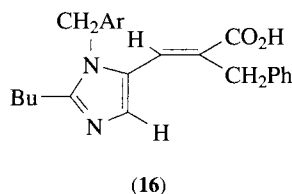
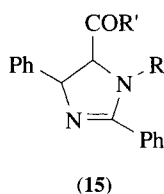
Figure 2 Dimensions (pm) for imidazole <85CHE717>, 1,3-dimethylimidazole-2-thione (**10**) <88CHE1309, 88JA2586>, a 5-methyl aminoimidazole-4-carboxamide (**11**) <87H(25)493>, and tinidazole (**12**) <84CC491>.

In tinidazole (**12**) the 3,4-bond is shortened and the 4,5-bond is lengthened presumably because of the contribution of structure (**14**). Determination of the crystal structure of (**12**) was necessary to demonstrate unequivocally that it was the 5-nitro compound. Metabolites of (**12**) are 4-nitro compounds, providing the first example of an *in vivo* 5-nitro to 4-nitro migration <84CC491>. Combined x-ray and ^{13}C NMR methods have been of value in assigning structures to some 4-nitroimidazoles <92H(34)1385>.



The orientation of lithiation of 1-methyl-2-phenylthioimidazole at C-5 was confirmed by x-ray and NMR analysis <92CPB2681>. In a series of 2-imidazolines (**15**) the substituents were shown to be *trans* to one another; the spatial arrangement of the carbonyl function depends on the nature of the nitrogen substituent <87CJC2217>. In 1-benzyl-4,5-diphenylimidazoles the 4,5-bond is slightly stretched, and the aryl rings are inclined to the imidazole plane by 82° (benzyl), 29.8° (4-phenyl), and 62.5° (5-phenyl) <90H(31)2187>. The stable carbene, 1,3,4,5-tetramethylimidazole-2-ylidene, has been shown to exist as a planar ring with the methyl groups slightly out of plane <92JA5530>, while in the ylidic 1,3,4,5-tetramethyl-2-methyleneimidazoline, the short C-2—CH₂ bond (135.7 pm) demonstrates the characteristic shortening of an ylidic single bond by electrostatic interaction <93CC1136>. Crystal structures of some 1-benzylimidazole-5-acrylic acids (**16**) confirm that the carboxyl group is coplanar with the ring, while the side-chain benzyl group lies closer to H-4, presumably to avoid steric interactions with the methylene hydrogens attached at N-1 <92JMC3858>.

X-ray studies have also revealed the ionic natures of imidazole quaternary salts <91ZN(B)1706>, the existence of clear parallels between the solid state and solution structures of imidazole and benzimidazole <83H(20)1713>, and the complete encapsulation of imidazolium perchlorate in benzo-30-crown-10. In the 1 : 1 complex the imidazole salt is coordinated to the host molecule by hydrogen bonding <89JOC1000>.



3.02.3.2 Dipole Moments

The measured dipole moments for imidazole and derivatives reflect more polarization in the ring than in pyrazole, but not sufficient to give an ionic structure. There has been an increase in the publication of calculated moments which, although subject to variation with the method used, give reasonable correlations with observed values, for example, imidazole: μ_{obs} , 12.24×10^{-30} ; π -SCF, 13.18×10^{-30} ; QCFF/P1, 12.94×10^{-30} ; MNDO, 11.61×10^{-30} ; 6-31G, 12.81×10^{-30} Cm $\langle 89\text{CHE1321}, 93\text{JA11906} \rangle$. Polar substituents may profoundly alter the magnitude and direction of the dipole, as in 1-phenylimidazole where the dipole is towards the aryl group (see CHEC-I). In imidazole-2-thione (18.92×10^{-30} Cm) and benzimidazole-2-thione (13.81×10^{-30} Cm) the large moments attest to dipolar forms $\langle 88\text{CHE1309} \rangle$, as does the moment (25.55×10^{-30} Cm) of 2-diazoimidazole-4,5-dinitrile $\langle 90\text{AHC}(48)65 \rangle$. Highly polar species like imidazole betaines $\langle 92\text{JOC4829} \rangle$ and benzimidazole-pyridinium inner salts $\langle 91\text{JOC4223} \rangle$ can have quite high dipole moments (30 – 50×10^{-30} Cm). The decrease in dipole moments on benzannulation of 1,1'-carbonyldiimidazole ($\Delta\mu = 5.67 \times 10^{-30}$ Cm) and the thiocarbonyl analogues ($\Delta\mu = 5.34 \times 10^{-30}$ Cm) corresponds with decreased reactivity of the benz compounds $\langle 83\text{BAU1934} \rangle$.

A study of simple 4- and 5-aminoimidazoles and their nitro analogues has been carried out in order to rationalize some of their properties. Moments calculated by the AM1 method suggest that 4-nitroimidazole should be much more polar than its tautomer (4-NO₂, $\mu_{\text{calc}} = 25.99 \times 10^{-30}$ Cm; 5-NO₂, $\mu_{\text{calc}} = 13.84 \times 10^{-30}$ Cm; 4(5)-NO₂, $\mu_{\text{obs}} = 24.62 \times 10^{-30}$ Cm). These results also support other evidence that the 4-nitro species is the major tautomer $\langle 92\text{JCS(P1)2779} \rangle$.

Barriers to nitro group rotation have been estimated at 42 – 67 kJ mol⁻¹, but the relative changes in dipole moment during this rotation are small, suggesting that the dipole moments of nitroimidazoles are largely determined by inductive affects. Resonance interactions are relatively unimportant despite coplanarity of the nitro groups and the ring. Calculated moments: 2-nitroimidazole: ground state, 20.02×10^{-30} Cm; torsional transition state, 19.78×10^{-30} Cm. Analogous results for 4-nitro- (27.46×10^{-30} , 26.49×10^{-30} Cm) and 5-nitro-imidazole (12.94×10^{-30} , 11.81×10^{-30} Cm) are in accord with experimental observations of the electrical effects of nitro groups in N-alkylation (see Section 3.02.5.2.6) $\langle 89\text{CJC1666} \rangle$. Resonance interactions from nitro groups do, however, become important in stabilization of Meisenheimer complexes in nucleophilic substitution (see Section 3.02.5.4).

Calculated dipole moments of 4- (10.74×10^{-30} Cm) and 5-aminoimidazole (13.41×10^{-30} Cm) demonstrate only a small polarity difference between the tautomers, implying similar solvent stabilization $\langle 92\text{JCS(P1)2779} \rangle$. A theoretical study of the 2-hydroxyimidazole $\rightleftharpoons$ 2-imidazolinone equilibrium, involving the AM1 quantum chemical model with inclusion of self-consistent reaction field technique to include solvent effects, has shown that although the geometries of the tautomers are little affected by the solvent reaction field, the dipole moment of the oxo tautomer is substantially altered (54.3% compared with 32.9% for the hydroxy form) $\langle 90\text{JCS(P2)195} \rangle$. The dipole moments of some 1-phenylimidazoles with halogen, nitrile, and aldehyde substituents have been measured $\langle 85\text{JOU191} \rangle$.

3.02.3.3 Proton NMR Spectroscopy

3.02.3.3.1 Aromatic systems

Imidazole shows only two distinct aromatic proton signals in its ¹H NMR spectrum (7.73 ppm, H-2; 7.14 ppm, H-4 and H-5) because of tautomerism. The NH signal may be observed in concentrated solutions in aprotic solvents with its position and half-width dependent on concentration and the solvent (see CHEC-I). The technique has been used to study the hydrogen bonding of imidazoles $\langle 85\text{JMR262} \rangle$. Although the H-2 signal is usually at lower field than the H-4(5) signals, strongly

electron-withdrawing groups can alter this order (see CHEC-I). Table 2 lists a selection of determined chemical shifts determined since the mid-1980s.

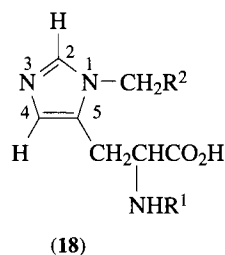
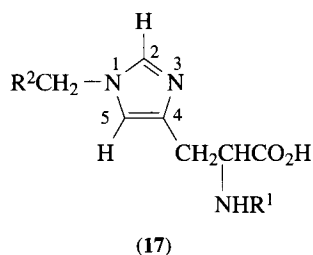
Table 2 ^1H and ^{13}C NMR data for imidazoles (ppm).^{a,b}

Compound	Proton signals (ppm)				Carbon signals (ppm)			
	H-2	H-4	H-5	Me-1	C-2	C-4	C-5	Me-1
Imidazole	7.73	7.14	7.14		136.2	122.3	122.3	
1-Me	7.47	7.08	6.88	3.70	138.7	130.2	121.0	34.2
4-Br-1-Me	7.32		6.87	3.68	137.4	115.0	119.4	33.9
5-Br-1-Me	7.53	7.00		3.62	138.3	129.5	103.7	32.6
4-Cl-1-Me	7.27		6.79	3.66	136.1	129.3	115.9	33.9
5-Cl-1-Me	7.45	6.92		3.59	137.4	126.0	118.3	31.5
4-I-1-Me	7.33		6.97	3.69	139.2	81.2	125.5	33.5
5-I-1-Me	7.63	7.13		3.61	140.0	137.0	70.7	34.8
4-CHO-1-Me	7.55		7.62	3.79	139.5	142.5	125.6	34.0
5-CHO-1-Me	7.65	7.79		3.96	144.2	143.3	131.7	34.2
4-Ph-1-Me	7.35		7.05	3.52	137.8	141.9	115.8	33.1
5-Ph-1-Me	7.67	7.13		3.65	139.0	127.2	133.4	32.5

Source: Benjes and Grimmett (94UP 302-02). ^aSolvents are CDCl_3 for 1-substituted imidazoles; D_2O for others.

Protonated or quaternized imidazoles have their protons deshielded (δ 8.5–7.6, δ 12.4–12.5), while coordination also shifts the signals to lower field. In cobalt(III) complexes of imidazoles these coordination shifts are explained on the basis of induced rehybridization of the ring carbons on coordination of the withdrawing metal centre at N-3 (δ 16.3–15.7). The spectral parameters of azolium ions in 98% sulfuric acid show coupling constants in the range 1.5–3.0 Hz for $^3J(^1\text{H}-^1\text{H})$ and $^4J(^1\text{H}-^1\text{H})$. For $^2J(^1\text{H}-^{13}\text{C})$ and $^3J(^1\text{H}-^{13}\text{C})$ the values are around 6 Hz except for couplings involving imidazolium ions [$^2J(\text{C}-4, \text{H}-5) \sim 12$ Hz; $^3J(\text{C}-4, \text{H}-1) \sim 3$ Hz] (90MRC807).

Differentiation of 1,4- and 1,5-disubstituted imidazoles has frequently proved difficult, but proton NMR offers a useful approach using cross-ring coupling constants to identify the isomers. It can, of course, only be a valid method if sufficient appropriate ring protons are present. Usually, $J_{2,5}$ is larger than $J_{2,4}$ (1.1–1.5 Hz; 0.9–1.0 Hz, respectively) (δ 8.2 JHC253, 89CPB1481, 90CHE407). If the 4- or 5-position of 1-methylimidazoles holds a strongly electron-withdrawing group, the methyl signal experiences greater deshielding in the 1,5-isomer (89H1627, 94UP 302-02). The value of the nuclear Overhauser enhancement (NOE) approach has become very clear, especially for assigning such isomeric structures. In the differentiation of the *N*-substituted histidines (17) and (18), the intensity of the *N*-methylene signals was enhanced in isomer (17) when either H-2 or H-4 was irradiated; in the 1,5-isomer (18) only irradiation of H-2 produced an effect (85JOC5878). The effect has also been successfully used to assign the configurations of *E*- and *Z*-1-(2'-alkenoyl)imidazoles (93H(36)1381), and there are other examples (85CJC866, 94CC583, 94T2641, 94UP 302-02).



A preparative study of diazo coupling of imidazole was assisted by ^1H NMR which unequivocally assigned the product regiochemistry (see Section 3.02.5.3.7) (89JCS(P2)2055).

In *para*-substituted 1-arylimidazoles the δ values for H-2 and H-5 diminish as the donor power of the *para*-substituent increases unless 2- and 5-substituents inhibit ring coplanarity (87JHC1757). The methylene signals of 1-benzylimidazoles usually appear in the region 5–6 ppm. When an azole moiety replaces phenyl as in bis(imidazol-1-yl)methane the methylene signals shift to 6.18 ppm (82JHC1141). As the hydrocarbon bridge increases in length the signals move upfield, e.g., 1,2-bis(imidazol-1-yl)ethane, 4.28 ppm; 1,2-bis(benzimidazol-1-yl)ethane, 4.62 ppm. Benzannulation deshields the methylene protons (88JHC771). Quaternary salts of methylenedimidazoles have also

been studied with the effects of chelates of Eu and NOE experiments used to assign signals $\langle 83JHC1245 \rangle$.

The success achieved in synthesizing aminoimidazoles has naturally prompted studies of their spectra. The *N*-amino group of 1-amino-2-nitroimidazole appears at 6.7 ppm (DMSO- d_6); the NH_3^+ signals of 1-aminoimidazole hydrochloride appear in the region 6.33–7.16 ppm $\langle 82S592 \rangle$. In 4(5)-aminoimidazoles the amino protons resonate at around 3.8 ppm unless there is a strong electron-withdrawing group nearby, for example, 4-amino-1-benzyl-2-phenylimidazole-5-carbaldehyde, $\delta(\text{NH}_2) = 5.83$ ppm $\langle 89S530 \rangle$.

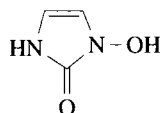
While no studies devoted specifically to benzimidazoles have been published since the mid-1980s, there have been papers dealing with benzimidazole 1-oxides (where H-2 resonates at 8.35 ppm) $\langle 88JCS(P1)681 \rangle$, benzimidazole-2-thioethers $\langle 91SC1789 \rangle$, 1- and 2-fluoralkylbenzimidazoles $\langle 84CHE422 \rangle$, and derivatives of 4- and 5-chlorobenzimidazole $\langle 91JOU2132 \rangle$. A combination of ^1H , ^{13}C , and ^{19}F NMR proved valuable in a study of the transmission of electronic effects in 5- and 6-substituted derivatives by comparing the benzimidazoles with the π -isoelectronic species, naphthalene, and quinoline $\langle 84CHE1011 \rangle$.

3.02.3.3.2 Non-aromatic systems

Although imidazolinones are in tautomeric equilibrium with the aromatic hydroxy compounds, it is convenient to discuss their NMR spectra under this heading.

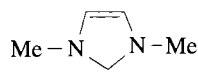
2-Imidazolines (**5**) with bulky groups in the 4- and 5-positions tend to prefer the *trans*-configuration, and ^1H NMR studies are of value in assigning such structures $\langle 83S940, 87CJC2217 \rangle$. Any H-2 signal usually appears around 7 ppm $\langle 86H(24)2871 \rangle$, but electron-withdrawing groups can cause downfield shifts, for example, in 2-imidazolin-4(5)-one the H-2 signal appears at 8.15 ppm in DMSO- d_6 $\langle 84LA831 \rangle$. Any 4- and 5-protons in these compounds appear around 3–4 ppm, although substituents can modify this $\langle 83JGU2293 \rangle$.

The 2-methylene signals of 3-imidazolines (**6**) resonate in the region 4.6–4.8 ppm $\langle 86H(24)2871 \rangle$. In 1,4,5-trimethyl-4-imidazolin-2-one the *C*-methyl groups have chemical shifts of 1.94 and 1.98 ppm, the *N*-methyl signal appears at 3.12 ppm, and the NH at 11.49 ppm $\langle 81JCS(P2)310 \rangle$. In DMSO- d_6 the 4- and 5-protons of 1-hydroxy-4-imidazolin-2-one (**19**) appear as a pair of doublets at 6.13 and 6.42 ppm; the NH and OH signals are at 9.90 and 10.36 ppm respectively $\langle 87S1058 \rangle$.



(19)

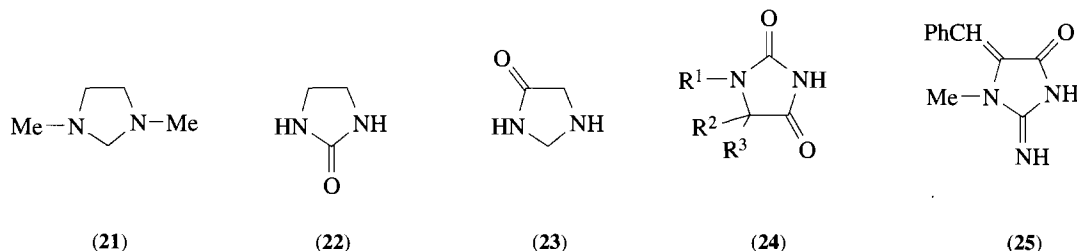
1,3-Diaryl-4-imidazolines can be converted into stable carbenes at C-2 which have H-4(5) resonating at 7.02 ppm (conversion into a 2-alane adduct shifts this signal to 7.42 ppm), while the 1,3-dimethyl carbene (**20**) has the ring proton signal at 6.92 ppm. These chemical shifts very much resemble those of 1-methylimidazole (Table 2). The 1,3,4,5-tetramethyl carbene has methyl signals at 2.01 (*C*-methyl) and 3.48 ppm (*N*-methyl) cf. methyl shifts for 4-methyl-, 2,23, and 1-methylimidazole, 3.70 ppm $\langle 92JA5530, 92JA9724 \rangle$.



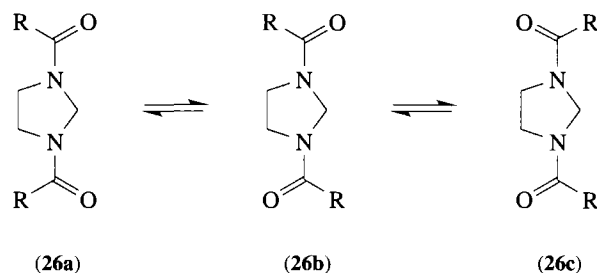
(20)

In the fully saturated species, 1,3-dimethylimidazolidine (**21**), the 2-methylene group appears at 5.2 ppm, the 4- and 5-protons are at 4.3 ppm, and the methyl signals are at 3.4 ppm $\langle 79JA1048 \rangle$. Whereas the methylene signals of 2-imidazolidinone (**22**) are found at 3.64 ppm in $\text{CF}_3\text{CO}_2\text{D}$, the 1,3-dimethyl analogue has signals at 3.27 (CH) and 2.75 ppm (Me) in CDCl_3 $\langle 81JCS(P2)317 \rangle$. The 4-isomer (**23**) has chemical shifts of 3.07 (5- CH_2), 4.18 (2- CH_2), 4.28 (1-NH), and 8.14 (3-NH) $\langle 86H(24)25, 88LA993 \rangle$. Long-range couplings between 2- and 5-protons of 4-imidazolidinones have a

measurable value only for those protons in *trans*-arrangements. This observation is the basis of a useful technique for distinguishing geometric isomers <84OMR(22)176>. A combination of NMR and CD spectral techniques has defined the conformations and ring chirality of 4-imidazolidinones in which the steric effects of substituents are important <85T611>. Studies of ^1H and ^{13}C NMR, and crystallography have been successfully applied to the determination of hydantoin (**24**) conformation <79JCS(P2)653>, and comparison of the NMR spectrum of (**25**) with those of model compounds shows that it exists as the imino rather than the amino tautomer <91CHE52>.



Variable temperature ^1H and ^{13}C NMR studies of 1,3-diacylimidazolidines indicate that at low temperatures the individual conformers (**26a–c**) can be assigned by the use of model compounds. Thus, at 50°C for (**26**) (R = Ph) and at 25°C for (**26**) (R = Bu^t) the 2-methylene and 4,5-proton shifts appear as singlets. As the temperature is lowered these peaks broaden and split until below –20°C for (**26**) (R = Ph) and –70°C for (**26**) (R = Bu^t) separate signals are observed for all three conformers <87JCS(P2)1701> (see also Section 3.02.4.2.3).



Scheme 2

In 4*H*-imidazoles there are seldom protons in the 4-position, but when there is one, its signal appears around 5.2 ppm. Protons at C-2 have been reported around 7.6 ppm. 2-Methyl groups are found at 2.16–2.50 depending on other ring substituents, while geminal methyl groups in the 4-position appear in the range 1.43–1.63 unless the ring is quaternized when they are shifted to lower field <84AHC(35)413>.

In 4,4-dimethyl-2-phenyl-4*H*-imidazoles the H-5 shift at 8.77 ppm is typical of an imine hydrogen <87JCS(P1)1389>. In 2*H*-imidazoles 4- and 5-protons are usually in the range 7.98–8.57 ppm; methyl groups at these sites appear at 2.3–2.5 ppm, while 2-methyl signals lie in the range 1.3–1.7 ppm <84AHC(35)375>. In aprotic solvents 1,2,3-trimethyl-2-phenyl-2*H*-benzimidazole shows signals for the *N*-methyl group and 5- and 6-protons which broaden with time and eventually disappear <85CHE1397>.

3.02.3.4 Carbon-13 NMR Spectroscopy

3.02.3.4.1 Aromatic systems

Chemical shifts for a number of simple imidazoles and benzimidazoles were listed in CHEC-I along with details of use of the technique in structural and tautomeric studies. Since then ^{13}C NMR studies have become routine, and some reported chemical shifts are listed in Table 2. The technique has been used for distinguishing between isomeric imidazoles, often using comparisons with model compounds <82JHC33, 82JOC144, 83T3797, 86TL1943>. In 1-alkyl-5-nitroimidazoles the C-4 signal appears in the region 131–134 ppm; C-5 in the isomer is at 119–123 ppm <86TL1943>. McKillop *et al.* have

used the technique for assigning structures to 1,2-disubstituted 4- and 5-nitroimidazoles. In DMSO- d_6 the chemical shifts of the unsubstituted carbon and that bearing the nitro group are found to be around 119 and 148 ppm for *N*-unsubstituted 4(5)-nitroimidazoles, whereas in the 1,2-disubstituted 4-nitro compounds the respective shifts are ≈ 122 and ≈ 145 ppm. For the 1,2,5-isomers comparable values are ≈ 132 and ≈ 138 ppm. The chemical shift of C-2 is also significant, appearing 3–6 ppm further downfield in the 5-nitro than in the 4-nitro series. Furthermore, when the 2-substituent is methyl its carbon signals are also diagnostic (13.40–14.66 ppm for the 5-nitro series; 11.87–12.85 ppm for the 4-nitro series). The close correspondence between the 1-methyl-4-nitro spectra and that of 4(5)-nitroimidazole clearly signifies that the latter exists as the 4-nitro tautomer in deuterated DMSO $\langle 83T3797 \rangle$. A similar study of 1-alkyl-4(5)-aminoimidazole-5(4)-carboxamides defines their regiochemistry. In the 4-amino isomer the C-4 signal is shifted upfield by about 10 ppm. compared with the 5-amino isomer; a similar shielding effect is noted with the C-5 shifts. Furthermore, an amide function at C-5 deshields C-2 more than one at C-4 $\langle 82JHC33 \rangle$. Carbon-13 NMR shifts for nitroimidazoles have also appeared elsewhere $\langle 84JHC1647, 90JOC3702 \rangle$.

A simple equation, based on adding increments for substituents, has been developed for evaluation of ^{13}C shifts in imidazoles $\langle 82H(19)1633 \rangle$, and a more elaborate statistical method has also been reported $\langle 82JOC144 \rangle$.

The methylene carbon signal in bis(imidazol-1-yl)methane appears at 28.2 ppm (cf. 26.2 ppm for the benzimidazol-1-yl analogue, and 34.2 ppm for the 1-methylimidazole methyl carbon) $\langle 82JHC1141 \rangle$. In 2-diazo-4,5-dicyanoimidazole the C-2 signal is at 112.2 ppm, upfield of the usual imidazole C-2 signal (136.2 ppm). The contributions of resonance structures which place a negative charge in the 2-position may be responsible $\langle 90AHC(48)65 \rangle$.

Substituents in the aryl ring of 1-arylimidazoles can affect the chemical shifts of the imidazole ring carbon atoms, but these effects are diminished when steric hindrance inhibits coplanarity and hence full interannular delocalization (see CHEC-I). The degree of hindrance can be deduced from a study of the $\delta_{\text{C-2}}$ values, and $\delta_{\text{C-3}} - \delta_{\text{C-2}}$ can be diagnostic of the amount of hindrance from a 2- or 5-substituent. Delocalization is extensive provided that $\delta_{\text{C-2}}$ is in the region 118–121 ppm and if $\delta_{\text{C-3}} - \delta_{\text{C-2}}$ is around 9.0–10.6 ppm. Hindrance is present if $\delta_{\text{C-2}}$ is around 124.5–125.5 ppm and $\delta_{\text{C-3}} - \delta_{\text{C-2}}$ is 3.3–4.6 ppm. In the absence of any 2- or 5-substituents $\delta_{\text{C-2}} = 121.7$, $\delta_{\text{C-3}} - \delta_{\text{C-2}} = 8.4$ ppm $\langle 87JHC1757 \rangle$.

As with the proton spectra, quaternization or coordination of a metal to imidazoles induces downfield shifts in the ^{13}C spectra $\langle 83IC678 \rangle$. The stable 2-carbenes which can be made from imidazolium salts have ^{13}C signals for C-2 in the region 215–220 ppm. $\langle 92JA5530, 92JA9724 \rangle$. Chemical shifts for a number of 2-imidazolones $\langle 92H(34)1385 \rangle$ and the corresponding thiones $\langle 92JHC1001 \rangle$, and for 4-imidazolone $\langle 84LA831 \rangle$ have been reported.

As mentioned above and elsewhere (see Section 3.02.4.3) ^{13}C NMR studies are of value in studies of tautomerism $\langle 83H(20)1713, 86ZC378 \rangle$, especially solid state ^{13}C NMR $\langle 83H(20)1713 \rangle$. Such solid state studies on imidazole (and pyrazole) show that there are three distinct signals for the annular carbon atoms (imidazole: C-2, 136.3; C-4, 126.8; C-5, 115.3 ppm). Proton exchange does not occur in the solid, hence the compounds resemble their crystal structures. Comparison with the corresponding chemical shifts for 1-methylimidazole (137.6, 129.3, 119.7 ppm) implies that the tautomerism has been frozen in the solid state $\langle 81CC1207 \rangle$. Introduction of a paramagnetic impurity is effective in obtaining CP-MAS spectra of biomolecules in the solid state. When doped with Cu^{2+} it is possible to obtain the above spectrum of imidazole, a process difficult with the pure molecule because of the long proton spin-lattice relaxation times $\langle 81JA6011 \rangle$. The technique has been applied to prototropic tautomerism in benzimidazole where it was shown that the chemical shift of the solid and low-temperature solution spectra resembled *N*-methyl model spectra. The method has also been applied to silylotropy (see Section 3.02.4.3) $\langle 83H(20)1713 \rangle$. Solid-state examination of 2,2'-bi-1*H*-imidazole also reveals "frozen" tautomerism; there are four carbon signals for the 4,4',5,5'-carbons compared with one in solution $\langle 91MI 302-01 \rangle$.

A study of the ^{13}C NMR spectra of 2-(2'-pyridyl)benzimidazoles and their quaternary salts has shown that tautomerism is blocked in the quaternized species, and that hydrogen bonding between the benzimidazole NH and the pyridine N can also render the benzene ring carbons non-equivalent $\langle 89JHC387 \rangle$.

3.02.3.4.2 Non-aromatic systems

In the 2*H*-imidazoles the C-2 signal appears in the region 101–119 ppm with C-4 and C-5 from 158–165 ppm. Methyl substituents at C-2 resonate around 24 ppm $\langle 84AHC(35)375 \rangle$. In the 4*H*-

compounds, most recorded examples have a dialkylamino group at C-5 (which gives signals in the region 179–189 ppm) and geminal methyl groups at C-4 (C-4 appears in the range 73.2–74.2 and the methyl groups at 22.1–23.7 ppm). The chemical shift range for C-2 (162.7–180.7 ppm) is a function of the wide range of substituents <84AHC(35)413>. In 4,4-dimethyl-2-phenyl-4*H*-imidazole the unsubstituted C-5 signal (193.1 ppm) is typical of an imine <87JCS(P1)1389>. The characteristic chemical shifts of the ring carbons make it possible to establish the position of the *N*-oxide function in some 4*H*-imidazole *N*-oxides <88CHE1355>.

The ^{13}C NMR technique has been used in studies of tautomerism in 3-imidazoline 3-oxides (see Section 3.02.4.3.2) <91CHE155>. A 3-oxide function induces an upfield shift of 30–33 ppm in the C-4 signal consistent with an increase in electron density at that atom <85CHE205>. Generally, the chemical shift of the nitrene carbon in these compounds lies in the region 117–152 ppm depending on the electronegativities of the 1-, 4-, and 5-substituents <85CHE210>.

Structures of 1-substituted 2-alkylthio-4(5)-methyl-2-imidazolines have been explored using ^{13}C NMR <83JGU2293>. The C-2 signal of a 1,3-disubstituted 4-imidazoline-2-thione appears at 159–161 ppm; in the corresponding imidazolidinethione it shifts to 181–184 ppm <92JHC1001>. The chemical shifts for 1-phenyl-2-thioxo-4-imidazolidinone were found to be 183.4 (C-2), 172.1 (C-4), and 49.1 (C-5). The phenyl group slightly shields the C-2 signal <82OMR(19)27>.

3.02.3.5 NMR Involving Other Nuclei

Few references to these NMR variants had appeared when CHEC-I was published, but since then interest has increased. Variations in the ^{14}N quadrupole parameters of the NH in imidazoles are primarily determined by the hydrocarbon bonding environment. There are much smaller variations found for the multiply bonded nitrogen <83JCS(P2)1391>. Nitrogen-15 studies generally substantiate earlier ^{14}N results, and the technique has potential structural applications to isomeric imidazoles. In 4- and 5-nitroimidazoles the ^{15}N resonances can be identified and assigned. These signals appear at -18 ± 1 and -25 ± 1 ppm for the 4- and 5-nitro compounds respectively. The ring nitrogen signals are also unique for each series. For 4-nitroimidazoles N-1 is deshielded (207 ± 3 ppm) and N-3 is shielded (130 ± 3 ppm); comparative values for the 5-nitro series are 220 ± 4 and 120 ± 1 ppm <83HCA1537>. In 1-acetylimidazole there is a large deshielding effect for N-1 ($+50$ ppm) in comparison with 1-methylimidazole. N-3 is deshielded by only $+10$ ppm. Only small shielding effects are observed in *C*-methylimidazoles <83HCA1537>. Comparison of pyrrole with imidazole and indole with benzimidazole demonstrates that the deshielding of the pyrrole-type nitrogen is about 15 ppm. Shielding increases with fusion of a benzene ring. Observed shieldings for 1-methylimidazole were N-3, $+218.5$; N-1, $+118.1$ ppm; for 1-methylbenzimidazole the respective values were $+236.4$ and $+136.3$ ppm. All compounds in this study were dissolved in DMSO with a 0.01 mol L^{-1} increment of $\text{Cr}(\text{acac})_3$ for each nitrogen <84OMR(22)215>.

In the solid state the ^{15}N shifts for imidazole are 150 ppm (NH) and 222 ppm ($=\text{N}-$). The average of these two is close to the single signal at 186 ppm found in solution. A pH decrease results in progressive upfield shifts in the solution ^{15}N NMR signal from 186 to 155 ppm reflecting protonation of both annular nitrogens. A similar study has been made with histidine. Such pH dependence of the ^{15}N shifts in histidine and in compounds like imidazole-4-alkanoic and -alkenoic acids has made it possible to calculate the pK_a values for the acid species, as well as providing a reasonably accurate idea of the positions of tautomeric equilibria in these compounds <82JA1192, 82JA3945>. Examination of the ^{15}N shifts for some 1-vinyl-imidazoles and -benzimidazoles confirms that the 'pyrrole-nitrogen' resonates in a stronger field than the 'pyridine-nitrogen', and that substituents cause small (≤ 15 ppm) effects, for example, 1-vinylimidazole: N-1, 183.9; N-3, 260.7 ppm; 1-vinylbenzimidazole: N-1, 164.0; N-3, 245.1 ppm <91CHE845>. The ^{15}N resonances of imidazole bound to iron(III) porphyrin have been located as potentially powerful probes for examining the nature of the iron-imidazole interaction in haemoproteins <89CC1419>.

Analysis of isomeric product ratios from reactions of imidazoles with perfluoroalkyl halides has been achieved by use of ^{19}F NMR <84JOC1060, 90TL1279>.

The natural abundance ^{17}O NMR spectra of some 1-substituted-2-thiohydantions show shifts in the region 340–360 ppm <87H(26)773>.

3.02.3.6 Ultraviolet Spectroscopy

3.02.3.6.1 Aromatic systems

The high degree of aromatic stability of imidazole and its simple alkyl derivatives means they have little absorption in the near ultraviolet. The effects of substituents on the

spectrum were discussed in detail in CHEC-I. Late applications of the technique are surveyed below.

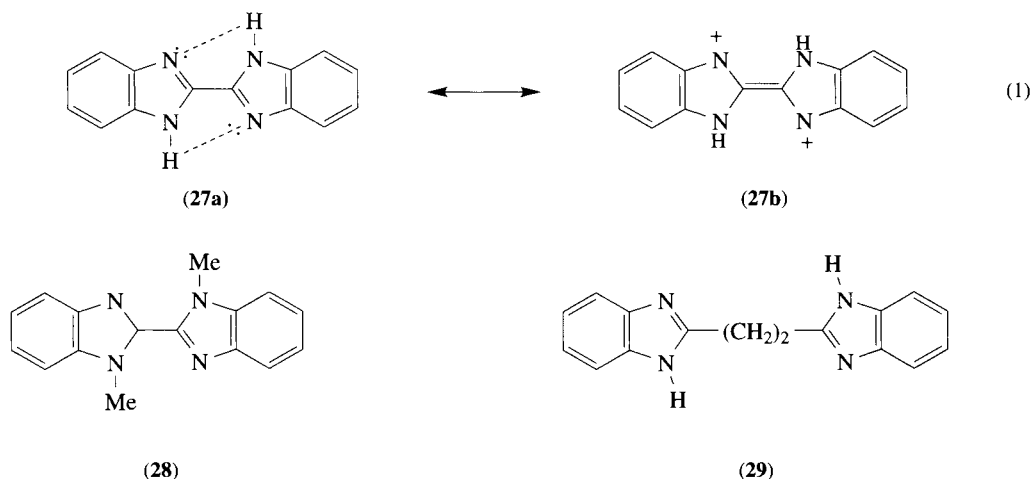
The observation that 2-diazoimidazoles have bands in the region 312–367 nm whereas the 4-isomers absorb at 308–314 nm provides a method of independent analysis of the isomers. There is also a change in $\lambda_{\max}$ on protonation of the 2-diazo compounds, again at variance with 4-diazoimidazoles <81JCS(P1)1433, 87JMC2222, 90AHC(48)65>. Differentiation of the 4- and 5-nitro derivatives of 1-methyl-2-(2'-pyridyl)imidazole is possible because the former has branched and the latter linear conjugation. This means that the 5-nitro isomer should have its main absorption band at higher wavelength. Experimental values were: 4-nitro isomer, $\lambda_{\max}$ 297, 322(sh) nm; 5-nitro isomer, $\lambda_{\max}$ 325, 238 nm <87S385>. Similar use of UV spectral analysis was able to differentiate the isomers of 4(5)-bromo (or chloro)-1-methyl-5(4)-nitroimidazole <83T3797>. A protected ribosyl group at N-1 in place of methyl increases the UV maxima, but still allows isomer differentiation <92JCS(P1)211>. A further application of the technique to substituent orientation is with 4-carbamoylimidazolium-5-olates <83JHC875>.

UV techniques continue to be used for pK_a determinations <86JHC921> and in tautomerism studies <86ZC378, 91H(32)329>.

Studies of complexes of iodine with imidazoles have demonstrated that the 1:1 charge transfer complexes are of the "n- σ " type with donation of the electron pair from N-3. Formation constants determined for the complexes with 1-methylimidazole, methimazole, and clotrimazole indicate strong donor-receptor interaction, implying an expected effect on thyroid metabolism of these imidazoles <83BSB923, 86H(24)1955>.

In 2-substituted benzimidazoles the chloromethyl and cyanomethyl derivatives have lowest energy transitions of the π - π^* type; but those of 5-chloro-2-trichloromethyl-, 2-trifluoromethyl-, and 2-chloro-benzimidazoles are of the charge-transfer type. In the corresponding monocations and monoanions the lowest energy transitions are charge transfer and π - π^* respectively. The presence of a methylene group between the heterocycle and the exocyclic heteroatom reduces direct interactions <87JCS(P2)1465>.

Studies of the absorption and fluorescence spectra of some bi-benzimidazoles have demonstrated that there is hydrogen bonding in (27a, b) as well as considerable interannular conjugation (Equation (1)), (i.e., some dipolar contribution). While (28) can still have dipolar contribution, intramolecular hydrogen bonding is now not possible. Furthermore, interaction of the nitrogen lone pairs with solvent molecules rotates the benzimidazole rings to bring the methyl groups into an *anti* relationship (although the rings are still coplanar). This manifests itself as a blue shift in the long wavelength absorption band, and a concomitant decrease in its intensity. Spectral characteristics of (29) are very similar to those of benzimidazole; the two rings have no direct interaction <89CJC1200>.



3.02.3.6.2 Non-aromatic systems

When they have no conjugating substituents 2*H*-imidazoles absorb in ethanol $\approx$ 240 nm (log $\epsilon \approx$ 3). Addition of one or more aryl groups shifts this principal absorption to 261–276 nm (log ϵ 3.71–3.97). No UV data has been reported for 2*H*-imidazole mono-*N*-oxides, but the 1,3-dioxides

have a peak around 347 nm <84AHC(35)375>. Nearly all reported spectra of 4*H*-imidazoles are modified by conjugating substituents, for example, 2,4,4-trimethyl-5-phenyl-4*H*-imidazole absorbs at 282 nm ($\log \epsilon$ 3.99) <84AHC(35)413>. Spectra have been reported for 5-substituted 4*H*-imidazole 1-oxides and 1,3-dioxides <88CHE1355>.

Imidazolines and imidazolidines show little marked UV absorption in the absence of chromophoric groups (see CHEC-I). In aqueous solution 2-imidazoline-4-one has λ_{max} at 259 nm <84LA831>.

3.02.3.7 Infrared Spectroscopy

3.02.3.7.1 Aromatic systems

Infrared spectroscopy is mainly of value in studies of substituted imidazoles and benzimidazoles, for example, 1-acylimidazoles (see CHEC-I). It has been used for the characterization of imidazolenitriles ($\nu_{\text{CN}} \approx 2200 \text{ cm}^{-1}$) <85JOC5892>, and 4-aminoimidazole-5-carbaldehydes (ν_{CHO} 1641; ν_{NH_2} 3177, 3421 cm^{-1}) <89S530>. A decrease in the carbonyl stretching frequency was noted in 1-(*p*-substituted)phenylimidazole-4-carboxylates as the *para* substituent changed from H to OCH_3 <87JHC1757>. In 4(5)-alkoxycarbonylimidazole-5(4)-carboxamides the shift in the ester carbonyl peak to lower wave numbers has been shown to involve hydrogen bonding which is not associated with an annular NH <87JHC303>. A combination of infrared and ^1H NMR has allowed determination of the regiochemistry of nitro (or amino) and chloro substituents when 2-(*p*-aminophenyl)-4(7)-or-5(6)-chlorobenzimidazoles were nitrated and subsequently reduced <91JOU2132>.

3.02.3.7.2 Non-aromatic systems

Simple tetraalkyl 2*H*-imidazoles show a peak near 1575 cm^{-1} ($\text{C}=\text{N}$ stretch), while a characteristic band between $1600\text{--}1620 \text{ cm}^{-1}$ has been identified with aryl derivatives. In a series of 2,2-diaryl 1,3-dioxides the $\nu_{\text{C}=\text{N}}$ and $\nu_{\text{N}=\text{O}}$ bands lie in the ranges $1560\text{--}1619$ and $1120\text{--}1180 \text{ cm}^{-1}$ respectively <84AHC(35)375>.

The 4*H*-imidazoles are reported to have two bands associated with unsaturation in the ring with frequencies quite sensitive to substituents. In 2,4,4-trialkyl-5-alkylthio-4*H*-imidazole, for example, these bands appear at $1613\text{--}1621$ and 1511 cm^{-1} <84AHC(35)413>. *N*-Oxide derivatives (e.g., 5-acyl-2-aryl-4*H*-imidazole 3- and 1,3-dioxides) have been studied <88CHE1355>.

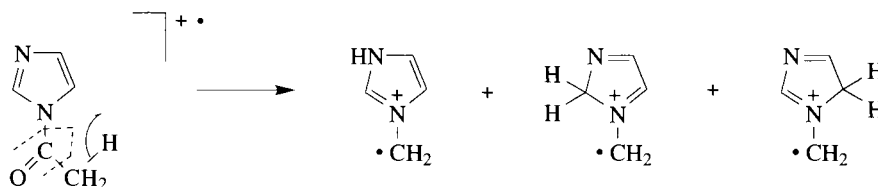
The carbonyl stretching frequency of 1-hydroxy-2-imidazolone appears at 1660 cm^{-1} ; the corresponding ethers absorb in the region $1685\text{--}1690 \text{ cm}^{-1}$ <87S1058>. The “elusive and unstable” 2-imidazolin-5-one had ν_{CO} 1680 cm^{-1} ; the carbonyl stretching frequency of 4-imidazolidinone was 1680 cm^{-1} <88LA993>, while the NH peaks were at 3400 and 3240 cm^{-1} <86H(24)25>. The absorption bands of some hydantoin analogues have been tentatively assigned <85PS23>.

3.02.3.8 Mass Spectrometry

Typical fragmentation patterns were detailed in CHEC-I. Apart from its use as a structural tool, mass spectrometry has also been applied to studies of prototropic equilibria and hydrogen bonding, thermal rearrangements, and proton affinity (see Section 3.02.4.2.2). Fast atom bombardment mass spectrometry is a ‘soft ionization’ technique which requires no sample heating, and allows one to see clusters of hydrogen bonded molecules. Its use in a study of imidazole hydrogen bonding showed a base peak $(\text{ImH} + \text{H})^+$ and also the dimer (m/z 137). Similar spectra of complexes with trimethylphosphate typically show peaks at masses corresponding to the hydrogen bonded complex, free imidazole as $(\text{M} + 1)^+$, and the free electron donor <86CJC1277>.

Collisionally activated dissociation (CAD) spectra have been used to investigate the structures of ions formed by the decarbonylation of 1-acetylimidazole under electron impact (see also CHEC-I). The results are best explained by the formation of nonclassical methyleneazolum ions (Scheme 3). The loss of CO_2 from ethyl imidazole-1-carboxylate does not produce these ions but leads instead to ionized 2 (or 4)-methyl-4(or 2)-*H*-imidazole <84BSB1057>. Thermal rearrangements of 1-acetyl- to 2- and 4-acetyl-imidazoles have been clarified by the observation that in the mass spectrum of 2-acetylimidazole the base peak is at m/z 110, and this loses a CH_3 radical, CO and ketene. For the 4-acetyl isomer the base peak (m/z 95) arises from loss of methyl from the parent radical cation

<84BSB1067> (see also Section 3.02.5.1.2). Mass spectrometry has also been used in a study of the rearrangement of dihydrobenzodiazepines to benzimidazoles (see Section 3.02.8.2.3) <83CHE318>, and in structural assignment of hydroxyhydantoin isomers <91OMS(26)125>.



Scheme 3

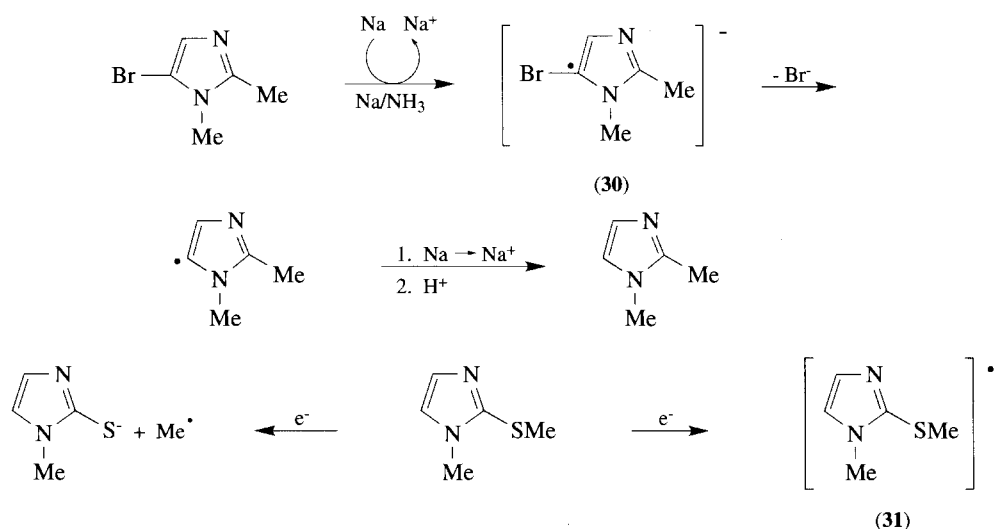
Benzimidazoles have rather high stabilities to electron impact so that the base peak is usually the parent radical ion. Substituents often leave before the aromatic system <84CHE669, 84MI 302-01, 88JOU2191>. This means that mass spectrometry can be used as a probe in synthesis <94T2485>. The loss of two or three hydrogen atoms from the parent ion is characteristic of phenyl substituents. In aryl-substituted benzimidazoles there are two competing pathways absent from those in the alkyl analogues, namely loss of HCN and of a substituent (e.g., 1-phenyl, 2-phenyl) from the parent. If a methyl group is introduced at N-1 the HCN loss is suppressed, and loss of the 2-substituent is promoted. This leads to a rearrangement which expands the imidazole moiety to a six-membered ring <84CHE669>. The observation has been made that in the mass spectra of *N*- and *C*-alkylimidazoles, the alkyl fragment ion has a much higher intensity in the *N*-substituted isomer <88JHC1845>. As a diagnostic method, however, this is clearly inferior to NMR methods.

3.02.3.9 Electron Spin Resonance

ESR studies have shown that the SOMO in 1-alkylimidazole radical cations corresponds to the π^3 orbital (as for pyrrole cations), but there is a nodal shift in the wave function which distributes most of the spin density unsymmetrically between the two nitrogen atoms <90JCS(P2)725>. Irradiation of halogen-substituted imidazoles fails to give the expected π^* radical anions; instead σ^* radical anions are formed with the SOMO primarily the C-halogen σ^* MO with little delocalization in the heteroring, i.e., a 3-electron σ band. One of the important uses of 'temperature resolved' ESR spectroscopy is to provide information about the structures of reactive intermediates. For example, the σ^* radical anions of 5-bromo- (**30**) and 5-iodo-1,2-dimethylimidazoles have been proposed as reactive intermediates in the reduction of 5-haloimidazoles (Scheme 4) <89TL1409, 90JCS(P1)919>, and the technique has also been used to study electron capture by 4- and 5-nitroimidazoles <88JCS(P2)1077>. Radical anions of the isomeric nitroimidazoles are similar with SOMOs in which 46% of the spin density is localized on the nitrogen atom of NO_2 , and about 20% on the adjacent C-4 and C-5 atoms. In 2-nitroimidazoles about 34% of the spin density resides on the nitro group. The same workers were able to show that 1-methyl-2-methylthioimidazole undergoes dissociative electron capture to form methyl radicals and thiolate. Presumably the radical anion (**31**) has a π^* SOMO with high density at C-4 or C-5. Therefore, in contrast to the haloimidazoles, there is no clear evidence for a C—SMe radical anion (Scheme 4) <90JCS(P2)975>.

Temperature-resolved ESR methods have also been employed to detect radical anions in the reduction of nitro- and nitroso-imidazoles; such species are putative intermediates in the mode of action of nitroimidazole antibiotics (see also Section 3.02.7.1.7) <85CHE688, 90TL3221>. Homolytic cleavage of the imidazole N—H bond gives a radical which ESR studies suggest has a π -type orbital (like an amino radical) involving all five ring atoms. *Ab initio* calculations show that in addition to the electronic ground state (predicted to be a π -type doublet of B_1 symmetry), the radical has π - and σ -type excited states of A_2 and B_2 symmetry respectively. The ground state π -radical is calculated to lie about 25 kJ mol⁻¹ above the σ -type radical <89JA7740>.

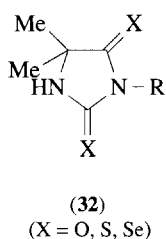
Other applications of the technique include examination of the nickel(II) complex with imidazole <86JA6470>, and mechanistic studies of the dehydrogenation of 1,2,3-trimethyl-2-phenylbenzimidazoline <84CHE817, 87CHE525>.



Scheme 4

3.02.3.10 Photoelectron Spectra

Photoelectron spectroscopy has demonstrated that there is no linear correlation between the ionization energies and pK_a values of azoles <84JHC269>. The gas phase photoelectron spectra of a series of hydantoin derivatives (32) have been compared with those of model compounds, and with the results of HAM/3 and CNDO/S calculations. Evidence is found for significant interactions between the π -orbitals and the chalcogen atoms for sulfur and selenium derivatives. In contrast, π -orbitals of the nitrogen atoms are localized in the whole series of compounds, especially in the oxy analogues and in monosubstituted derivatives <88JST(175)447>.



3.02.4 THERMODYNAMIC ASPECTS

3.02.4.1 Intermolecular Forces

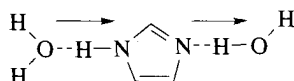
3.02.4.1.1 Melting and boiling points

N-Unsubstituted imidazoles have higher melting and boiling points than the *N*-substituted analogues because of their high degree of molecular association. In the *C*-nitroimidazoles the melting points increase in line with the dipole moments (1-methyl-5-nitro-, 51 °C; 1-methyl-2-nitro-, 102 °C; 1-methyl-4-nitro-, 133 °C; 2-nitro-284 °C; 4-nitro-, 308 °C) <89CJC1666>. Imidazole *N*-oxides are usually high melting solids <93CHE127>.

3.02.4.1.2 Solubility

Imidazoles with a free NH group are characteristically soluble in protic solvents, whereas *N*-substitution reduces intermolecular hydrogen bonding and increases solubility in covalent solvents. Highly polar substituents can alter this general rule.

The solubility of imidazole in water is a function of its hydrophilic nature (equilibrium constant for transfer from water to vapor, determined by vapor pressure measurements: $\log K(v/w) = -7.2$). Potential electronic interactions between solvation sites (33) do not seem to be present. When imidazole is *N*-methylated its hydrophilicity only decreases by a factor of 8, hence its hydrophilic character is not exceptional <87JA463>. The calculated (using semiempirical methods) *N*-shielding of imidazole is 3.93 ppm (cf. 4.6 ppm experimental value). For 1-methylimidazole the observed shielding of N-1 decreases by 3.6 ppm and that of N-3 increases by 9.2 ppm on hydration compared with the calculated values (1.87, 10.72 ppm, respectively) <83OMR(21)501>. Imidazole *N*-oxides are only sparingly soluble in nonpolar solvents, but more soluble in polar solvents.



(33)

3.02.4.1.3 Chromatography

Difficulties associated with their polar natures and intermolecular association make gas chromatography of *N*-unsubstituted imidazoles difficult, but they are conveniently separated as *N*-acetyl or other *N*-substituted derivatives <90JHC673>. Adsorption chromatography on silica gel or alumina, or partition on cellulose have been useful techniques <70AHC(12)103>, and there are later references, for example, TLC and column chromatography on silica gel of benzazoles <85H(23)2895>, and flash chromatography of alkylimidazoles <88JHC1845>. Reversed phase HPLC has allowed efficient separation of isomeric 2- and 4(5)-trifluoromethylhistidine-containing peptides <90TL5705>, and nitro- and nitroso-imidazoles <88JMC323>.

3.02.4.2 Thermochemistry

3.02.4.2.1 Aromatic stability

Heteroaromatic aromaticity has been reviewed <85CHE717, 91H(32)127, 92CHE241>. For studies of heteroaromaticity the method of Principal Component Analysis has been proposed. It uses the SIMCA method to treat geometric, energetic, and magnetic variables, and identifies two types of aromaticity, "classical" and "magnetic". The Hess-Schaad resonance energy (calculated as the difference between the HMO π -system energy and the empirical isolated π -bond energies) for imidazole is 24.3 kJ mol⁻¹. The alternative Dewar resonance energy (calculated using AM1 heats of formation) is 64.4 kJ mol⁻¹ <91H(32)127>. Examination of Kerr constants, dipole moments, and magnetic anisotropy suggests that imidazole and 1-methylimidazole have around 60% the electron delocalization of benzene; the "pyridine"-nitrogen apparently localizes charge to some extent <81AJC1835>. The structural aromaticity index (bond order difference) allocates imidazole about 43% the aromaticity of benzene (cf. pyrazole $\approx$ 61%). Empirical resonance energies for imidazole and benzimidazole were quoted as 53.1 and 203.8 kJ mol⁻¹, respectively; the comparable Hess-Schaad REPE indices were 0.042 and 0.050 (cf. pyrazole 0.055) <85CHE717>. Obviously the results of MO calculations vary depending on which values are chosen for the heteroatom parameters and which nonaromatic models are used. The Principal Component Analysis results have disclosed that the best available measure of classical aromaticity is afforded by Bird indices (based on geometric criteria), bond order differences, and heats of formation. Magnetic anisotropy is best measured by magnetic susceptibility. From the plotted results it can be seen that, in terms of classical aromaticity, imidazole is less aromatic than benzene and the diazines, but more aromatic than oxazole. Imidazole is less magnetically aromatic than benzene and pyrrole, but more so than pyrazole and the triazoles <89JA7, 90JPC853, 90JPC870, 91H(32)127>.

A Bird aromaticity index (I_A), introduced in 1992, based on the extent of variation of ring bond orders, is directly proportional to resonance energy <92T335>.

There is likely to be significant localization of the 4,5-bond in *N*-substituted imidazoles. This

follows from the observations that 4-aminoimidazoles are less stable than the 2-isomers, that 4-substituents are readily lost under hydrogenation conditions, the apparent difference in magnitude of electronic transmission from C-5 to C-2 and vice versa (see also Section 3.02.2), and the differing abilities of *C,N*-dimethylnitroimidazole isomers to stabilize carbanions (see also Section 3.02.7.1.3). Such observations imply that imidazoles may resemble the fusion of an alkene with an amidine <81JOC4717>.

Substituents have little effect on ring aromaticity. In hydroxy- and thiol-imidazoles the I_A values are almost identical with that of the parent. These I_A values are obtained from x-ray data on mesoionic compounds which can be accepted as models for the anticipated zwitterions which play important roles in the tautomeric equilibria (see also Section 3.02.4.3.1) <94H(37)249>.

A number of attempts have been made to measure or calculate the relative stabilities of isomeric imidazoles, for example, fluoroimidazoles <88H(27)1803>, diazoimidazoles <87JMC357, 87JMC2222, 87JOC5538, 90AHC(48)65>, nitro- and amino-imidazoles <89CJC1666, 92JCS(P1)2779>, 2-hydroxyimidazole, and 2-imidazolone <90JCS(P2)195>.

These results are discussed along with the appropriate functional group properties, as are the consequences of measurements of heats of hydrolysis for acylimidazole acetals (see Section 3.02.7) <87CJC1951>.

Attempts to distil 1-methoxyimidazole 3-oxide *in vacuo* caused a violent explosion at 180°C. Subsequent thermal analysis of the compound revealed a large exothermic decomposition in the range 140–180°C. The analogous 1-hydroxyimidazole 3-oxide exhibited a similar exotherm at 200–250°C <84CBR30>.

3.02.4.2.2 Other thermodynamic aspects

There has been considerable interest in azole proton affinities which can be measured by the use of pulsed high-pressure mass spectrometry. Such gas phase protonation enthalpies (ΔH^{600}) must be close to ΔH^{298} because ΔC_p is negligible. Results obtained (ΔH^{298} kJ mol⁻¹: imidazole, -929; 4-methylimidazole, -941; 1-methylimidazole, -954; cf. pyrazole, -890) are lower than these calculated in *ab initio* studies. They have been used to rationalize basicities and tautomeric properties <86JOC1105>. Numerous other studies of thermodynamic basicity have been made, and reference is made to these in the appropriate section (see Sections 3.02.4.3.1 and 3.02.5.2.2) <83AG(E)323, 83JCS(P2)1869, 85JGU1423, 86JA3237, 88CHE469, 90JA1303, 91JOC179>.

Calorimetric studies have been carried out on aqueous solutions of benzimidazole to determine the influence of temperature and supporting electrolyte on the acid-base equilibrium. It was shown that over the temperature range 298.15–318.15 K at several ionic strengths the change in heat capacity of the dissociation of the conjugate acid (benzimidazolium) is small and virtually independent of the nature and concentration of the supporting medium. Both benzimidazole nitrogens can be shown to be less basic than those of imidazole. Furthermore, the entropy change for the dissociation of benzimidazole is more negative than for the dissociation of benzimidazolium. Apparently, the neutral molecule dissociates to form ions around which hydrate shells form, inducing a substantial entropy decrease <87JGU575>.

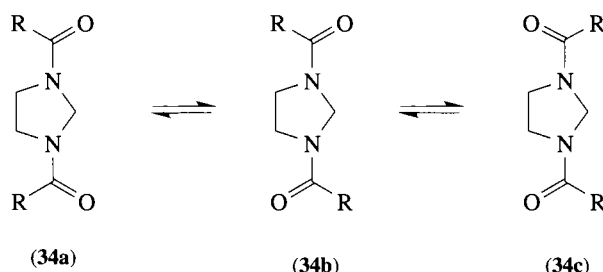
As part of a study of the isomerizations, pyrazole to imidazole and 1-methyl- to 4-methylimidazole, isomerization enthalpies have been determined from the experimental heats of formation. For the former rearrangement ΔH^{298} was calculated as -42.7 kJ mol⁻¹ (cf. experimental value, -40.2 kJ mol⁻¹), whereas 4-methylimidazole was calculated to be more stable by 27.6 kJ mol⁻¹ than its 1-methyl isomer <86JOC1105>. In view of the known thermal rearrangement of 1- to 2-methylimidazole it would be of interest to apply similar measurements of isomerization enthalpy to the species in this transformation.

Ionization potentials have been determined for imidazole (8.81 eV) and pyrazole (9.25 eV), along with fragmentation energies involved in their mass spectra <86JA677>. Gas-phase enthalpies of formation of tautomers have been calculated for 4(5)-amino- and 4(5)-nitro-imidazoles (see Section 3.02.4.3.1) <92JCS(P1)2779>.

3.02.4.2.3 Conformations

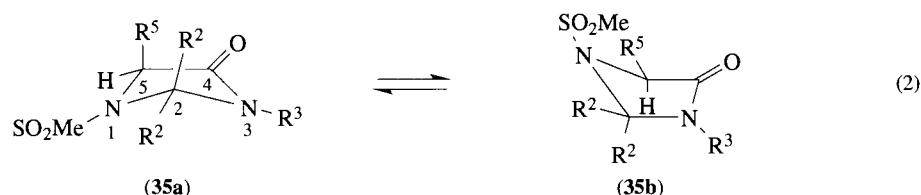
The use of variable temperature ¹H and ¹³C NMR has allowed determination of the relative proportions of 1,3-diacylimidazolidine conformers (**34a–c**) (Scheme 5). At 243 K (R = phenyl), (**34b**)

is favored over (34a) by 6.3 kJ mol^{-1} and over (34c) by 3.2 kJ mol^{-1} ; when R = butyl at 193 K (34b) is favored over (34a) by 1.5 kJ mol^{-1} and over (34c) by 1.2 kJ mol^{-1} <87JCS(P2)1701>. Dynamic NMR studies, allied with molecular mechanics calculations, have also been of value in conformational analysis of 1,3-disubstituted imidazoline-2-thiones <87JOC5177>.



Scheme 5

4-Imidazolidinones (heterocyclic analogues of γ -lactones) have their ring geometry governed by similar factors to 5-oxazolidinones. The envelope conformation with the amide group, C-2, and C-5 atoms in one plane, and N-1 deviated from the ring is preferred. Any ring chirality is determined by bulky substituents. Thus, in the 1-alkylsulfonyl derivatives (35a, b) (Equation (2)) the conformer with the 5-substituent axial should predominate in the equilibrium. The equatorial conformer is disfavored because of steric interaction of the 5-substituent with the alkylsulfonyl group. Any substitution of C-2 with bulky substituents would, however, be expected to alter this preference <85T611>.



3.02.4.3 Tautomerism

3.02.4.3.1 Annular prototropic tautomerism

Imidazoles and benzimidazoles unsubstituted on nitrogen exhibit fast prototropic tautomerism which leads to equilibrium mixtures of unsymmetrically substituted compounds, for example, 4(5)-substituted imidazoles, 4(7)- or 5(6)-substituted benzimidazoles. The proton exchange is an intermolecular process (which may involve a protic solvent), and is so fast on the NMR time scale that only one species is usually apparent in the spectrum. *N*-Substituted azoles cannot exhibit such tautomerism, and strongly acidic media also inhibit proton exchange. Much work since the mid-1980s has focussed on determination of the proportions of isomers in tautomeric mixtures, with theoretical studies applied to the gas phase (and solution), and solid state studies are also receiving considerable attention. Extrapolation of the results of gas phase and solid state studies to solution, though, can only be less than perfect.

An earlier review article <76AHC(S)1> described the application of a Hammett treatment to the problem. Qualitatively, 4(5)-substituted imidazoles with electron-donating groups ($\sigma_m < 0$) favor the 5-tautomer; those with electron-withdrawing groups ($\sigma_m < 0$) favor the 4-tautomer. There are, however, no reported examples of imidazoles with strong donor groups at C-4(5). The substituent effects appear to be largely inductive in these compounds. Charton's method for determination of the tautomeric equilibrium constant ($K_T = [4\text{-RIm}]/[5\text{-RIm}]$) used the relationship $\log K_T = 3.2 \sigma_m$ where the value 3.2 is used for $\Delta\rho$, but a $\Delta\rho$ value of >4 fits the experimental values rather better <76AHC(S)1>. Most quoted K_T values have been calculated from $\text{p}K_a$ data relating the isomeric *N*-methyl "model" imidazoles to the tautomeric species (Table 3). When there are two

electron-withdrawing groups in the 4- and 5-positions K_T still favors the more electronegative group being at C-4, for example, 4(5)-nitro-5(4)-chloroimidazole, $K_T = 118$ (76AHC(S)1).

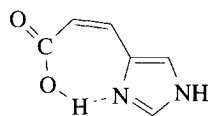
Table 3 K_T values for 4(5)-R imidazole.^{a,b}

R	K_T	R	K_T
H	1	Cl	44.5; 90 ^c
Ph	10–37	CH ₃	0.66–3.2, 1.1 ^c
NO ₂	320–500	I	19 ^c
Br	63–152, 47 ^c		

Source: mostly from Elguero *et al.* (76AHC(S)1). ^a $K_T = [4\text{-RIm}]/[5\text{-RIm}]$. ^bDetermined from pK_a measurements on 1-methyl-4-R- and 1-methyl-5-R 'models' or from the NH compounds and only one of the *N*-methyl isomers. ^cBenjes and Grimmett (94UP 302-02).

The ways in which tautomerism has been examined includes solution ¹H and ¹³C NMR (83H(20)1713, 83T3797, 86JHC921, 86ZC378), electronic spectroscopy and magnetic circular dichroism (82T1571), ultraviolet spectroscopy (86ZC378, 86JHC921), and theoretical methods (76AHC(S)1, 83JCS(P2)1869, 86BSF(2)429, 86ZC378, 90JA1303, 92JCS(P1)2779, 90JCS(P2)202). Of particular note are a series of solid state NMR studies.

In the ¹⁵N NMR spectrum of solid imidazole the two signals (see Section 3.02.3.5) indicate that tautomerism is very slow in the solid state. The average (186 ppm) is the same as the shift observed in solution. As the solution pH decreases the ¹⁵N signal moves progressively upfield until both nitrogens have been protonated (82JA1192). The chemical shifts of compounds like histamine, imidazole-4-acetic acid, and *cis*- and *trans*-urocanic acids show ¹⁵N NMR shifts which are pH dependent, allowing the calculation of pK_a values, and determination of reasonably accurate positions for the prototropic equilibria. Hydrogen bonding accounts for the greater stability of the 4-tautomer of *cis*-urocanic acid (36) (82JA3945), and there are other similar examples (89JHC387, 91CHE966).



(36)

In the solid state 2-methylimidazole is also found to exhibit two ¹³C (CP/MAS) chemical shifts for C-4 and C-5 (125.0, 115.7 ppm). The average (120.3 ppm) is close to that reported for imidazole in deuterated DMSO (121.2 ppm). These results imply that solid state chemical shifts can be used instead of *N*-methyl models in tautomerism studies (87H(26)333). For imidazole the solid state ¹³C shifts are 137.6 (C-2), 129.3 (C-4), and 119.7 (C-5) (81JA6011). No proton exchange occurs in the solid, and the data support a structure resembling the crystal structure. Cooling of imidazole solutions has not been successful in detecting individual tautomers, but it is well known that the compound exists in equal tautomeric equilibrium, as does pyrazole (81CC1207). For benzimidazole there are clear parallels between the solid state and solution spectra (see Table 4). The splitting of the C-4 signals in the CP-MAS spectrum is too large to be a quadrupole effect, but it is as yet unexplained (83H(20)1713). A solid state study of 2,2'-bi-1*H*-imidazole also showed four signals for the 4,4',5,5'-carbon atoms compared with the single signal in solution (91MI 302-01).

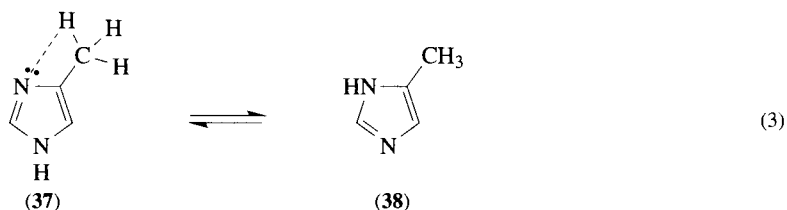
Table 4 ¹³C NMR chemical shifts (ppm) for benzimidazole.

	C-2	C-4	C-5
Solid	143.1	118.3, 120.4	123.0
DMSO- <i>d</i> ₆	142.0	115–119	121.0–121.6
CDCl ₃	143.1	119.7	121.5

The traditional method of determining K_T values has involved measuring pK_a values for isomeric *N*-methyl models, although less accurate estimates can be made using the pK_a values of the unsub-

stituted species and one of the *N*-methyl isomers (see Table 3). The method is, however, very sensitive to errors in pK_a determination, especially if the model isomers have similar pK_a values, for example, 1,4- and 1,5-dimethylimidazoles. Nevertheless, it has been usefully applied to the tautomerism of substituted histidines $\langle 83ACS(B)809, 86JHC921 \rangle$, for example, spectrometric pK_a measurements gave a $K_T = 4.8$ in favor of the 4-nitro tautomer in the methyl ester of *N*^z-acetyl-4(5)-nitrohistidine $\langle 86JHC921 \rangle$. This seems rather a low value when compared with those determined for 4(5)-nitroimidazole (Table 3). The close correspondence between ^{13}C NMR spectra of 4(5)-nitroimidazole and the 1-methyl-4-nitro "model" clearly adds to earlier evidence that the 4-isomer is dominant in solution $\langle 83T3797 \rangle$, probably because of the greater solvation of that more polar isomer $\langle 92JCS(P1)2779 \rangle$. Similarly, only the 4-isomer of 4(5)-phenylimidazole is visible in the ^{13}C NMR spectrum in DMSO-*d*₆, even though calculations (PPP-CI) of electronic transitions and UV measurements point to a mixture of tautomers in ethanol $\langle 86ZC378 \rangle$.

Theoretical studies of intrinsic basicities (PA) and tautomeric equilibria in the gas phase depend on calculation of the lone pair orbital energy (ϵ_N). The more acidic NH (lower q_H value) is more readily removed from the equilibrium $\langle 83JCS(P2)1869 \rangle$. Such calculations of tautomeric equilibria of methylimidazoles are basis-set dependent because the differences are so small, and solvent effects may be critical. Using the assumption that the *N*-methylation affect is constant in both gas phase and in solution, calculation (4-31G) suggests that the 4-methyl species (37) should be more stable than its 5-isomer (38) (Equation (3)); interactions between a methyl hydrogen and the adjacent nitrogen lone pair could be a stabilizing factor for (37) $\langle 90JA1303 \rangle$. Earlier studies of this equilibrium based on pK_a measurements had suggested that 5-methylimidazole predominates in aqueous solution (e.g. $K_T = 0.66$ $\langle 76AHC(S)1 \rangle$), but small errors in pK_a values of the model compounds can greatly affect the K_T value obtained from them. Predicted pK_a differences between 4- and 5-methylimidazoles ($\Delta pK_a = 0.02$) and 1,4- and 1,5-dimethylimidazoles ($\Delta pK_a = 0.14$) point to a K_T value of close to unity, since confirmed by measurements in 1994 $\langle 94UP 302-02 \rangle$. In aqueous solution there must be about equal proportions of the two isomers.



Application of MO calculations (AM1) to the 4- and 5-amino- and -nitro imidazoles have established their molecular geometries, enthalpies of formation, dipole moments, and ionization potentials. The calculated enthalpies of formation in the gas phase imply that the 4-amino tautomer is the slightly more stable, while in solution the small polarity difference between the tautomers ensures that both should be present. Although 5-nitroimidazole is more stable than 4-nitroimidazole (by 4.2–6.3 kJ mol⁻¹) in the gas phase, the much more polar 4-tautomer is dominant in solution $\langle 92JCS(P1)2779 \rangle$.

Calculation (INDO) of the energy barriers to the [1,5]-sigmatropic shift of a proton from nitrogen to an adjacent carbon to give a 2*H*- or 4*H*-imidazole (non-aromatic tautomers of imidazole) shows that activation energies above 210 kJ mol⁻¹ are required $\langle 86BSF(2)429 \rangle$. Amino-substituted 2*H*- and 4*H*-imidazoles, however, may be more stable than the 1*H*-forms $\langle 84AHC(35)375 \rangle$.

Related to prototropy is silylotropy. At room temperature, solutions of 1-trimethylsilylbenzimidazole show an average ^{13}C NMR spectrum, but once the tautomerism is frozen the molecule loses its symmetry $\langle 83H(20)1713 \rangle$.

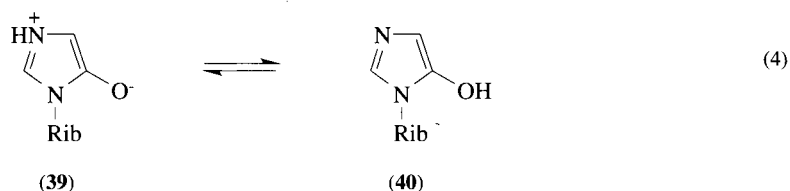
3.02.4.3.2 Substituent prototropic tautomerism

This section received considerable attention in CHEC-I, and later results have been discussed $\langle 91H(32)329 \rangle$. Aminoimidazoles usually exist as such, but matters are more complex for "hydroxy" and "thiol" imidazoles. A variety of theoretical and experimental methods have been used in the studies which suggest that hydroxyazoles are the most complex. When the hydroxyl group is α or γ to an annular nitrogen the compound can exist in two forms, unless there are electron-withdrawing

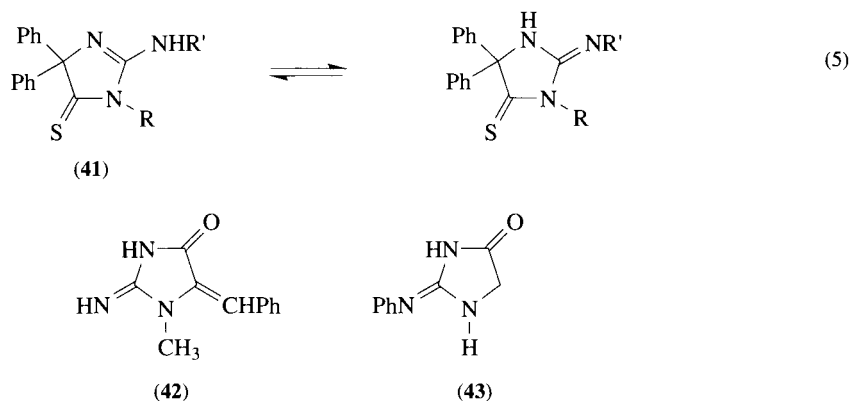
groups near the nitrogen, or non-polar solvents, or substituents that can hydrogen bond to an OH group in such a way that it is stabilized $\langle 91H(32)329 \rangle$.

Values of K_T calculated for oxo- and hydroxy-imidazoles using the AM1 model agree well with gas phase data. When solvent effects are included by means of a SCRF technique, the results are in full agreement with experimental data in aqueous solution. It is not possible, however, to use these calculated energies for isolated molecules in order to predict relative tautomer stabilities in solution since solvent effects may be specific and different for different tautomeric forms. Polar solvents which favor charge separation can preferentially stabilize species with a degree of charge separation. For 2-hydroxyimidazole (or 2-imidazolone) calculations predict the experimentally observed oxo form in solution. The geometries of the two tautomers are little affected by solvent reaction field effects, but the dipole moment of the oxo form is substantially altered in comparison with that of the hydroxy form $\langle 90JCS(P2)195 \rangle$.

A review has highlighted the roles of zwitterions in hydroxyimidazole tautomerism, for example, an aromaticity index (I_A ; see Section 3.02.4.2.1) of 68 points to a zwitterionic species (39) rather than the hydroxy tautomer (40) which would have an I_A value of around 79 (Equation (4)) $\langle 94H(37)249 \rangle$. Thiols generally resemble the oxy analogues. Solid state IR and Raman spectroscopy point to imidazole-2-thiol existing in the SH form in the solid $\langle 89CCC2045 \rangle$.



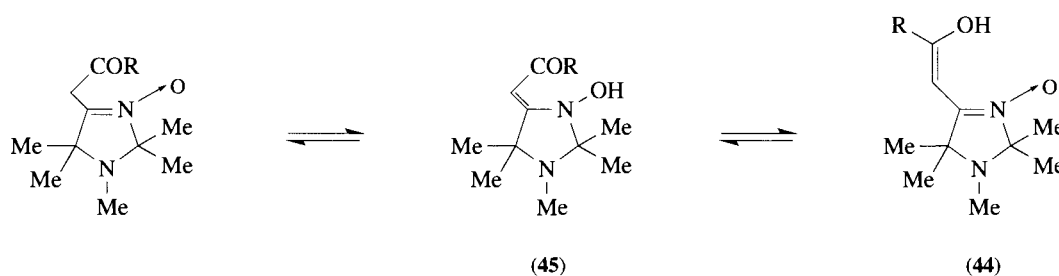
Although aminoimidazoles seldom exist as the imino modifications (the enthalpy of formation of 4-aminoimidazole is lower than either of the imino, 2*H*- or 4*H*-isomers $\langle 92JCS(P1)2779 \rangle$), 2-amino-4*H*-imidazoline-5-thiones (41) exist largely in that form when there is an alkylamine group in the 2-position ($R^1 = \text{alkyl}$). When R^1 is aryl or benzoyl, though, either the imino form (41) or a mixture of the two forms are found (Equation (5)). Similar behavior is observed in the solid state $\langle 90JOC1721 \rangle$, and both 5-benzylidenecreatinine (42) and 2'-phenylglycocycamidine (43) also exist mainly in the imino forms $\langle 91CHE52 \rangle$.



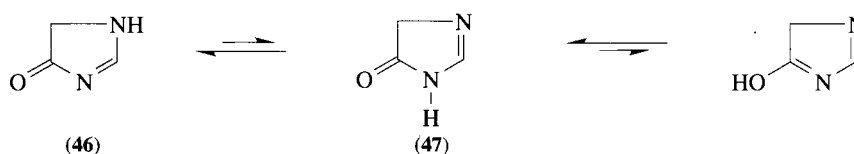
In both DMSO and chloroform, some 3-imidazoline 3-oxide derivatives have been found to exist as an equilibrium mixture of three tautomeric forms in which the enlonitrone (44) and enhydroxyaminoketone (45) species predominate (Scheme 6) $\langle 91CHE155 \rangle$. The tautomerism of imidazole *N*-oxides has been surveyed $\langle 93CHE127 \rangle$. In the proton NMR of 2-imidazolin-4(5)-one the coupling exhibited between CH_2 and NH point to (46) being the preferred form, even though theoretical studies suggest that (47) should be favored in both the gas phase and in solution (Scheme 7) $\langle 84LA831 \rangle$.

3.02.4.3.3 Ring-chain tautomerism

Azide-tetrazole tautomerism was discussed in CHEC-I. When imidazolidines react with phenyl-isocyanate the product may be cyclic or acyclic depending on the substituents (see also Section



Scheme 6



Scheme 7

3.02.6.3.1) <80H(14)1313, 90JOC1772>. Substituents also affect the equilibrium between 1-hydroxy-3-imidazoline 3-oxides and the open-chain hydroxyiminonitrones; electron-withdrawing groups in the 2-position and donors at C-4 lead to preference for the cyclic form <89MI 302-02>.

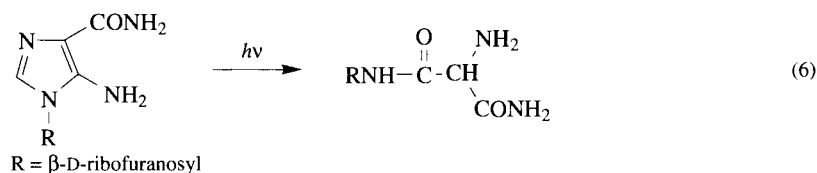
3.02.5 REACTIVITY OF THE FULLY CONJUGATED RINGS

Imidazole reactivity was fully covered in CHEC-I, and only a brief summary is included here. The neutral molecule is π -excessive, being subject to electrophilic attack at N-3, less readily at C-4(5), and seldom at C-2. In benzimidazole electrophiles preferentially attack N-3 and the benzene ring carbons. Nucleophilic substitution reactions usually require some form of electron withdrawal elsewhere in the system, with displacements of groups at C-2 often favored. Imidazolium species are naturally more susceptible to nucleophilic attack, and they only undergo electrophilic substitutions with difficulty (e.g. nitration, sulfonation). The corresponding imidazole anions, when they can form, are highly reactive towards electrophiles.

3.02.5.1 Unimolecular Thermal and Photochemical Reactions

3.02.5.1.1 Fragmentation

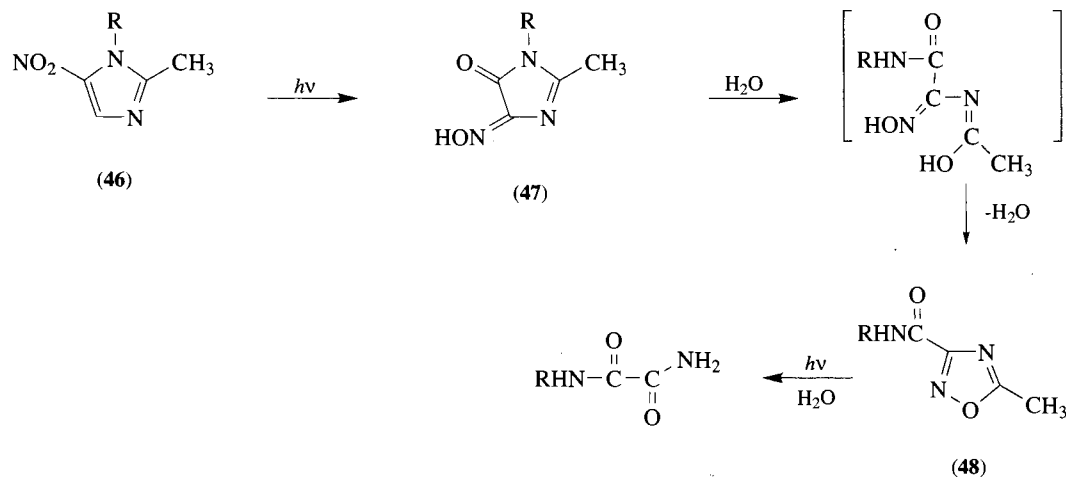
Although imidazole and its alkyl derivatives are stable even at high temperatures ($> 500^\circ\text{C}$) (see CHEC-I), other substituents can confer severe instability, for example, diazoimidazoles are light- and shock-sensitive <90AHC(48)65>. Fragmentation in the mass spectrometer has been covered already (see Section 3.02.3.8). Photochemical fragmentation is relatively common (Equation (6)) <87CPB3523>.



3.02.5.1.2 Rearrangements

When *N*-substituted 2-methyl-5-nitroimidazoles (46) are photolyzed in the presence of water the first products are 2-methyl-2-imidazoline-4,5-dione-4-oximes. This transformation follows the

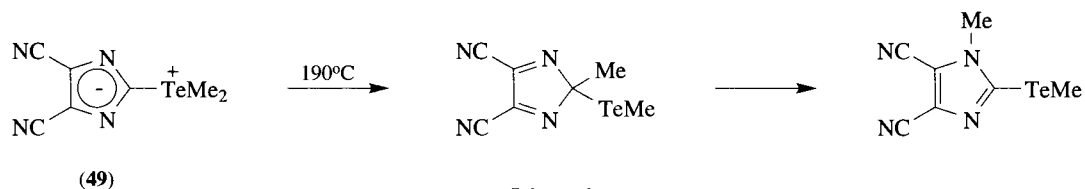
general pattern of photochemical rearrangements of nitroalkenes in that the nitro group initially rearranges to nitrite, followed by N—O bond cleavage and radical recombination at the 4-position. Subsequent hydrolysis of (47) opens the 1,2-bond enabling a rotation which brings the two hydroxyl rings into position to form the 1,2,4-oxadiazole (48). This ultimately ring opens to give an oxamide (Scheme 8) <87HCA171>.



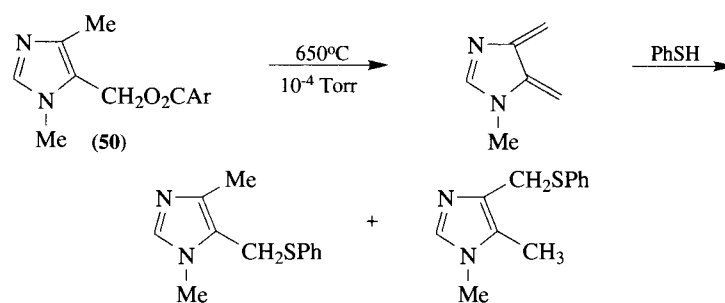
Scheme 8

The most common photochemical rearrangement in the azoles is the pyrazole $\rightarrow$ imidazole isomerization (isomerization enthalpy $\approx 42 \text{ kJ mol}^{-1}$). Any reverse reaction should be similar to the isomerization of oxazole to isoxazole (via an azirine intermediate) <B-80MI 302-01, 84JHC627, 86CHE133>. Photooxidative cleavages are discussed under the oxidation reactions (see Section 3.02.5.3.11), while rearrangements of *N*-nitro-, *N*-acyl-, and *C*- and *N*-alkenylimidazoles are discussed under reactions of the appropriate functional group (see Section 3.02.7).

Ylides of (49) undergo a modified Stevens rearrangement at 190°C (Scheme 9) <91CB699>. When (50) and its isomer were flash pyrolyzed the product was able to be trapped with thiophenol to give an identical mixture of adducts (Scheme 10) <90TL1487>.



Scheme 9

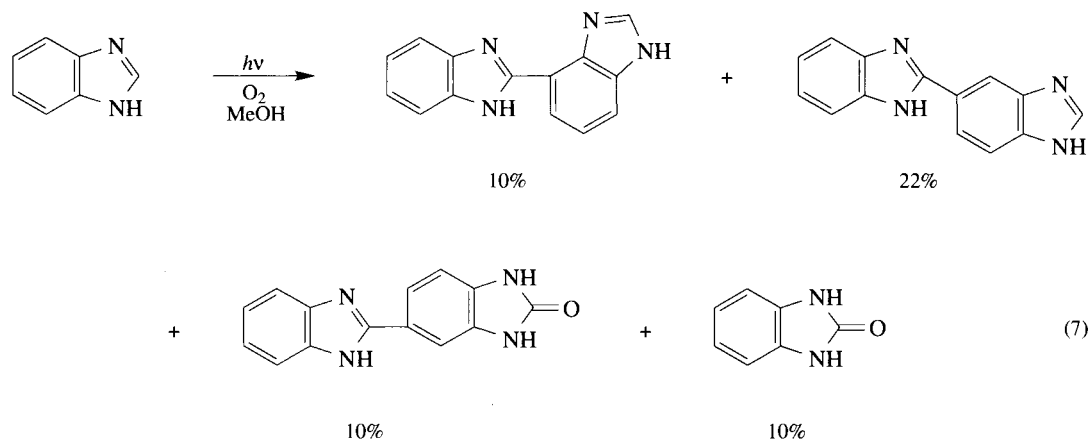


Scheme 10

3.02.5.1.3 Polymerization and disproportionation

When benzimidazole is photooxidized with singlet oxygen in methanol mainly dimeric products are isolated <85CZ231>. 2-Aminobenzimidazole behaves similarly, but 2-chlorobenzimidazole was

found to lose chlorine, forming a variety of solvent-dependent products. The 2-trifluoromethyl analogue gives a dimer with no fluorine loss, but 2-phenylbenzimidazole appears to be resistant (Equation (7)) <82AJC775>.



3.02.5.2 Electrophilic Attack at Nitrogen

3.02.5.2.1 Introduction

Such reactions can be formally related to those of tertiary amines since attack is at the multiply bonded nitrogen in neutral imidazoles. In the anionic species either nitrogen can react. Substituents play an important role in determining reactivity and product regiochemistry. Benzimidazoles are usually less reactive than imidazoles, and this is in line with their decreased basicity. Indeed, a knowledge of basic pK_a values can provide a useful gauge of reactivity. Substituent effects appear to be largely inductive, and although steric effects can be important, the hindrance is necessarily less than in six-membered heterocycles. A summary of these factors appeared in CHEC-I along with discussion of reaction sequence. A particular problem with reactions of the neutral molecule is its tautomeric nature, since the dominance of a particular tautomer can have a major effect on the regiochemistry of *N*-substitution.

3.02.5.2.2 Proton acids at neutral azoles: basicity of imidazoles and benzimidazoles

The high basicity of imidazole in comparison with other azoles has been attributed to the stability of the symmetrical imidazolium cation. That pyrazole is less basic can be ascribed to extra destabilization of the π -system on protonation <81JHC1189>. Imidazole's pK_a value of close to seven has ramifications for the biological activity of the histidine unit, for example, the two imidazole rings of His12 and His119 in Ribonuclease A act as both acid and basic catalysts in the hydrolytic cleavage of RNA <91ACR317>. Some pK_a values for substituted imidazoles are tabulated in Table 5.

Substituents have the usual effects on basicity with the very strongly electron-attracting groups (e.g., NO_2) exerting mainly inductive, but also some resonance effects depending on the position of the substituent. The sharp contrast between the pK_a values of isomeric 4- and 5-substituted imidazoles is noteworthy, and has been utilized in tautomerism studies (see CHEC-I). Understanding the behavior of organic bases in solution requires some knowledge of their gas phase (intrinsic) basicities (proton affinities (PA)) which can be determined by ICR methods; a number of publications have dealt with the determination of imidazole PA values, comparisons with other azoles, and with aqueous basicities. Discussion of such results with the aid of *ab initio* or semiempirical calculations has become common, as have calculations of the PA values. Good correlations have been found between pK_{BH^+} values and the orbital energy of the unshared electron pair on the basic nitrogen <83JCS(P2)1869, 84JOC4379>.

Gas phase basicity values for imidazole lie in the range 920–941 kJ mol^{-1} (cf. pyrazole ≈ 890 kJ mol^{-1}) <83JCS(P2)1869, 84JOC4379, 86JOC1105, 88CHE469>. Calculated values may poorly predict absolute

Table 5 Basic pK_a values of imidazoles.

Substituent	pK_a	Substituent	pK_a
H	6.99 ^a	1-Me-2-Br-4,5-(CN) ₂	2.7 ^f
1-CH ₂ OH	6.37 ^b	1-Me-2-(2'-pyridyl)	5.70 ^g
1-(CH ₂) ₂ NH ₂	5.90 ^b	2-(2'-pyridyl)	5.46 ^g
1-CH ₂ OEt	6.40 ^b	2-CH ₂ OH-4,5-Me ₂	7.88 ^h
1-(CH ₂) ₃ NH ₂	6.50 ^b	2-CH ₂ OH-4-CMe ₂ CO ₂ H	7.38 ^h
1-CH(OEt) ₂	5.97 ^b	2-CH ₂ OH-4-CMe ₂ CO ₂ Me	6.18 ^h
1-Me	7.12 ^c	2-CH ₂ OH	6.73 ^h
1-CH ₂ CO ₂ H	2.19 ^b	1-PO(OEt) ₂	6.04 ⁱ
1-COMe	3.60 ^b	2-Et	7.73 ^c
1-COPh	3.34 ^b	2-Ph	6.48 ^c
1-Me-2-NH ₂	8.54 ^c	2-Br	3.79 ^c
1-Me-2-Br	3.82 ^c	2-Cl	3.55 ^c
1-Me-2-F	2.30 ^c	2-F	2.40 ^c
1-Me-2-NO ₂	-0.05 ^d	2-SMe	5.95 ^c
1-Me-4-NO ₂	0.6 ^d	Benzimidazole	5.4 ^j
1-Me-5-NO ₂	2.3 ^d	Benzimidazole	5.69 ^k
1-CH=CH ₂	5.14 ^c	Benzimidazole 1-oxide	7.86 ^l

Sources: ^a<85JGU1423>, ^b<87CJC1951>, ^c<91JMC2056>, ^d<89CJC1666>.^e<84JHC171>, ^f<89H(29)1325>, ^g<89JHC893>, ^h<88JA5205>, ⁱ<88JOC2204>.^j<84JHC171>, ^k<87JGU575>, ^l<88JCS(P1)681>.

PA values, but good correlations exist in series of related compounds. Thus, when fully optimized geometries of the neutral molecules and the corresponding cations (using STO-3G) are obtained, it is possible to quantitatively evaluate the effects of methyl substituents. The azolium ions have been found to be more sensitive to methyl substituent effects than their conjugate bases. Indeed the effect of a methyl group on PA comes primarily (> 70%) from interactions in the charged form. Methyl groups vicinal to the basic centre (N-3) confer extra stabilization because of methyl hydrogen-lone pair interactions, but a methyl group at N-1 has a different influence due to partial loss of hyperconjugation. Some quoted PA values (kJ mol⁻¹) include: imidazole, 935; 2-methylimidazole, 954; 1-methylimidazole, 950; 4-methylimidazole, 946 <84JOC4379, 90JA1303>. Other results are comparable <86JOC1105, 89CHE423>, and extra methyl groups are base-strengthening, for example, 2,4,5-trimethylimidazole, 975 kJ mol⁻¹ <83JCS(P2)1869, 90JA1303>. The proton affinity for 1,2,4,5-trimethylimidazole is only 21 kJ mol⁻¹ less basic than 1,8-bis-dimethylaminonaphthalene (proton sponge). Plots of gas phase basicity against aqueous phase basicity gives different straight lines for NH- and 1-methyl-imidazoles <90JA1303>.

Certainly it is possible to estimate that in the gas phase imidazole is a stronger base by around 8 pK units than pyrazole (cf. $\Delta pK_{aq} \approx 4.6$) <86JA3237>. Imidazoles (and pyrazoles) display a considerable attenuation in basicity in aqueous solution compared with the gas phase, but on passing from water into acetonitrile the basicity of imidazole again increases substantially. Calculations (MNDO) of the total energies of the neutral and protonated forms show that the charge on imidazolium is much more delocalized than that on pyrazolium <81JHC1189, 84JOC4379, 88CHE469>.

It is interesting to compare intrinsic basicities of imidazoles (and pyrazoles) with a much softer acid than H⁺. Predictions suggest that although imidazole will be more basic than pyrazole by 77.8 kJ mol⁻¹ with a proton as reference acid <84JOC4379>, with ammonium ion the difference would only be 54.4 kJ mol⁻¹, ion-permanent dipole interactions being largely responsible. Both azoles behave as reasonably hard bases with their hardness decreasing on methyl substitution. Analysis of the HOMO energies should give a rough measure of the polarizability (and hence relative softness) of each system, and it has been shown that the variations in absolute hardness parallel the calculated ionization potentials of the bases <87JOC1713>.

The relationship between proton affinity and ϵ_N (lone pair orbital energy) implies that tautomeric pairs differ in their intrinsic basicities, and hence their aqueous pK_a values can be estimated (e.g., 4-methylimidazole, 7.63; 5-methylimidazole, 7.41; cf. 4(5)-methylimidazole, 7.52) <83JCS(P2)1869>. Somewhat higher values have been reported elsewhere <89CHE423>.

Ab initio calculations have shown that in nitroimidazoles the protonated 2- and 4-isomers are more stable (by 920 kJ mol⁻¹) than their conjugate bases (4- and 5-nitro tautomers have the same conjugate acid), and 4-nitroimidazolium is more stable than 2-nitroimidazolium by ≈ 29 kJ mol⁻¹ <89CJC1666>. Direct prediction of basic pK_a values of 2-substituted and 1-methyl-2-substituted imidazoles has been achieved from the three dimensional structures using a comparative molecular

field analysis approach. These calculations were based on unsolvated, unprotonated species in a vacuum, considering only one tautomer, which may account for the small discrepancies, for example, 2-phenylimidazole, 6.48 (obs.), 6.33 (calc.); 2-fluoroimidazole, 2.40 (obs.), 2.35 (calc.); 1-methyl-2-bromoimidazole, 3.82 (obs.), 3.76 (calc.) <91JMC2056>.

Studies of the intrinsic basicity of histamine have demonstrated that the annular and exocyclic nitrogens have approximately equal basicities, with ring protonation slightly favored. This accounts for the observation that histamine forms bidentate chelates with metal ions. There is, however, a large difference in aqueous solution <93JA1450>. Proton affinity calculations for *N*-aminoazoles (using STO-3G) suggest that the amino group exerts a purely inductive effect <89CHE1021>.

Correlations between pK_a values and the equilibrium constants for the formation of iodine complexes with imidazoles suggest that the charge transfer complexes are of the "n"-type involving donation of the unshared electron pair at N-3, for example, K_{CT}^{293} , pK_a listed: imidazole, 202, 6.95; 1-methylimidazole, 333, 7.33; 4-phenylimidazole, 152, 6.10; 4,5-diphenylimidazole, 141, 5.90 <83BSB923>.

Fusion of a benzene ring in the 4,5-positions of imidazole is considerably base-weakening <84JHC269>. The influences of temperature and supporting electrolyte on acid-base equilibria in aqueous solutions of benzimidazole have been studied using calorimetric methods. In the temperature range 298.15–318.15 K at several values of ionic strength the heat capacity of the dissociation $BzImH_2^+ \rightleftharpoons BzImH + H^+$ is found to be small, and virtually independent of the nature and concentration of the supporting electrolyte. Both annular nitrogens of benzimidazole are less basic than those of imidazole <87JGU575>. Although imidazole is a stronger base than benzimidazole in aqueous solution the reverse should be true in the gas phase. When the relative PA values were determined by mass spectrometric methods it was shown that benzimidazole (PA 954–962 kJ mol⁻¹) protonated around 40 times faster than imidazole (PA 934 kJ mol⁻¹). The reason for the difference between gas phase and solution basicities is mainly a function of the polarizability effect of the annulated ring system; this effect disappears in aqueous solution by dispersion of the positive charge through hydrogen bonds <83AG(E)323>. (See also <83H(20)1713, 84JHC269>).

The protonation of a number of nitro-substituted 2-benzimidazolones has been shown to occur on the oxygen, and the usual base-weakening effects of successive nitro groups were observed <83JOU376>.

3.02.5.2.3 Proton acids at imidazole anions: acidity of imidazoles

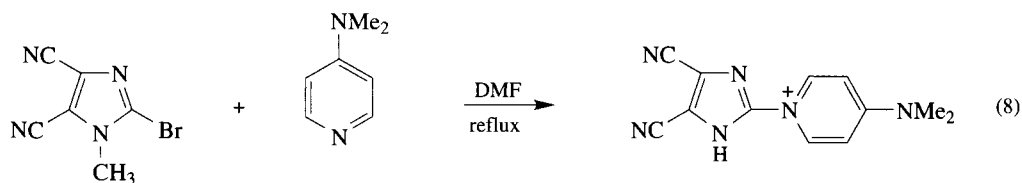
Imidazoles and benzimidazoles with a free NH group are weak acids, but sufficiently acidic to be able to form anions in the presence of strong bases <87AHC(41)187, 88CHE469>. This property becomes important in transformations such as *N*-alkylation and metallation. Whereas most metal salts hydrolyze very readily in aqueous media, they can be prepared and isolated from anhydrous aprotic solvents. Thus, *N*-lithiated imidazoles, prepared under such conditions, react in turn with copper(I) cyanide and an alkyl lithium to give cuprates $[R(Im)Cu(CN)Li_2]$ which are useful carbanion sources <92TL1041>. Some determined acid pK_a values appear in Table 6.

Table 6 Acidic pK_a values for imidazoles and benzimidazoles.^a

Compound	pK_a	Compound	pK_a
Imidazole	14.9	1-Methylbenzimidazole	13.50 ^e
2,4,5-(CN) ₃	2.1 ^b	2-Me-1-NH ₂	14.24 ^c
Benzimidazole	13.22; ^c $\approx 11^d$	2-Cl-1-NH ₂	9.04 ^c
1-NH ₂	12.83 ^c	1,2-(NH ₂) ₂	15.60 ^c
2-Ph	13.2 ^c		

Sources: ^a See also CHEC-I. ^b <89H(29)1325>. ^c <89CHE180>. ^d <87JGU575>. ^e <83CHE997>.

These values infer the almost complete absence of any π -interaction between an *N*-amino group and the benzazole ring system. Interactions must be almost entirely inductive <89CHE180>. The tricyanoimidazole forms a very stable anion, and forms stable salts with cations such as tetramethylammonium. Even two cyano groups can make a good leaving group out of imidazole. Hence the reaction (Equation (8)) in which the methyl group is lost illustrates how much strongly electron-withdrawing substituents can stabilize the imidazole anion <89H(29)1325>.



Most of the data on NH acidities of imidazoles and benzimidazoles is easily comparable, having been obtained in aqueous solution or in common organic solvents. Direct calorimetric determination of the enthalpy change on dissociation, $\text{ImH} \rightarrow \text{Im}^- + \text{H}^+$, gave a value at 298.15 K of $61.16 \pm 0.38 \text{ kJ mol}^{-1}$ and a $\text{p}K_a$ of 14.43 ± 0.05 , not too different from earlier values $\langle 85\text{JGU1423} \rangle$. The corresponding enthalpy change for benzimidazole was $55.98 \text{ kJ mol}^{-1}$ with $-\Delta S^\circ = 28.8$. That the entropy change is more negative than for the dissociation of the conjugate acid, BzImH_2^+ , is a function of the anions becoming surrounded in solution by hydrate shells causing an entropy decrease. Changes in ionic strength do not appear to greatly affect the $\text{p}K_a$ value $\langle 87\text{JGU575} \rangle$.

Although imidazole is a stronger acid than pyrazole in the gas phase (by 2.6 $\text{p}K_a$ units) and in DMSO (by 1.3 $\text{p}K$ units), pyrazole is a slightly stronger acid (by 0.2 $\text{p}K$ units) in aqueous solution. This can be explained in terms of the equilibrium shown in Equation (9).



In the gas phase electrostatic repulsion between adjacent lone pairs of electrons shifts the equilibrium to the left $\langle 86\text{JA3237}, 88\text{CHE469} \rangle$. Similarly, in aqueous solution benzimidazole is a stronger acid than imidazole, but its acidity decreases when dissolved in DMSO ($\text{p}K_a$ 16.8) or acetonitrile ($\text{p}K_a$ 25.6).

Because of the importance of metal bonding to histidine in metalloproteins, there have been numerous studies of the $\text{p}K_a$ values of imidazoles σ -bound to transition metal ions. Usually the coordination decreases acid strength substantially (by 4–6 $\text{p}K$ units with LM^{3+} systems) because of σ -donation from ligand to metal; backbonding effects from metal to ligand are minimal $\langle 93\text{AHC}(58)123 \rangle$.

The effects of *meso* substituents on the acidities of benzimidazoles have been examined by potentiometric titration of a series of 2-substituted benzimidazoles in acetonitrile. The 2-substituents appear to exert primarily inductive effects on the acidity centre, with the $\text{p}K_a$ dependent on σ_m . Acetonitrile was chosen because glass electrodes are inaccurate at pH values of > 11 in water (these compounds are very weak acids). As acetonitrile has a self-protolysis constant, $\text{p}K_s$, of 33.3 (cf. water, $\text{p}K_s$ 14) it becomes possible to study the acidic properties of such slightly dissociated compounds. In 2-acetylbenzimidazole the acidity is weakened by an intramolecular hydrogen bond. In the 2-*S*-vinyl derivative the acidity centre is sterically shielded by the β -hydrogens of the solvated substituent (see Table 7) $\langle 83\text{CHE997} \rangle$.

Table 7 Acidic $\text{p}K_a$ values for 2-substituted benzimidazoles in CH_3CN .

2-Substituent	$\text{p}K_a$	2-Substituent	$\text{p}K_a$
Me	26.43	OEt	24.92
Et	26.36	SMe	24.51
H	25.60	$\text{SCH}=\text{CH}_2$	23.70
Ph	25.36	Cl	21.95
NO_2	18.75	COMe	18.75

Source: Kashik *et al.* $\langle 83\text{CHE997} \rangle$.

3.02.5.2.4 Metal ions

(i) Simple complexes

Imidazole forms coordination complexes with transition metal ions with coordination numbers four or six (see CHEC-1). The modes of binding have been outlined $\langle 87\text{MI 302-02}, 93\text{AHC}(58)123 \rangle$. This

section is largely concerned with the bonding of the nitrogen lone pair electrons (σ -donation) to unfilled d orbitals of the transition metal, although π -coordination from the ligand is also common. Such coordination perturbs the d orbitals of the metal and the molecular orbitals of the ligand. In the case of imidazoles, this removes the basic properties and effectively blocks reactions such as protonation, alkylation, acylation etc. The coordination also modifies reactivity at other ring positions by a combination of electronic and steric factors $\langle 83AQ99, 93AHC(58)123 \rangle$.

Since the heterocycle can have available to it more than one mode of coordination, preparation of metal complexes may lead to isolation of either kinetic or thermodynamic product. A tautomeric system like 4(5)-methylimidazole coordinates with $\text{Co}(\text{NH}_3)_5^{3+}$ to give a mixture of two isomers. The more sterically hindered of these (where the metal is "ortho" to the methyl group) can cyclize intramolecularly on heating to give the more remote isomer as the thermodynamic product $\langle 83IC2693 \rangle$, and there are other similar examples $\langle 91JCS(D)3031 \rangle$.

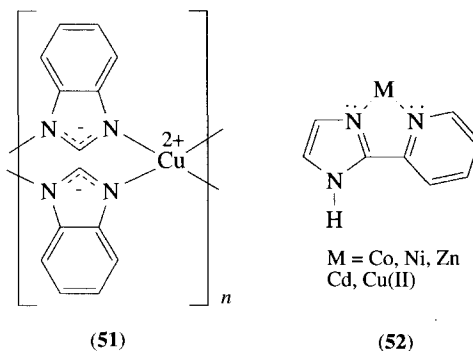
Examples of reactions of coordinated imidazoles are discussed later (see Section 3.02.5.3.5), but some conception of the effects of such coordination can be obtained by observation of the ^1H NMR spectra where complex formation usually causes deshielding $\langle 89BSF472 \rangle$. The biological activity of metal complexes of imidazoles and benzimidazoles has been reviewed $\langle 85RCR676 \rangle$.

The metal complexes of 1-vinylimidazole ($\text{p}K_a$ 5.90) with Co^{II} , Zn^{II} , Ni^{II} , and Cd^{II} are less stable than those with 1-ethylimidazole ($\text{p}K_a$ 7.23), as might be expected in view of the comparative basicities $\langle 89JCR(S)240 \rangle$.

When benzimidazole acts as a corrosion inhibitor for copper this involves formation of a coordination polymer which results from aerial oxidation of the initial benzimidazole- Cu^0 complex to give a film of bis-benzimidazolatocopper $^{2+}$ (**51**) on the metal surface $\langle 89JCS(P2)33 \rangle$.

(ii) Chelate complexes

Histidine is the best-known bidentate chelating agent here, but there are others, for example, transition metal complexes with 2-(2'-pyridyl)imidazole may involve a five-membered chelate ring (**52**) $\langle 92G73 \rangle$. Similarly 1-methyl-4-nitroimidazole chelates with Ru^{II} through an annular nitrogen and a nitro oxygen $\langle 88CJC117 \rangle$. Silver complexes of 4-nitroimidazole are similar $\langle 92CJC943 \rangle$.

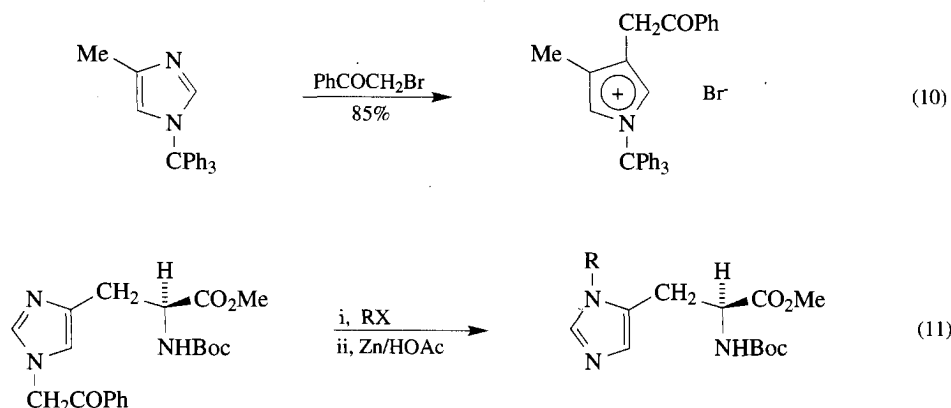


3.02.5.2.5 Alkyl halides and related compounds: compounds without a free NH group

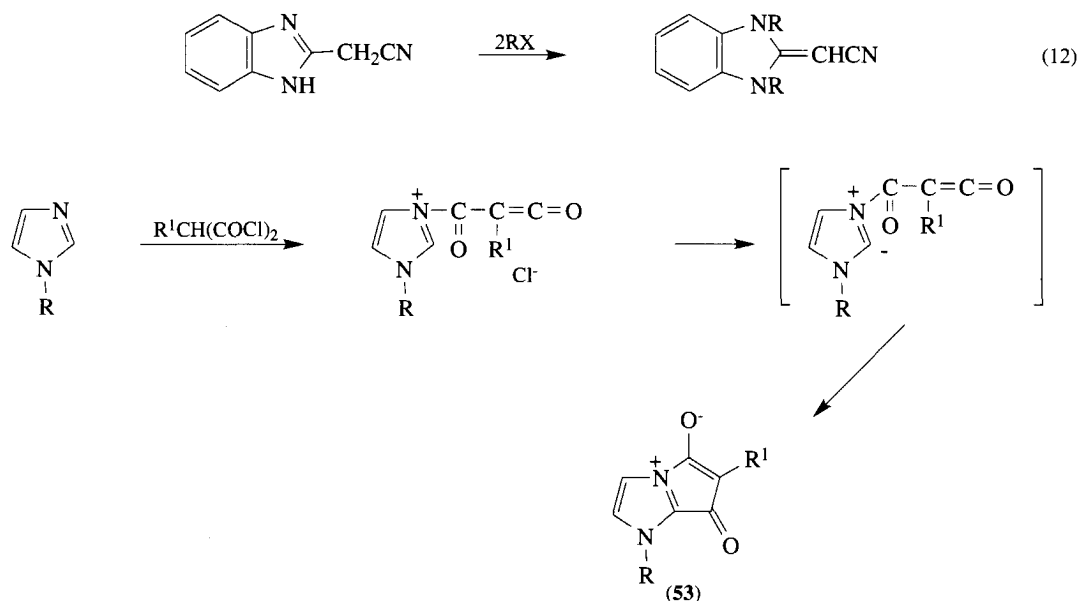
The quaternization of 1-substituted imidazoles is usually a facile reaction unless steric factors intervene, or strongly electron-attracting groups are present $\langle 82JHC253, 86MI 302-03, 87AHC(42)1, 88AHC(43)174, 93SC209, B-94MI 302-01 \rangle$. Thus, 1-acylimidazoles can only be alkylated at N-3 with powerful alkylating agents such as methyl fluorosulfonate or trialkyloxonium fluoroborates $\langle 81AG(E)612 \rangle$. The quaternary salts are best made in anhydrous conditions by alkylation of 1-alkylimidazoles $\langle 82CHE620, 83BCJ2073, 84TL3251, 86CPB4916, 87S1110, 88TL5361, 89JCS(P1)837, 89JMC504, 89JMC2301, 91ZN(B)1706, 92H(33)21, 92JHC1621, 94LA211 \rangle$, of 1-alkyl(or aryl)-2-amino- $\langle 83S861 \rangle$ or -2,3-diamino-benzimidazole $\langle 89CHE168 \rangle$, of 1-silyl- $\langle 91ZN(B)1706 \rangle$, of 1-acyl- $\langle 84TL1715, 85UKZ860, 88JOC2889, 91ZN(B)1706 \rangle$, and of 1-alkoxy-imidazoles $\langle 82CHE830, 90S795 \rangle$. Similarly, reactions of 2-chloroazoles $\langle 91JOC4233 \rangle$ or acylating agents $\langle 83CPB1213, 87S1110, 92CB1939 \rangle$ with 1-alkylimidazoles give quaternary salts. Such quaternary species can improve reactivity with nucleophiles $\langle 86CPB4916 \rangle$, and the acylalkyl salts are good acylating agents $\langle 85UKZ860 \rangle$. The 2-acylation of 1-methylimidazole proceeds via an azolium salt $\langle 84TL1715, 86CHE587 \rangle$ (see Section 3.02.5.5.3). Begtrup and Larsen's

approach to the specific synthesis of imidazole quaternary salts in terms of a series of reaction potentials <90ACS1050> is discussed in Section 3.02.5.2.6. High yields (65–80%) of 1-glycosylimidazoles can be obtained by heating 1-tetrahydropyranylimidazoles with a protected ribofuranose in dry acetonitrile in the presence of silylating agents <94CC583>.

While many quaternizations give good yields (Equation (10)) <87S1110>, even trimethyloxonium fluoroborate would not methylate 1-dimethylaminosulfonylimidazole <89JCS(P1)1139>. With 1-phenylimidazoles though, there is insufficient electron withdrawal to prevent ready quaternization with alkyl halides. This allows regiospecific synthesis of 3-substituted L-histidines by alkylation of *N*-butoxycarbonyl-1-phenacyl-L-histidine methyl ester at N-3, followed by reductive removal of the phenacyl group (Equation (11)) <87JOC3591>.



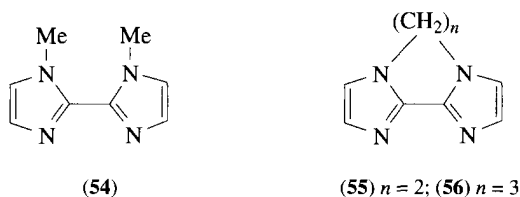
When there is a suitably placed acid hydrogen the quaternary salt can eliminate hydrogen halide (Equation (12)) <88CHE281>. Quaternization of 1-(α -cyanoethyl)-imidazoles or benzimidazoles by alkyl halides, followed by the action of base on the salts induces a Hofmann-type elimination to give the 1-alkylimidazole (54–91%) <94S102> (see also <94LA211>). Pseudo cross-conjugated mesomeric betaines (**53**) are formed when 1-alkylimidazoles are treated with aryl(chlorocarbonyl)ketenes, alkylmalonyl dichlorides, or carbon suboxide (Scheme 11) <84JOC3672, 88JOC2889>.



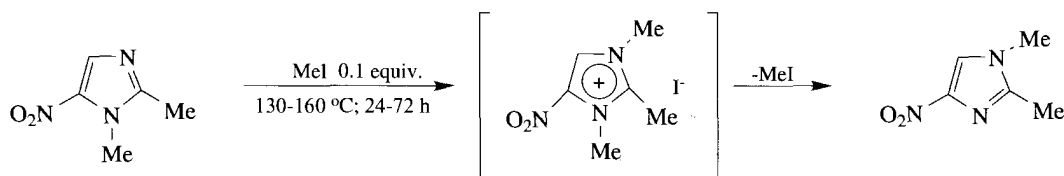
Scheme 11

Examination of the relative rates of *N*-alkylation of a series of 2,2'-biimidazoles has demonstrated that, irrespective of the nature of the alkylating agent, the reactivity order is (**56**) > (**55**) > (**54**), with a maximum (**56**):(**54**) ratio of 3.7 for reaction with chloromethoxymethane. Since reaction of (**56**)

should be the most susceptible to steric hindrance, the reason must be lone-pair cooperation <81AJC2569>.



Uracil nucleosides react with 1-methylimidazole in the presence of phosphoryl chloride to give 4-substituted pyrimidin-2-(1*H*)-one nucleosides via quaternized imidazole species <85CPB2575>. Quaternary salts are believed to be intermediates in the thermal isomerization of 5- to 4-nitroimidazoles in the presence of catalytic quantities of iodomethane (Scheme 12) <88TL5361>. There is a similar transposition of 1,2-dimethylimidazole-5-nitrile.

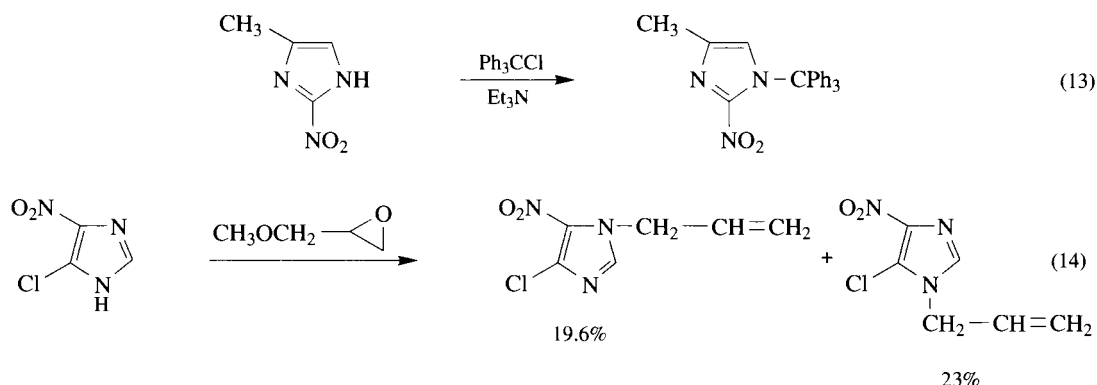


Scheme 12

3.02.5.2.6 Alkyl halides and related compounds: compounds with a free NH group

Alkylation of *N*-unsubstituted imidazoles and benzimidazoles can take place by S_E2' or S_E2cB mechanisms depending on the reaction conditions (reaction of the neutral molecule or anion) (see CHEC-I). Some reactions are difficult to classify in that the base might not completely deprotonate the heterocycle, or conditions may be such that both processes can occur. Phase transfer catalytic procedures have been usefully adapted to S_E2cB processes. Diazomethane treatment frequently gives unexpected product orientations reflecting the lack of knowledge about the mechanism(s) followed by this reagent. The field has been reviewed <B-94MI 302-01>.

A wide variety of reagents and solvents has been used for reaction with the imidazole free base (S_E2' conditions). Yields are seldom high because the acid produced eventually deactivates the substrate, and it is also difficult to avoid quaternary salt formation. Alkylation reagents used include alkyl halides <82JHC253, 82JOC1324, 84JHC133, 84JHC171, 86MI 302-03, 88CHE281, 89CPB1481, 91JHC401, 91JPR665, 91SC427, 92JOC2963, 93SC209>, dihaloalkanes <89JOC3057>, dialkyl sulfates <82IJC(B)1022, 87JMC150, 94H(37)735>, dimethyl carbonate <87LA77>, SEM chloride <92JOC2963>, trialkyl orthoformates <83JA2382>, oxiranes <82CHE649, 82JHC659, 86MI 302-03, 91JHC401>, butyrolactone <92CHE1274>, cyclopropylketones <87JOC1863>, and unsaturated (Michael) reagents <83S861, 84BAU1738, 84JHC1907, 84JOU1008, 86BAU129, 86JOC3420, 87IZV2122, 87JHC561, 90JOC3702, 90ZC286, 91JPR665, 93JCS(P1)2615, 93JOC974>. Although the neat reagents may be used, such solvents as acetonitrile <91JCR(S)350>, ethanol <86MI 302-03>, methoxyethanol <82JOC144>, DMF <82JOC144, 84JHC311, 91JHC401, 93JOC4642>, its dimethyl acetal <84S740>, THF <92JOC2963>, xylene <92CHE1274>, or DMSO <90JOC3702> are common, with added HMPA when unreactive alkylating agents are employed. The addition of triethylamine <82JHC253, 84JHC133, 84JHC171>, pyridine <90JOC3702>, potassium carbonate <88SC805, 89S530, 91SC427, 93JOC4642>, or potassium fluoride <91JCR(S)350> as catalysts to scavenge hydrogen halides is often advantageous, but may lead to a change in mechanism to S_E2cB . Thus, tritylation in the presence of triethylamine may involve the imidazole anion, particularly with acidic substrates like 2-nitroimidazole (27–35% yield) and 4-methyl-2-nitroimidazole (40% yield). Steric effects account for the isolation of only the 1,4-isomer in the latter instance <82JHC253>. Similarly, the tritylation of histidine <82JOC1324> and other 4-substituted imidazoles gives only 1,5-products (Equations (13) and (14)) <82JHC253, 87S1110>.



Dimethyl carbonate has been recommended as a less toxic alternative to dimethyl sulfate or methyl iodide; yields of 1-methyl-imidazoles and -benzimidazoles are in the range 57–91% with this reagent [\(86S382, 87LA77\)](#).

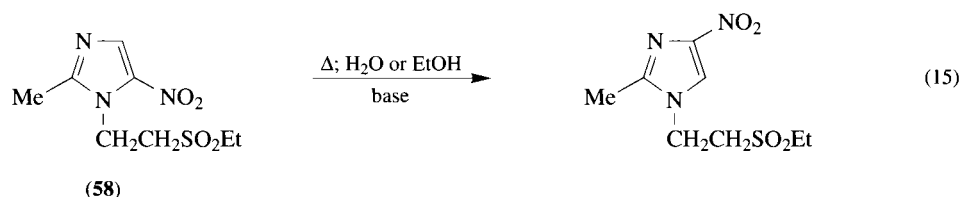
The *N*-alkyl products formed when imidazole is treated with halogenocarbonyl reagents in the presence of triethylamine are capable of nucleophilic displacement of the azolyl moiety [\(84JHC133\)](#). With trialkylorthoformates in the presence of catalytic quantities of acid, under conditions which remove the alcohol as it is formed, greater than 80% yields of 1-dialkoxymethylimidazoles are formed. This group is a good *N*-protecting group capable of removal by stirring with aqueous or methanolic acid or even with aqueous acetone [\(83JA2382\)](#). Another high-yielding variant involves allowing imidazoles to react with alcohols in the presence of ruthenium, rhodium, or iridium trialkylphosphite complexes [\(92CL575\)](#).

N-Glycosylimidazoles (related to nucleosides) are of interest in the preparation of novel chemotherapeutic agents, hence selective *N*-glycosylation techniques are of interest. The palladium-catalyzed addition of vinyl epoxides and allyl acetates to imidazoles provides one such route to imidazole nucleoside analogues [\(91JCS\(P1\)2603, 91JOC4990\)](#). The silyl-Hilbert-Johnson method is another in which the imidazole is silylated, then treated with a suitable peracetylated carbohydrate derivative in the presence of trimethylsilyl triflate catalyst. With 4-carbamoylimidazolium-5-olate, for example, the major product is the 1-glycosyl-5-carbamoyl isomer with only low yields of the 1,4-isomer and *N*-1, *N*-3-product. Yields of the 1,4-isomer can be increased by the addition of one equivalent of SnCl_4 to the trimethylsilyl derivative [\(84JHC529\)](#).

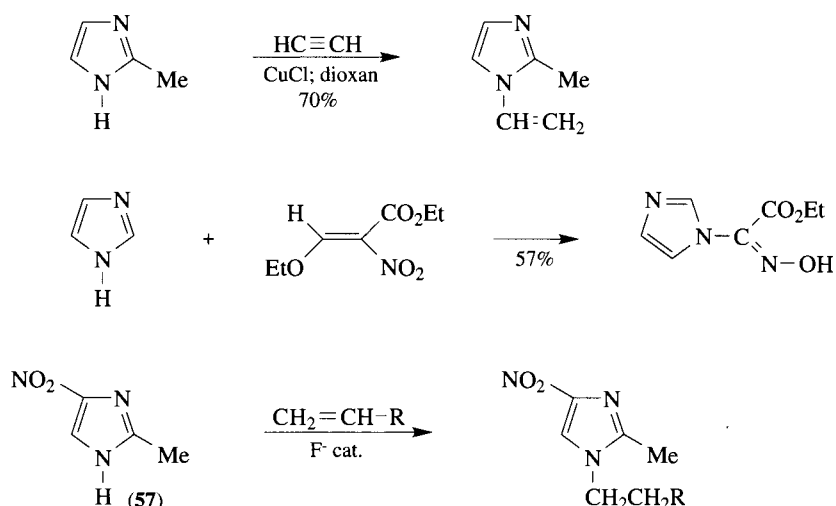
Examination of the mechanism of alkylation of imidazole and benzimidazole with phenacyl bromide suggests that the enhanced reactivity of the reagent is due to a special combination of field and conjugative effects [\(82JCS\(P2\)135\)](#).

There are many examples of Michael addition of unsaturated reagents to imidazoles. Some of these reactions involve the neutral species of the heterocycles, but others may be reactions of the anion. A number of examples are shown in Scheme 13 [\(84JHC1907, 87IZV2122, 91JCR\(S\)350\)](#). Fluoride ion catalyzed addition of 2-methyl-4-nitroimidazole (**57**) to suitable Michael acceptors gives almost quantitative yields of the 1-substituted 4-nitro isomers [\(90JOC3702, 91JCR\(S\)350\)](#).

Earlier attempts to prepare one of the two possible isomers had employed the facile-base-catalyzed rearrangement of the readily available [1-(2-alkyl(or aryl)sulfonyl)ethyl]-2-methyl-5-nitroimidazole which is made as one isomer from 2-methyl-4-nitroimidazole and ethylvinylsulfone [\(89JCS\(P1\)1352, 90JOC3702\)](#). Such base-catalyzed migrations in tinidazole (**58**) and analogous compounds seem to be specific for compounds with an *N*-alkyl- or *N*-aryl-ethylsulfone group which is eliminated as alkyl(or aryl)vinylsulfone followed by re-alkylation of the more reactive annular nitrogen. When 2-methyl-4-nitroimidazole is refluxed with ethylvinylsulfone under the same conditions as the rearrangement, the 4-nitro isomer is formed exclusively (Equation (15)) [\(89JCS\(P1\)1352\)](#).



In 1991 KF coated on alumina was used to induce this rearrangement [\(91SC443\)](#). Other methods



Scheme 13

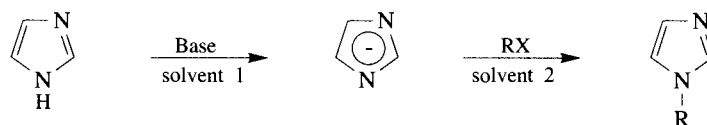
include addition of the nitroimidazole to Michael acceptors using pyridine in DMSO at 135–140°C (10 hours) <90JOC3702>, or with KF in acetonitrile at 80°C (0.5 hour) <91JCR(S)350>. It now seems that a number of Michael acceptors work in the same way as ethylvinylsulfone, for example, acrylonitrile, acrylic acid, ethyl acrylate, and methylvinyl ketone. Earlier reports that the adducts were 5-nitro compounds have been disproved by ^{13}C NMR studies <90JOC3702>.

Reactions in sufficiently basic medium to form the imidazole anion usually give higher yields since acids are not produced as by-products and quaternary salt formation can be suppressed. As well, the anion is much more reactive than the neutral molecule. Problems associated with the $\text{S}_{\text{E}}2\text{cB}$ process may include lack of solubility of the alkylating agent in the basic medium (or of the anion in a solvent which dissolves the alkylating agent), and any base-induced side reactions, for example, eliminations in some alkyl halides, rearrangements of some 4-substituted imidazoles, hydrolysis of other substituents such as ester groups. Phase transfer catalytic methods can help in some instances, and Begtrup and Larsen's separation of the reaction into two steps is an appealing alternative (see below) <90ACS1050>.

Traditionally the imidazole is dissolved in ethanol containing sodium ethoxide, in aqueous sodium hydroxide, or in a sodium–liquid ammonia medium before being treated with alkylating agent. Sodium or potassium hydride in THF, DMF, or DMSO <83JOC3745, 85AJC1873, 86JOC1891, 86TL4095, 87JCS(P1)1437, 87JHC689, 90JOC1399, 93H(35)433, 94T2641>, powdered KOH in acetone ('super base') <81SI24>, potassium *t*-butoxide in DMF at 100°C <92CC939>, and potassium carbonate in DMF <91SC427, 93JOC4642> are alternatives. The silver or copper salts of the imidazole can be used <81PJC1055, 84JHC1905> as can alkylammonium salts <89H(29)1325, 89SC1309>. Thus, the silver salts of 5-hydroxymethyl-4-nitroimidazole and 4-nitroimidazole-5-carbaldehyde were methylated and tritylated to give mixtures of isomers. The use of a weak base such as potassium carbonate in DMF to scavenge hydrogen halide may not always imply an $\text{S}_{\text{E}}2\text{cB}$ process; indeed the high proportion of 1,5-product formed on benzylation of 4-hydroxymethyl-2-propylimidazole suggests an $\text{S}_{\text{E}}2'$ process <93JOC4642>, yet the same medium gave rise to the 1,4-isomer on alkylation of 2-methyl-4-nitroimidazole <91SC427>. Perhaps the latter substrate is a strong enough acid to generate its anion more readily. Both steric and electronic factors will favor the 1,4-product.

Begtrup and Larsen <90ACS1050> have divided the reaction into two steps. In the first the sodium salt of the imidazole is prepared and isolated in a dry state. Then the dissolved or suspended salt is treated with alkylating agent (Scheme 14).

Yields are high (e.g., 1-methylimidazole, 98%), and the allocation of individual "reaction poten-



Scheme 14

tials" to the alkylating agents, solvents, etc. adds another dimension to the method. These alkylation capabilities, which are approximately additive, have been quantified by normalization to pK_a units (based on an arbitrary value given to methyl iodide) and they are then related to the pK_a of the azole so that monoalkylation will occur in 75% yield or better if the following relationship is satisfied:

$$20 - \{P_a(RX) + P_a(\text{solvent}) + P_a(\text{temp.}) + P_a(\text{time})\} \leq pK_a(\text{azole})$$

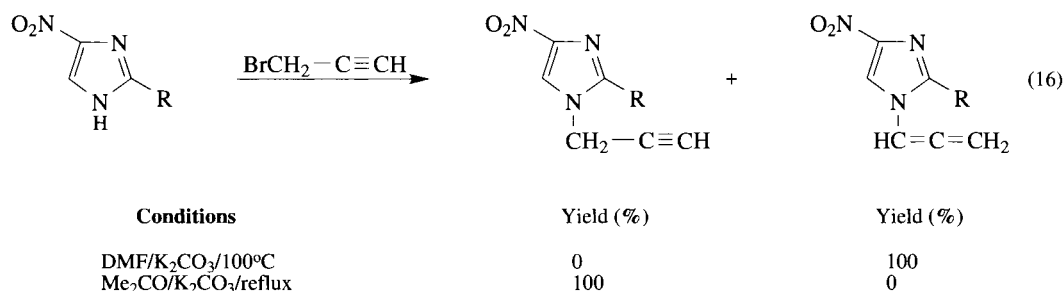
The P_a values are alkylation potentials for the reagent, solvent, temperature, and reaction time. A similar relationship has been devised for quaternization:

$$20 - \{P_q(RX) + P_q(\text{solvent}) + P_q(\text{temp.}) + P_q(\text{time})\} \leq pK_{BH}^+(\text{alkylazole}).$$

Dialkylation (quaternary salt formation) can be avoided by ensuring that the sum of the alkylation potentials is lower than the pK_{BH}^+ of the 1-alkylazole. When the pK values of the imidazole and 1-alkylimidazole are similar, quaternization can be minimized by use of stoichiometric quantities of alkylating agent, a solvent which readily dissolves the imidazole anion, and by using the smallest possible sum of reaction potentials <90ACS1050>.

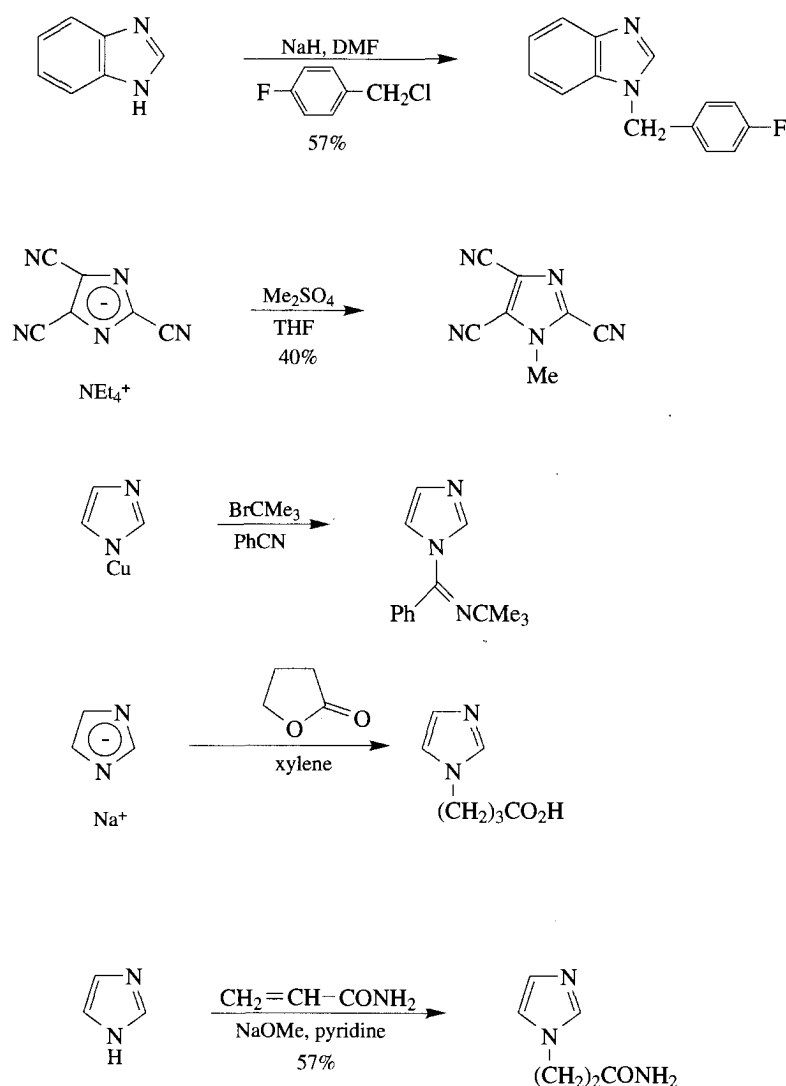
Alkylation of susceptible side-chain groups (thiol, carbonyl, etc.) may interfere, but these are discussed later (see Section 3.02.7). The variety of alkylating agents used in S_E2cB processes includes alkyl halides <83JOC3745, 83LA1078, 86TL4095, 87JCS(P1)1437, 87JHC689, 88JOC1107, 89S530, 89SC1309, 90JOC1399, 91JHC1941, 91ZN(B)1706, 92JHC1621, 92ZOB2576, 93CHE4462>, dimethyl sulfate <85JMC987, 87S385, 89H(29)1325, 89JHC1627, 90CHE407, 94H(37)735>, butyrolactone <85CHE1251, 92CHE1274>, oxiranes <81JMC601, 85JMC987>, and unsaturated reagents <84JHC1905, 85CHE1251, 88IZV1882, 88JHC225, 93JCR(S)506>. Some examples are shown in Scheme 15.

It is not always easy to *N*-alkylate nitroimidazoles. They are unreactive <92CC939>, and their anions are insoluble in non-hydroxylic solvents. In hydroxylic solvents the alkyl halides are hydrolyzed or may eliminate to form alkenes. An alternative approach preforms the tetrabutylammonium salts of the nitroimidazoles, allowing efficient alkylation in DMF, dioxan, or chloroform in good yields <89SC1309>. When 4-nitroimidazoles are alkylated with propargyl bromide, 1-propargyl- and 1-allenyl-products are formed with high selectivity. At higher temperatures, and in the presence of stronger bases the thermodynamically more stable allenyl isomers predominate (Equation (16)) <93JCR(S)506>. The isolation of 1-substituted-4-nitro products strongly suggests that the anion is reacting (see below).



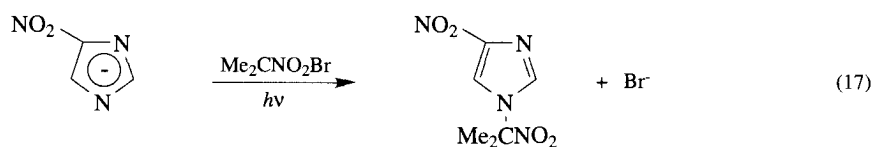
The 1-tributyltin derivatives of benzimidazole or its 2-trifluoromethyl derivative react readily with alkyl halides to give the 1-alkyl analogues <84TL5555, 92JOM(423)361>. Although a variety of alkyl halides give good yields (allyl bromide, 65% bromocyclohexane, 50%), very reactive halides (benzyl and phenacyl bromides) also react at C-2 when that position is vacant <84TL5555>. Otherwise, the "super base", KOH-acetone, is necessary for such a poorly nucleophilic anion as 2-trifluoromethylbenzimidazolyl <89CHE1>. It is noteworthy that *N*-alkylation predominates with imidazole sodium and potassium salts. With harder cations such as lithium and magnesium which are tightly bound to the nitrogen, *C*-alkylation becomes more important, and solvent can affect the *N*:-*C*-alkyl ratio (see also discussion of phase transfer catalysis below).

Anions of 4-nitro-imidazoles and -benzimidazoles have been shown to undergo $S_{RN}1$ reactions with a range of halogenonitroalkanes to give *N*-(1-nitroalkylazoles). Such radical reactions are also effected under oxidizing conditions as when nitroimidazole anions add to the anion of 2-nitropropane (using catalytic quantities of potassium ferricyanide and sodium persulfate as oxidants). In one of the propagation steps the nitroalkane radical reacts with the imidazole anion to generate a radical anion which forms the product on reaction with another molecule of halogenonitroalkane. The overall reaction is described by Equation (17). The reactions are regiospecific for the 1,4-isomers,



Scheme 15

and nucleophilic attack by the nitroimidazole anions on the radical intermediate, $[\text{Me}_2\text{CNO}_2]^{\cdot}$, is under kinetic control, occurring at the more nucleophilic ring nitrogen, at a rate which depends on steric factors <86TL1943, 86TL6209, 87JCS(P1)2819>.



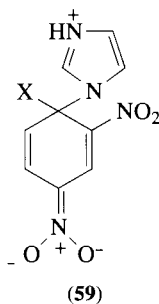
Separation of the alkylating agent from the basic medium can be achieved by the use of phase-transfer catalytic procedures (see CHEC-1) <83CHE1141, 84AHC(36)175, 89CHE1>. Both liquid-liquid and liquid-solid methods can be used. The former employs a two phase organic-aqueous base system with theazole dissolved as the anion in the aqueous layer and the alkylating agent in the organic layer. Stirring and/or heating for some hours with an added phase-transfer catalyst (e.g., tetrabutylammonium bromide) is needed. The solid-liquid technique suspends potassium carbonate and/or potassium hydroxide in the organic solvent with the heterocycle, alkylating agent, and phase transfer catalyst <82JHC1141>. Crown ethers have been used particularly as solid-liquid phase-

transfer reagents <80JOC3172, 86S382, 87LA77, 91S709>. The tetrabutylammonium bromide catalyst (and tetralkylammonium salts of imidazoles) is effective because the counter cation is only loosely bound to the azole anion (like Na^+ and K^+). Methylation of imidazoles in 70–95% yields was achieved with dimethyl carbonate, pulverised potassium carbonate, and 18-crown-6, although 4-nitroimidazole gave a lower yield (57%) <87LA77>. The solid–liquid technique tends to give slightly better yields than the liquid–liquid method <92H(34)1365>, and subjection of the reaction mixture to ultrasonication may be helpful <93SC1783>.

Examples of phase-transfer catalysis applications include methylation of benzimidazole in 38% yield <81AJC1729>, benzylation (76% yield) and tritylation (80%) of the same substrate <85H(23)2895>, and other benzimidazole alkylations <91BSF255>. Tetrabutylammonium sulfate has been used in the aminoalkylation of imidazole (60%) and benzimidazole (50%) with 2-chloroethylamine <91SC535>, while methylene-1,1'-diimidazole and other di-imidazoles and -benzimidazoles were made with the appropriate dichloroalkane under phase transfer conditions <83JHC1245, 88JHC771, 92H(34)1365>. See also <83CHE1141>.

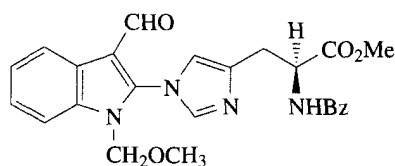
Diazomethane has been used on numerous occasions to *N*-methylate imidazoles and benzimidazoles <82IJC(B)1022, 87S385, 89JHC1627>. Although yields are often high, with unsymmetrical imidazoles the orientation may be difficult to predict. The mechanism is not yet clear and the ratios of products frequently differ from those of conventional $\text{S}_{\text{E}}2'$ or $\text{S}_{\text{E}}2\text{cB}$ processes <B-94MI 302-01>.

Although activated aryl halides can *N*-arylate imidazole anions, less reactive reagents require the extreme conditions of Ullman-type processes (see CHEC-I). With the more reactive aryl halides (e.g., 2,4-dinitrochlorobenzene) the process can be rationalized in terms of the conventional nucleophilic aromatic substitution mechanism in aprotic solvents of high relative permittivity, with chloride ion catalyzing the formation of the intermediate in acetonitrile solution. In benzene the reaction is strongly catalyzed by tetrabutylammonium chloride and weakly catalyzed by pyridine. The corresponding reaction with 2,4-dinitrochlorobenzene is also strongly catalyzed by imidazole. Catalysis by amines can be explained by the reaction occurring via complexes formed from reactants and catalysts. When imidazole is the nucleophile, the proposed transition state for the uncatalyzed decomposition of the intermediate resembles (59) <93JCS(P2)905>. Such σ -complexes have been reported previously with 4,6-dinitrobenzofuroxan and imidazole or 1-methylimidazole; but only the imidazole anion is able to form a similar σ -*N*-complex with 1,3,5-trinitrobenzene in DMSO <83TL493>. These *N*-complexes, which are formed under kinetic control, subsequently rearrange to form the more stable *C*-adducts <82TL4079, 85CJC866>.



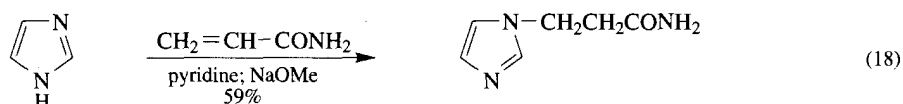
N-Arylation of protected histidine with 2-chloro-1-methoxymethylindole-3-carbaldehyde gives the Trp-His fragment (60) of moroidin <92S731>. A series of 2-substituted imidazoles gave moderate yields (>33%) of their *N*-aryl derivatives when heated in DMSO with *p*-fluorobenzoic esters <90JMC1091>, while both imidazole and benzimidazole were *N*-arylated in good yields by *p*-fluoronitrobenzene under solvent-free phase transfer conditions <93SC1947>. Other arylation approaches have included reactions of the heterocycles with arynes or diaryliodonium salts <84S709, 87TL3071>, photochemical arylations <88CPB4693>, thermolysis of aryllead triacetates <92TL659>, and the use of organobismuth reagents <85JCS(P1)2667, 88TL1115>. In most instances yields are only moderate, and the scope of the reactions is limited; indeed some have not yet been applied to imidazole or benzimidazole <92TL659>. However, treatment of azoles with *p*-tolyllead triacetate at 90–110°C in the presence of copper(II) acetate gives 1-*p*-tolylimidazole (82–86%) and 1-*p*-tolylbenzimidazole (98%) under much milder conditions than the Ullman method <92TL659>. Activated 2-chloroazoles react with *N*-alkylazoles to form *N*-azolylazolinium salts <91JOC4233>.

In general, substitution at an annular nitrogen of imidazole can be kinetically or thermodynamically controlled. Whereas alkylation and arylation give mixtures of isomers, acylation,

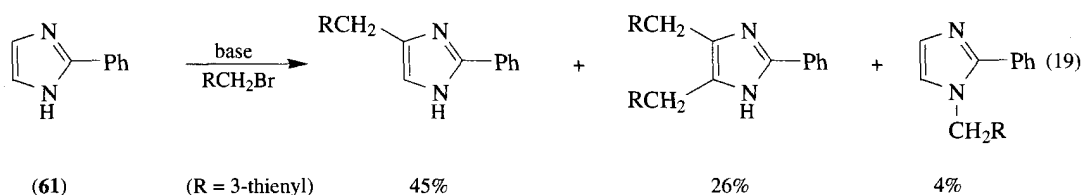


(60)

metallation, and silylation give the more stable isomer. Although the products of the base-catalyzed Michael addition of acrylamide to imidazole or benzimidazole have an sp^3 N—C bond like *N*-methyl, one would not expect thermodynamic control. The *retro*-Michael reaction, however, allows thermodynamic equilibrium to be reached (Equation (18)) <88JHC225>.



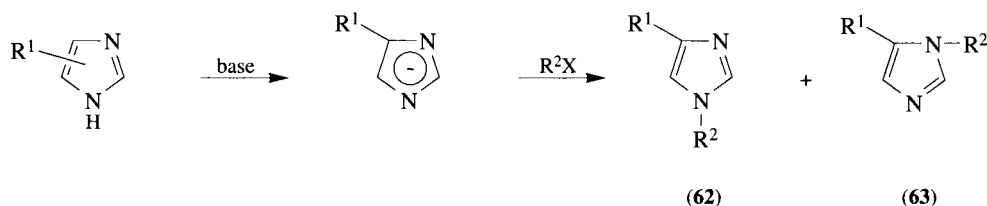
It is widely accepted that most *N*-alkylation processes can be described in terms of S_E2' (imidazole reacts) or S_E2cB (imidazole anion reacts) mechanisms (except for diazomethane reactions), but the affects of substituents on isomeric product ratios are less clear. The usual preference for *N*- over *C*-substitution, too, has only been addressed since the mid-1980s. A number of 2-substituted imidazoles were found to be 4(5)-alkylated by soft electrophiles. Thus, 2-phenylimidazole (**61**) reacts with 3-thienylmethyl bromide to give mainly 4- and 4,5-di-substituted products; *N*-alkylation occurs only to a minor extent (Equation (19)). Similarly, the soft reagent, 2-methoxybenzyl chloride, also gives rise mainly to *C*-substituted products. Benzyl bromide, a harder electrophile, largely *N*-benzylates (**61**). The authors have suggested that direct *C*-alkylation may not have been observed before with imidazole anions because of C-2 deprotonation in the transition stages. When the 2-position is blocked, however, both C-4 and N-1 can be alkylated in basic medium <88JHC1845>. Much the same arguments apply to the alkylation of imidazole- or benzimidazole-2-thiones which have two alkylation sites. The sulfur is the "soft" centre; the nitrogen is "hard." The difficulty is that soft electrophiles like alkyl bromides and iodides react preferentially with sulfur nucleophiles, so it is necessary to mask the sulfur group as, for example, *S*-trityl, when using such reagents. No such masking is needed in acylation since hard electrophiles like acetyl chloride or acetic anhydride prefer the hard nitrogen centre <91SC1789>.



When there is a large alkylating agent steric factors frequently dominate the reaction with an unsymmetrical imidazole whether in neutral or basic conditions. The 1-trityl-4-substituted isomer is usually formed exclusively <82JHC253, 87S1110>; in basic medium butylation of 2-methyl-4-propylimidazole gives a 92:8 ratio of 1,2,4- and 1,2,5-isomeric products <83JOC3745>. But steric hindrance is only one of a number of factors which can influence the composition of the isomer mixture formed when unsymmetrical imidazoles are alkylated. In both S_E2' and S_E2cB processes polar effects are also important, as are the nature of the alkylating agent and the solvent. In the S_E2' reactions the tautomeric nature of the substrate may well become the major directing factor, and one must also be aware that the reaction conditions used for making 1-alkylimidazoles may not confine the process specifically to one of the two mechanisms.

It is convenient firstly to examine the reactions which involve the imidazole anion (S_E2cB). The proportions of 1,4- (**62**) to 1,5-product (**63**) depend on the natures of R^1 and R^2 (Scheme 16). If R is electron attracting attack is favored at the more remote nitrogen; a large R^1 (or R^2) leads to the

same preference. Thus 4-nitroimidazole forms only 1-benzyl-4-nitroimidazole ((62): $R^1 = \text{NO}_2$, $R^2 = \text{CH}_2\text{Ph}$) when treated with benzyl chloride in aqueous sodium hydroxide (89SC1309, B-94MI 302-01).



Scheme 16

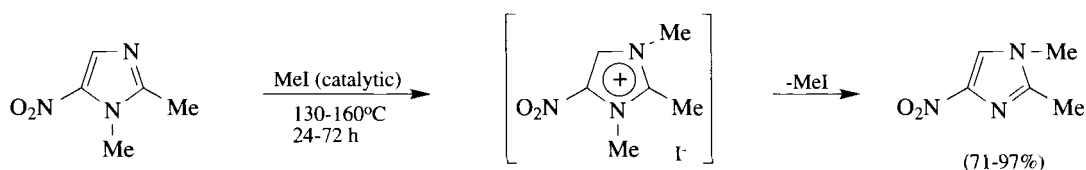
The additive natures of electronic and steric factors are obvious in the methylation, ethylation, and benzylation of 4-nitroimidazole (see Table 8). It seems that the dominant electronic effects of substituents are inductive since mesomeric effects affect electron density both α and γ to the substituent. Inductive effects will mainly be felt on the nitrogen adjacent to the substituent (R^1). Hammett correlations are also much better with σ_M or σ_I than σ_P constants (94H(37)735). When alkylations were carried out in DMF with potassium carbonate as base, again electron-attracting 4-substituents largely directed attack to give the 1,4-isomers, but some ratios could not be reconciled in terms of inductive effects alone (93JOC4642). It is, however, not certain that all of these reactions were proceeding entirely by S_E2cB mechanisms.

Table 8 Isomer ratios^a from alkylation of 4-substituted imidazoles.^b

4-Substituent	Alkylating reagent		
	Me_2SO_4	Et_2SO_4	PhCH_2Cl
Br	2.6 : 1	3.2 : 1	1.6 : 1
Me	1.4 : 1	1.3 : 1	1.7 : 1
NO_2	8.6 : 1	16 : 1	^c
Ph	7.3 : 1 ^d	9.5 : 1 ^d	^{c,d}

Source: Benjes and Grimmett (94MI 302-01). ^a[62]:[63]. ^b10% NaOH(aq.), RT, 2 h. ^c1,4-isomer only. ^dNaOEt in EtOH.

The usefulness of product ratios as in Table 8 depends of the absence of any subsequent rearrangements of the initial *N*-alkylated products. Certainly base-catalyzed rearrangements are known (91SC443), and other rearrangement can occur via quaternary salts, but both of these require elevated temperatures and extended reaction times (Scheme 17) (88TL5361).

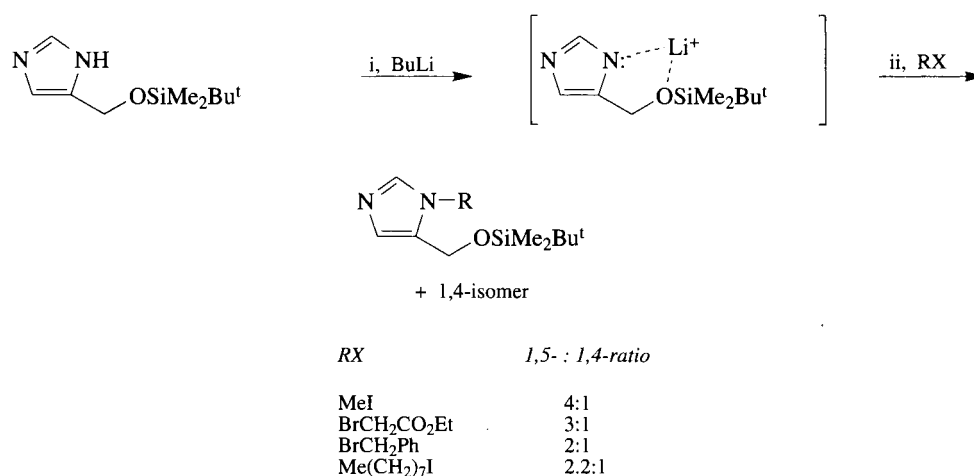


Scheme 17

Under the usual alkylation reaction conditions, though, such rearrangements are negligible or absent (94H(37)735). Although there have been many reports of alkylation isomer ratios, they apply to such a host of reaction conditions that comparison is rendered hazardous (85JMC987, 86MI 302-03, 90ACS1050, 91SC427, 93H(35)433, 93JOC4642, 94H(37)735, B-94MI 302-01). Temperature dependent studies of *N*-alkylation of methyl imidazole-4-carboxylate imply that the regiochemistry is entropy controlled (92ZOB2576).

Some 1,5-disubstituted imidazoles have been found to exhibit potent inhibitory activity against platelet aggregation and as thromboxane synthetase inhibitors. Hence synthesis of imidazole analogues of prostaglandin require 1,5-orientation. Good yields of these desired isomers are obtained when 4-*t*-butyldimethylsilyloxymethylimidazole is treated in succession with butyllithium and an

alkyl halide with added HMPA. This regiochemistry of alkylation implies stabilization of a vicinal anion (Scheme 18) <89CPB1481>.



Scheme 18

While steric and electronic factors are also important in neutral alkylations, it is sometimes necessary also to invoke tautomeric considerations to account for observed isomer ratios. The high proportion of 1,5-isomer isolated on alkylation of 4-nitroimidazole is not what one would expect on steric and electronic grounds. Only when it is realized that the major tautomer is reacting is the observed regiochemistry explained (see Section 3.02.4.3.1). Table 9 lists some isomer ratios <94H(37)735, B-94MI 302-01>. The ratios listed for diazomethane methylations differ from those of conventional S_E2' or S_E2cB processes, reflecting a different mechanism <B-94MI 302-01>. The alkylation of unsymmetrical benzimidazoles has also been summarized and discussed <B-94MI 302-01>.

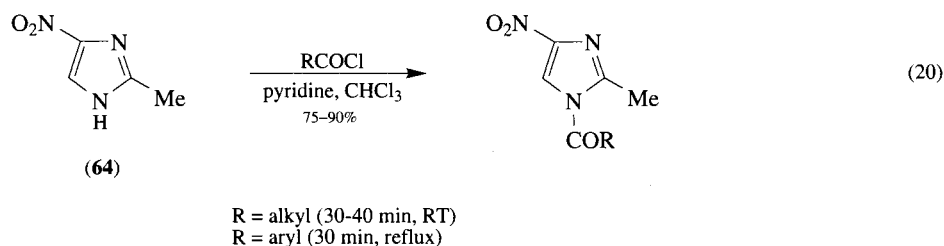
Table 9 Isomer ratios^a from *N*-alkylation of 4-substituted imidazoles.

4-Substituent	Alkylating reagent			
	Me ₂ SO ₄ /EtOH	Et ₂ SO ₄ /EtOH	PhCH ₂ Cl/EtOH	CH ₂ N ₂
Me	1.2 : 1	1.5 : 1	1.9 : 1	1.0 : 1
Br	1 : 11.5	1 : 7.5	1 : 5.7	1 : 2.6
NO ₂	1 : 50	1 : 35	1 : 10.2	1 : 16
Ph	4.0 : 1	12 : 1	b	1 : 2
CHO	1 : 3.6			1 : 4.4

^a[62] : [63]. ^b1,4-isomer only.

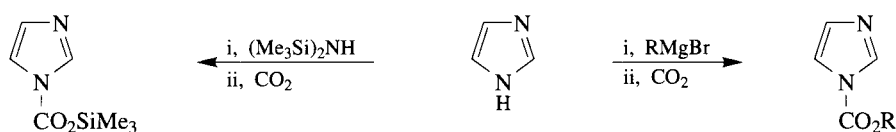
3.02.5.2.7 Acyl halides and related compounds

Unlike *N*-alkylation, *N*-acylation is a reversible process which gives the thermodynamic product with 4-substituted imidazoles. Steric effects play a much more important role in product regiochemistry. For example, 2-methyl-4-nitroimidazole (**64**) reacts with acyl halides in the presence of a tertiary amine base to give the 1-acyl-4-nitro products exclusively (Equation (20)). Such products are much better acyl transfer reagents than *N*-acylimidazoles because of the electron-withdrawing nature of the nitro group <92JCR(S)196>. Similar acetylation of 4-bromoimidazole gives 1-acetyl-4-bromoimidazole <89JCS(P1)1139>. 5-Aminoimidazole-4-carboxamide, though, forms a mixture of 1-acyl products with methyl chloroformate. The less stable isomer, 4-amino-1-methoxycarbonylimidazole-5-carboxamide, rearranges to the other isomer when warmed to 60°C in chloroform <85CHE205>.



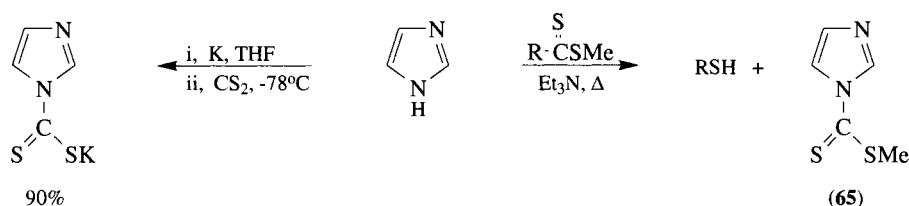
N-Formylimidazolium salts have been prepared by treating Lewis acid-base pairs of the type trimethylsilyl halide-1-methylimidazole with acetic formic anhydride; the products show promise as formyl transfer reagents <87CC317>. Analogous *N*-acyl-1-methylimidazolium salts can be prepared similarly <85UKZ860>. When 1-substituted imidazoles act as catalysts for the acylation of alcohols by acid chlorides or anhydrides, the quaternized species are presumably implicated <83CPB3724>. As mentioned earlier (see Section 3.02.5.2.6) there is a two-stage process for acylation of azoles <90ACS1050>.

Among the acylating agents which have been used with imidazoles and benzimidazoles are the monoethyl ester of oxalyl monochloride <81JOC211>, and its oxime <84JHC1907>, triethyl orthoformate <89JCS(P1)1139>, isocyanates <83JHC1103, 89JHC1401>, acetic anhydride <87S1110>, carbon suboxide <92JHC1033>, ketene dimer <86H(25)419>, and butyrolactone <92CHE1274>. Access to *N*-carboxylates of imidazole and benzimidazole can be via the Grignard reagents with an alkyl chloroformate, or by successive reactions with silylating agent and carbon dioxide (Scheme 19) <82JHC747, 85CHE205, 87H(26)1333>. High yields of 1-acylimidazoles can also be obtained from the nickel carbonyl induced reductive carbonylation reaction of 1,1-dibromo-2-(trimethylsilylmethyl)cyclopropanes with imidazole <83TL1255, 86CC26>. Transacylations in which carboxylic acids, alcohols, or thiols, react with carbonyldiimidazole and related compounds are also a potent source of 1-acylimidazoles under mild conditions <80CI(L)85, 83CL1819, B-86MI 302-02, 90SC2683>.



Scheme 19

N-Dithiocarboxylic acids are accessible by reaction of the imidazole anion with carbon disulfide, or by direct thioacylation. In the second reaction, the heterocyclic thiols, are displaced in preference to methanethiol because of their low pK_a values. Hence the ester (65) rather than the doubly heterocyclic ester is obtained (Scheme 20) <87H(26)1657>.



Scheme 20

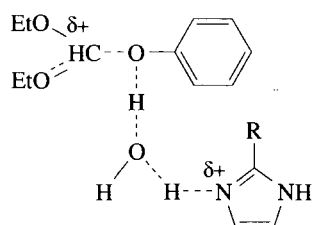
When there is more than one possible site for acylation (as in 4-aminoimidazole) the softer reagents such as acid chlorides and anhydrides react at the exocyclic site, whereas harder reagents such as chlorocarbonic acid esters acylate the annular nitrogen preferentially <84CHE204>.

A new route to 1,3-diacyl-2,3-dihydroimidazole involves diacylation of imidazole followed by borohydride reduction <90S951>.

At this juncture it is convenient to discuss the catalysis of ester hydrolysis by imidazole. The imidazolyl group of histidine is intimately involved in the mode of action of hydrolytic enzymes, and the two pathways believed to operate, general base catalysis and nucleophilic catalysis, were described in CHEC-I. In the latter, a 1-acetylimidazole is formed as an intermediate. General base catalysis has been proposed in the intramolecular thiolysis of *N*-propyl-2-thiomethylbenzamide

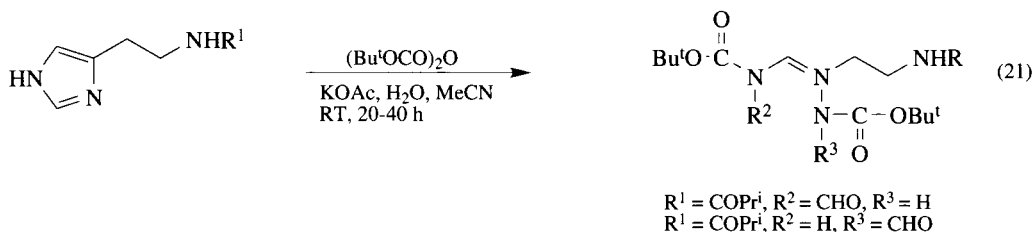
<92CJC62>, while nucleophilic catalysis may operate in the methanolysis of 4-nitrophenyl acetates. In this imidazole-catalyzed methanolysis there is a steric effect from a 2-methyl group, and imidazoles are known to be much more reactive than pyridines (which are general base catalysts) <90JCS(P2)669>. Nucleophilic catalysis activity is increased if the imidazole anion or coordinated imidazole are involved <87CC839>. Imidazole and its 1-methyl derivative are almost identical in activity, 2-methylimidazole is three times slower, and 4-methylimidazole is three times faster with 4-nitrophenyl esters at low amine concentrations. At high imidazole concentrations the ester hydrolysis is inhibited by methylimidazoles relative to imidazole, perhaps because of non-covalent complexation between the methylimidazole and the ester <89JOC5247>. The two imidazole rings of histidine-12 and -119 act as acidic and basic catalysts in the hydrolytic cleavage of RNA by the enzyme ribonuclease A <91ACR317>. A number of other studies of imidazole-catalyzed ester and amide hydrolyses exist <81CJC2358, 82JCS(P2)899, 83JCS(P2)4, 83JOC2036, 88JA5205, 88JCS(P2)2051>.

In the hydrolysis of diethylphenyl orthoformate no general base catalysis is observed. The steric effects of substituents on the imidazole catalyst are very small, and the activation parameters have been shown to have large negative entropies. These observations, in conjunction with a $^2\text{H}_2\text{O}$ solvent isotope effect, point to participation of water molecules in the transition state, i.e., at least one water molecule intervenes between imidazolium ion and the ortho ester (see (66)). General acid catalysis is assumed <87JCS(P2)669>.



(66)

Ring cleavage of *N*-acyl- and *N*-(arylsulfonyl)histamines with di-*t*-butyl carbonate presumably involves quaternizing *N*-acylation prior to ring cleavage <84JCS(P1)59, 89S825> (Equation (21)). The use of 1-acyl-4-substituted imidazoles as intermediates in the synthesis of sterically hindered 1,5-disubstituted imidazoles has been known for some years (see CHEC-I), and in 1993 was 'rediscovered' <93H(35)433>.



3.02.5.2.8 Lewis acids and other electrophiles

N-Phosphorylated imidazoles and benzimidazoles can be made by direct phosphorylation by halides, esters, amides, amidoesters, isocyanates, and thiocyanates of phosphorus-containing acids, or from reaction of phosphonic or phosphinic imidazolides with a sulfonic acid or anhydride <82CB1636>. Stable charge transfer complexes are produced when a 1:1 or 1:2 ratio of imidazole (or benzimidazole) and sulfur trioxide are refluxed in ether, dioxane, THF, or 1,2-dichloroethane. These complexes are stable on storage in the absence of water and have sharp melting points. Indeed, the benzimidazole SO_3 complex must be boiled for five hours in water to decompose it. On fusion, the complexes form the *C*-sulfonic acids (see Section 3.02.5.3.3) <87CHE1084>. Sulfonyl chlorides readily *N*-sulfonate imidazoles <94JMC332>.

Preparation of *N*-hydroxyimidazoles or their *N*-oxides by direct reaction with peracids is not a viable route <93CHE127>. Direct *N*-silylation of imidazoles and benzimidazoles is common <83CPB1213>. Although *N*-halogenated imidazoles are rather unstable, charge transfer complexes of

the 'n'-type form with iodine through the unshared electron pair at N-3. Equilibrium constants for their formation increase regularly with the electron-donating power of substituents, for example, K_{CT} values at 20°C (L mol⁻¹): 4,5-diphenylimidazole, 141; 4-phenylimidazole, 152; imidazole, 200; 1-methylimidazole, 333; 1,2-dimethylimidazole, 1165 <83BSB923>.

Imidazoles and benzimidazoles react with formaldehyde at 20°C in aqueous solution to give hemiaminals; the hydroxymethyl group is readily removed by mild acid hydrolysis <86H(24)2233, 89JOC2949>. The Mannich reaction of phenols with paraformaldehyde and imidazole is a similar process <94SC47>. There is evidence that cyanogen halides react with 1-substituted imidazoles to form *N*-cyanoimidazolium salts <88S470>, and imidazole itself also appears to give 1-cyanoimidazole with cyanogen bromide <89MI 302-04, 94UP 302-01>.

The *N*-nitration of suitably substituted imidazoles was detailed in CHEC-I, and late examples have been reported <84PJC311, 87PJC913, 89AJC1281, 91PJC515, 92AP(325)317, 92PJC943>.

Preparation of *N*-aminoimidazoles can be achieved by reaction with an aqueous solution of sodium hydroxyamine *O*-sulfonate. This gives a mixture of the 1-aminoimidazole and its 1,3-diamino quaternary salt, although the method only works for water soluble imidazoles <90AG(E)556>. Treatment of the sodium salt of 2-nitroimidazole with *O*-diphenylphosphinylhydroxylamine and dry *N*-methylpyrrolidine in DMF, followed by addition of benzaldehyde gives the *N*-benzylideneamino derivative (57%) which is readily converted into the 1-amino compound <82S592>. (See also <90AHC(49)117, 92AHC(53)86>.)

3.02.5.3 Electrophilic Attack at Carbon

3.02.5.3.1 Reactivity and orientation

Reagents and reaction conditions play important roles in determining the facility of reactions with imidazoles and benzimidazoles. Electrophilic substitution may occur with considerable ease if the neutral molecule or anion are involved (e.g., halogenation), but protonation or complexing with Lewis acids, can greatly reduce reactivity. Nitration of imidazole with mixed acids has $k_{rel} = 10^{-9}$ compared with benzene.

In imidazole the preferred site of attack is C-5. If this is blocked C-4 (or more rarely C-2) can be substituted, and multiple substitution is possible. In benzimidazole electrophilic attack favours the fused homocyclic ring. Substituents can modify this behavior in the usual ways. An *N*-methyl group has little activating effect, though it may cause a change in mechanism (e.g., halogenation). Some *C*-substitutions may involve an initial *N*-substitution, and addition-elimination processes are not unknown. As mentioned above, there are few examples in which C-2 attack is favored or even allowed (but see below: diazo coupling, halogenation, deuterium exchange). The Hammett σ^+ constant for the 4(5)-position of imidazole is around -1 ; for C-2 it is of the order -0.8 <86CHE587>. The electrophilic substitutions which do occur at the 2-position invariably involve pre-formation of an anion at that position. The 2-proton, which should be the least active in a conventional S_EAr sense, turns out to be the most labile over a wide pH range, and there is a marked rate acceleration on going from imidazole to imidazolium. Any negative charge generated at C-2 is stabilized by the adjacent pyrrole-type nitrogen <86CHE587>. Conditions which provide an anion at any ring carbon make electrophilic attack very facile, for example reactions via metallic derivatives (see Section 3.02.5.5), and the photolytic and thermolytic reactions of 2-diazo-4*H*-imidazoles which ultimately result in electrophilic attack at a carbene generated at C-2 (see Section 3.02.7.1.6).

3.02.5.3.2 Nitration

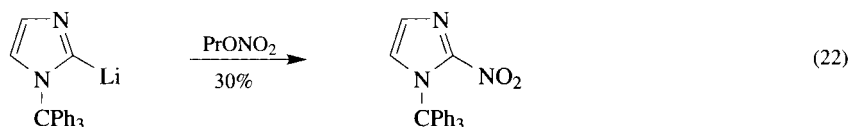
In spite of the increasing interest in nitroimidazoles as pharmaceuticals and in cancer therapy there has been little new material on nitration techniques. Perhaps the ozone-mediated nitration regime reported for alkylbenzenes might merit study as the reaction conditions are essentially neutral <93JCS(P1)1591>. Approaches through metallated species also offer promise (see below).

Imidazole is much less reactive to nitration than heterocycles like furan and thiophene. Nitration of 1-methyl-2-(2'-furyl)imidazole (and the thienyl analogue) in acetic anhydride occurs at the 5'-position; in polyphosphoric acid the imidazole ring is also 5-nitrated <89CHE1168, 91CHE1140>. Imidazole is, however, more reactive than thiazole: imidazole substituted at C-2 by 2-methyl-4-thiazolyl nitrates at both 4- and 5-positions without affecting the thiazole moiety <89JHC1627>.

Although a degree of nitrodehalogenation might have been expected <80AHC(27)241>, some 1-substituted 5-chloroimidazoles were 4-nitrated by mixed nitric-sulfuric acids <84JHC155, 89KFZ249>. The use of ^{13}C NMR techniques for unequivocal assignment of structure in 1-substituted 4- and 5-nitroimidazoles is noted here <83T3797> (see Section 3.02.3.4.1). Coordinated imidazole can be 4-nitrated under very mild conditions <83IC678>. In line with earlier results of 1-arylimidazole reactivity, 1-phenyl-5,7-dinitrobenzimidazole was found to be nitrated in the *para*-position of the phenyl substituent <92AJC525>. Other benzimidazole nitrations are discussed later (see Section 3.02.7.1.2).

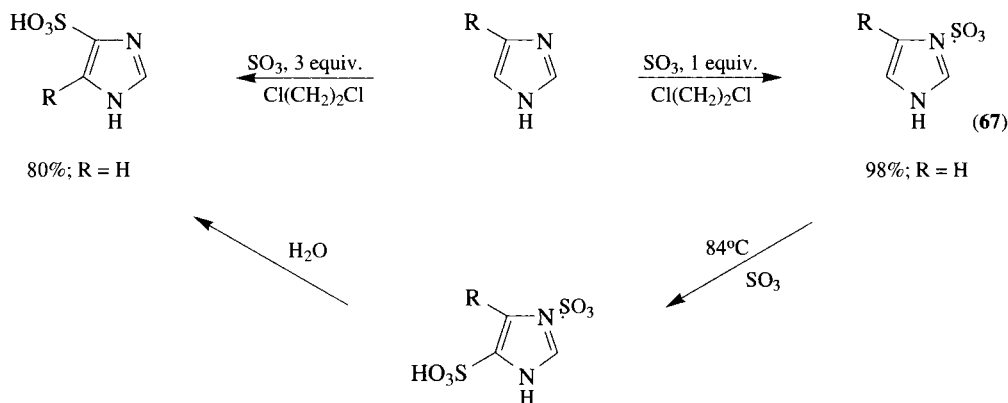
Nitration of 1,2-dimethyl-4-alkenyl- and -4-nitroalkyl-imidazoles occurs at the 5-position <90SC7>. In 1-methylimidazole 3-oxides nitration of the neutral molecule has been reported at C-2 <86CHE587, 93CHE127>, but 1-hydroxyimidazole 3-oxides are usually subject to ring cleavage in nitrating media. An exception is the 2-phenyl-5-nitro derivative which forms the 4,5-dinitro compound when treated with nitric and trifluoroacetic acids. It seems that the nitrating medium and the nature of the 2-substituent profoundly affect the tendencies to nitrate or destroy the imidazole ring <92ZOR2582>.

Although there have been very few references to imidazole nitrations via the anion the approach would seem to hold promise. Conversion of 1-methylimidazole into its 2-nitro derivative by successive lithiation and reaction with N_2O_4 <74URP437763> has led to further successful 2-nitrations of 1-substituted imidazoles using N_2O_4 , propyl nitrate, and tetranitromethane as quenching agents <80USP4199592, 82JHC253, 89JCS(P1)95, 94H(38)2487>. Correct choice of nitrating agent is crucial as it was found that 2-lithio-1-methyl- and 1-methoxymethyl-imidazoles would not nitrate with propyl nitrate <82JHC253>, whereas 2-lithio-1-tritylimidazole gave the 2-nitro product with that reagent with neither N_2O_4 nor nitronium fluoroborate being successful (Equation (22)) <89JCS(P1)95>.



3.02.5.3.3 Sulfonation

At elevated temperatures (160°C, 3 h) 50–60% oleum converts imidazole into its 4-sulfonic acid (83%). As in nitration, the imidazolium species is involved. The same product is isolated under much milder conditions using a threefold excess of sulfur trioxide in refluxing 1,2-dichloroethane. When only a 1:1 or 1:2 ratio of sulfur trioxide to imidazole is used, however, the charge transfer complex (67) is formed (Scheme 21). Similar results have been observed with mixtures of sulfur trioxide and dioxan, THF, diethyl ether, or dichloroethane, or with chlorosulfonic acid <83JOU1935, 87CHE1084> (see also Section 3.02.5.2.8). This method gives high yields of the 4-sulfonic acids of 4-methyl-, 2,4-dimethyl-, 2-bromo-, 2-bromo-4-methyl-, and 2-hydroxy-4-methyl-imidazoles, with the products frequently isolated as barium salts <87CHE1084>. When the charge transfer complexes can be isolated they are useful mild sulfonating agents in aqueous media <83JOU1935>. At 200°C with chlorosulfonic acid and thionyl chloride, 4-bromoimidazole forms 5-bromo-4-chlorosulfonyl-imidazole (41%) <86JCED257, 88JCED537>.



Scheme 21

3.02.5.3.4 Acid-catalyzed hydrogen exchange

Most hydrogen-exchange reactions are base-catalyzed (see Section 3.02.5.5), but S_EAr processes which occur through the conjugate acid of imidazole conform to this classification (see CHEC-I). Related to such hydrogen exchange processes are reactions like protodebromination and protodesulfonation. When 2-amino-4-bromo-1-methylimidazole or its 5-bromo isomer are refluxed in aqueous solution, with or without added cysteamine hydrochloride, they are converted into 2-amino-1-methylimidazole. In ^2HO the 4-bromo isomer gives the 4-deuterated product $\langle 93CJC427 \rangle$.

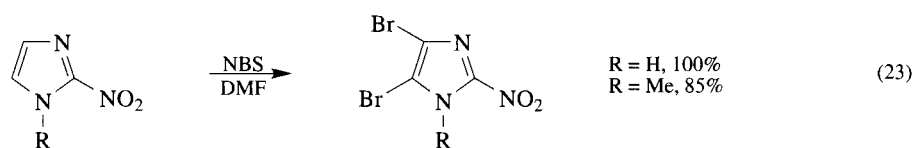
3.02.5.3.5 Halogenation

Halogenation of imidazoles and benzimidazoles has been reviewed $\langle 93AHC(57)291 \rangle$. Although imidazoles preferentially halogenate in the 4- or 5-positions, 2-halogenation is also possible, and it is difficult to prevent trihalogenation. In 1-substituted imidazoles C-5 is slightly more reactive than C-4. Partial rate factors have been determined and discussed in detail $\langle 90AHC(47)165 \rangle$. The synthetic importance of bromoimidazoles has increased since the advances in the use of lithiated imidazoles as intermediates; halogen-lithium exchange is one of the key processes for making these intermediates (see Section 3.02.5.5.1).

It is known that charge transfer complexes form between imidazoles and halogens $\langle 85JCS(P2)531, 88JA2586 \rangle$, and rather unstable *N*-halogeno derivatives can also form and rearrange to *C*-halogeno products. Hence *N*-halogenoimidazoles might be intermediates in some *C*-halogenation processes (see also Section 3.02.5.2.8) $\langle 93AHC(57)291 \rangle$.

Conventionally the reagents of choice for chlorination of imidazoles have been sodium hypochlorite or NCS. The products are usually 4,5-dichloro-, with smaller yields of trichlorinated product, for example, imidazole-2-carboxylic acid gave a 52% yield of the 4,5-dichloro acid. With NCS the initial mechanism may be radical with electrophilic chlorination taking over once the reaction has been initiated. Careful treatment of 1,1'-di-SEM-2,2'-biimidazole with NCS was found to give 4-chloro (36%) and 4,4'-dichloro (26%) products $\langle 87JHC689 \rangle$. Chlorination is possible at vacant ring positions even in the presence of electron-withdrawing substituents $\langle 83JCS(P1)809 \rangle$. 5-Aminoimidazole-4-carboxamide is 2-chlorinated by ICl $\langle 89MI 302-03 \rangle$. Clean monochlorination of all possible ring positions has been accomplished by the use of appropriate lithioimidazoles quenched with chlorine or hexachloroethane $\langle 86JHC1257, 90JHC673 \rangle$.

Tribromoimidazole, and tribromo-1-substituted imidazoles, form very readily with a variety of reagents $\langle 88S767, 93AHC(57)291 \rangle$, and even apparently deactivated compounds can be quite easily brominated at vacant ring positions, for example 4,5-dicyanoimidazole $\langle 91JA6178 \rangle$, 2-nitroimidazole $\langle 89JCS(P1)95 \rangle$, 2-methyl-4-nitroimidazole $\langle 86JHC913 \rangle$, and 1-methyl-2-nitroimidazole (Equation (23)) $\langle 93CJC427 \rangle$.

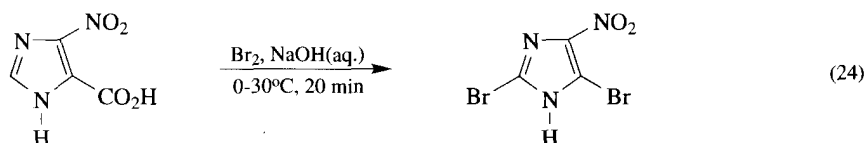


When imidazole is treated with one equivalent of NBS in DMF a mixture of mono-, di-, and tribromo products forms. From these 4-bromoimidazole can be isolated in 41% yield $\langle 89JCS(P1)95 \rangle$. Under similar conditions 1-methylimidazole gives mainly its 5-bromo derivative $\langle 81PJC1659 \rangle$.

Although bromine water converts 1-methyl-2-nitroimidazole into the 4,5-dibromo derivative, slower bromination in dioxan can lead to a mixture of monobromo isomers. Attempts to brominate 2-amino-1-methylimidazole in aqueous solution gave only *cis*- and *trans*-2-amino-4,5-dihydro-4,5-dihydroxyimidazolium species $\langle 93CJC427 \rangle$. Usually monobromoimidazoles can only be prepared by polybromination followed by reduction with sodium sulfite or triphenylphosphine $\langle 91CB1639, 92SC2971 \rangle$, but approaches through lithiated intermediates offer promise $\langle 86SC1161 \rangle$. Suitable quenching agents include bromine, NBS, alkyl bromides, and *N*-bromodiethylamine $\langle 83JCS(P1)271, 85H(23)417, 93AHC(57)291 \rangle$. The reactions are, however, not always successful as it was not possible to prepare the 5-bromo derivative from 5-lithio-1-methyl-2-nitroimidazole $\langle 89JCS(P1)95 \rangle$, and trans-metallations can complicate matters. Successive reductions which treat 2,4,5-tribromoimidazoles in turn with butyllithium and water provide an alternative route to mono- and dibromoimidazoles $\langle 87JCS(P1)1445, 87JCS(P1)1453 \rangle$, and two or more equivalents of butyllithium can form 2,5-dilithio

derivatives of imidazoles, thereby affording further versatility. Bromine atoms in 1-substituted 2,4,5-tribromoimidazoles can be replaced in a stepwise manner by hydrogen in the sequence $2 > 5 > 4$ <85H(23)417, 87JCS(P1)1445, 87JCS(P1)1453>.

The reagent, bromine-DMF- K_2CO_3 , which does not affect other acid- or base-sensitive substituents, has been recommended as a general brominating agent for imidazoles. The bromine-DMF complex is probably the active reagent, while potassium carbonate scavenges HBr. Comparative yields for 5-bromination of 1-benzyl-4-bromo-2-methylimidazole were: bromine/acetic acid/80°C/10 h, 68%; bromine/chloroform/reflux/20 h, 65%; bromine/DMF/ K_2CO_3 /3 h, 91% <92JOC3240>. Bromodecarboxylation (similar to the Borodin-Hunsdiecker reaction) is known (Equation (24)) <82CHE539>. Bromination of 1-methyl-2-(2'-furyl)imidazole (and the thienyl analogue) in acidic medium (in which the imidazole moiety is protonated) gives mainly furan (or thiophene) bromination; in neutral medium though both heterocyclic rings are attacked <89CHE1168, 91CHE1140>.



Interest in cyanogen bromide as a brominating agent for imidazoles has been rekindled. It seems that bromo products can be made in this way, for example, 1-benzylimidazole reacts with cyanogen bromide in the presence of 4-dimethylaminopyridine to give 1-benzyl-2-bromoimidazole, perhaps via an ylide mechanism. Cyanogen chloride and the pre-formed adduct of cyanogen bromide and 4-dimethylaminopyridine, however, gives 2-cyanoimidazoles <86JOC1891, 88S470>.

Studies of the kinetics of bromination of imidazoles coordinated to cobalt(III) imply that in aqueous solution proton abstraction from a Wheland intermediate is rate limiting at low pH, while bromine addition becomes rate determining in more nearly neutral conditions. Rate constants are large enough to imply preassociation of the substrate with bromine before deprotonation. It is not possible to prepare monobromo complexes with bromine in water or DMSO because the 4-bromo species is so rapidly rebrominated. With the 1-methylimidazole-cobalt(III) complex, however, the reaction is sufficiently slow to allow 5-monobromination <91JA2656>. Site selectivity for the neutral and anionic ligand was found to be $4 > 5 \gg 2$, and it appears that at pH values above 5 the conjugate base of the complex is involved (this cannot form with the 1-methylimidazole complex). In neutral or alkaline conditions aqueous bromination of the complexes is accompanied by a degree of oxidation or nucleophilic substitution <86AJC1465, 91AJC981, 91IC1635, 91JA2656, 91JCS(D)3031>.

Imidazole also iodates rapidly via the anion, and though 1-substituted imidazoles react more reluctantly with iodine (the mechanism cannot be the same), most imidazoles can be polyiodinated with a variety of reagents including potassium iodide in aqueous base, iodine-iodic acid, iodine in carbon tetrachloride, and *N*-iodosuccinimide (NIS). The involvement of *N*-iodo species in *C*-iodinations may need to be considered since such species are known to form, especially in basic media <93AHC(57)291>. Care must be taken when reading the literature prior to 1981 because of the ramifications of an incorrect assignment of 4,5-diiodoimidazole as the 2,4-isomer <81JOC1781, 87AJC1399>.

Methods are available for the preparation of 2,4,5-triiodoimidazole <83JCS(P1)735>, 4,5-diiodoimidazole <91JOC4296, 91JOC5739>, and then, using reductive methods, 4-iodoimidazole <83JCS(P1)735, 91JOC5739>. Access via lithiated imidazoles is also an attractive route to 2- <90JHC673>, 5- <83JCS(P1)271, 90S761>, and 2,4-diiodoimidazoles <85H(23)417>.

Optimum iodinating conditions for monoiodination of histidine use a 1 : 1 ratio of iodine to azole; diiodination requires a 2 : 1 ratio <83CPB386>. In 1994 ICl in hexane has been used to 5-mono- and 2,5-di-iodinate histidine <94BSF30>. Although 4-nitroimidazoles are resistant to iodination with ICl in acetic acid, iodine peroxide, ceric ammonium nitrate with KI, and iodine in sodium hydroxide, a mixture of KI, acetic and nitric acids gives high yields (85–93%) of 5-iodo derivatives <94SC353>.

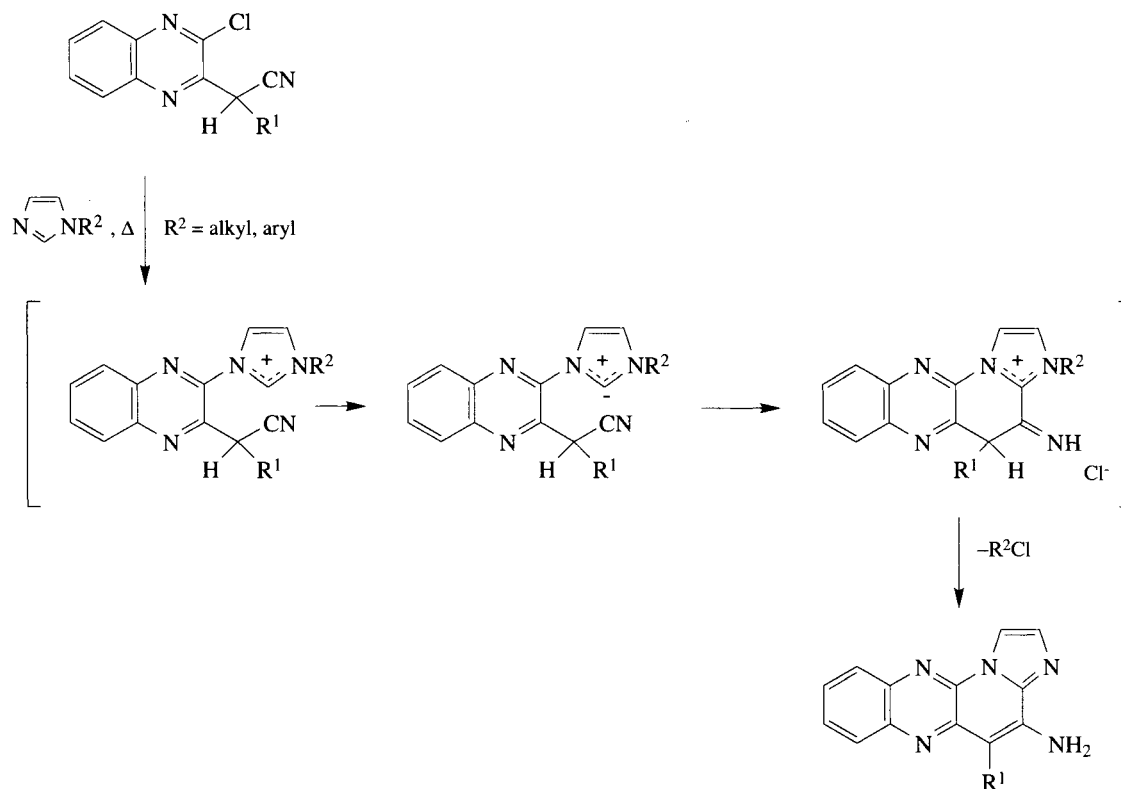
Fluorination procedures are seldom electrophilic, but metallic derivatives are sources of C-anions susceptible to such fluorination. Thus perchloryl fluoride converts 2-lithio-1-methylimidazole into 2-fluoro-1-methylimidazole <81PJC1659>. Organotin groups, too, are easily replaced on treatment with fluorine or caesium fluoroxysulfate <86BSF930>.

In benzimidazoles, the least susceptible position to electrophilic halogenation is C-2. An exception is the use of NBS supported on silica gel which 2-brominates benzimidazole, perhaps because the support holds the 2-position close to its surface in proximity to the activated NBS <86TL1051>. Anionic benzimidazoles can be iodinated in the 2-position <90JHC673>.

3.02.5.3.6 Acylation and alkylation

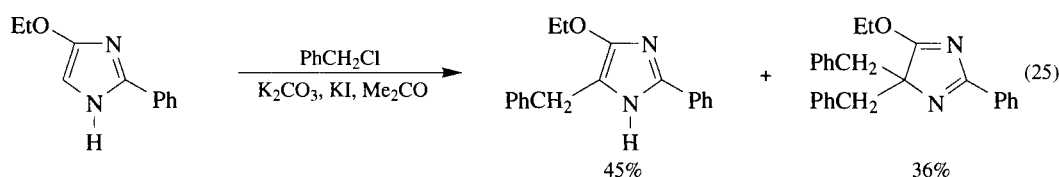
Direct Friedel–Crafts acylation or alkylation will not occur with imidazoles because Lewis acid catalysts deactivate the azole. Acylation via deprotonation is known (see Section 3.02.5.5.3), and it is also possible to prepare C-alkyl- and C-acyl-imidazoles via the lithium derivatives $\langle 94\text{H}(38)2487 \rangle$. In particular, the use of DMF as quenching agent has provided access to 2- $\langle 86\text{JOC}1891, 90\text{JCR}(S)58, 91\text{JMC}1363, 92\text{BCJ}373 \rangle$, 4- $\langle 82\text{OPP}409, 85\text{JHC}57, 92\text{TL}5865 \rangle$, and 5-carbaldehydes $\langle 88\text{JOC}1107, 89\text{JOC}1439, 89\text{S}530, 92\text{CHE}53 \rangle$. There are numerous examples of the application of similar methods to the preparation of imidazoles with ketone, carboxylate, and alkyl substituents $\langle 85\text{H}(23)417, 86\text{CPB}4916, 94\text{H}(38)2487 \rangle$. Sometimes aromatic aldehydes react with lithiated imidazoles to give ketones directly rather than the expected carbinols which oxidize *in situ* $\langle 91\text{CHE}556 \rangle$.

Direct C-alkylation of 2-substituted imidazoles with ‘soft’ alkylating electrophiles has been discussed earlier (see Section 3.02.5.2.6). Attempts to utilize the ylide mechanism of electrophilic substitution in which the acidic and basic properties of imidazole play equal roles are exemplified by the reactions of 2-quinoxalylacetonitriles with 1-alkyl- and 1-aryl-imidazoles to form condensed products (Scheme 22). Dequaternization only occurs when R^2 is alkyl $\langle 93\text{CHE}194 \rangle$.



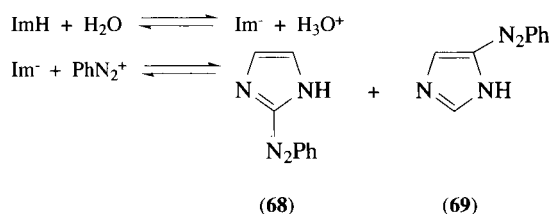
Scheme 22

In 4-ethoxyimidazoles the 5-position becomes more reactive towards electrophiles than the annular nitrogen, allowing 5-benzylation with benzyl chloride in the presence of potassium carbonate (Equation (25)). The Vilsmeier reaction gives the 5-carbaldehyde in 86% yield, and a number of unsaturated reagents also substitute at that site $\langle 88\text{CPB}1669 \rangle$.



3.02.5.3.7 Diazo coupling

Until 1989 some aspects of the diazo coupling reactions of imidazoles were quite unclear. It was known that *N*-substituted imidazoles will not react, and that *NH*-imidazoles react as the anion in the rate-determining step. Electron-withdrawing substituents hinder the coupling which occurs at C-2, C-4 or C-5 (see CHEC-I). A preparative scale reaction gave mainly 2-azo product with only a little of the 4-isomer <89JCS(P2)2055>. The key reaction has been defined as being between the imidazole anion and diazonium ion, using kinetic and pressure studies backed up by MNDO calculations. The reaction rate increases as the pH increases, and the rate variation with pressure has allowed calculation of the volume of activation ($\Delta V_{\text{obs}}^{\ddagger} = -29 \text{ L mol}^{-1}$) as a large negative value which indicates additional solvation in the transition state, i.e., prior dissociation of the anion, with water acting as the base, and subsequent coupling (Scheme 23).



Scheme 23

Calculation of the heats of formation (ΔH_f^θ) for substitution in the anion gave $+450 \text{ kJ mol}^{-1}$ for (68) and $+451 \text{ kJ mol}^{-1}$ for (69). Such low values demonstrate how energetically favored this pathway is (cf. for 4-substitution at the neutral molecule $\Delta H_f^\theta = 1142 \text{ kJ mol}^{-1}$; for 2-substitution the value is 1156 kJ mol^{-1}). Furthermore, the closeness of the values is in accord with experimental observations. Except in fairly acidic conditions the anionic species is probably involved in the major pathway. Reaction between the anion and diazonium ion should be encounter controlled, but the rate value obtained ($2.7 \times 10^7 \text{ L mol}^{-1} \text{ s}^{-1}$) is not quite high enough. This, however, can be explained in terms of some *N*-coupling which reduces the effective concentration of the diazonium ion. 1-Methylimidazoles react with *p*-nitrophenyldiazonium ion, but much more slowly than 2-methylimidazole. Presumably coupling with these compounds involves the neutral molecule, perhaps via *N*-coupling. The observation that some *C*-phenyl products are formed could point to radical involvement <89JCS(P2)2055>.

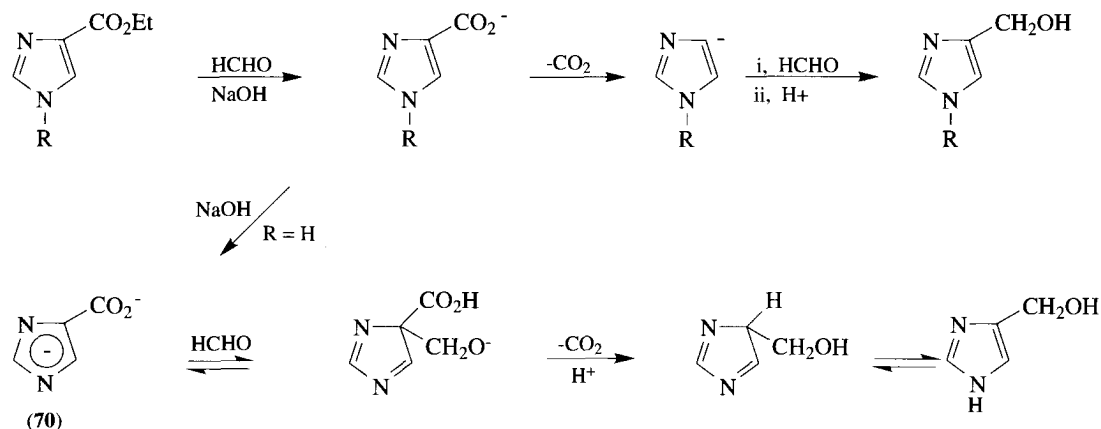
3.02.5.3.8 Nitrosation

With amyl nitrite in ethanolic sodium ethoxide, 4-phenyl- (but not 4-methyl- or 2-phenyl-)imidazoles give 4(5)-nitroso products as green solids. The reaction is again believed to involve the imidazole anion <87JOC1357>.

3.02.5.3.9 Reactions with aldehydes and ketones

Hydroxymethylation of imidazoles with formalin is well known. Attack can be at the 4(5)-positions, but it is frequently at the 2-position in simple 1-substituted imidazoles <82S1103, 92EJM551>. 1,4-Dimethylimidazole, however, gives the 5-hydroxymethyl derivative, and though it is usually difficult to induce substrates with electron-withdrawing groups to react, 1-methyl-5-nitroimidazole forms the 2-hydroxymethyl product (see CHEC-I). Whilst the reaction mechanism is uncertain, it could involve *N*-hydroxymethylation followed by rearrangement. Examples include 2-hydroxymethylation of 1,4-dimethyl-5-nitroimidazole in DMSO <87JMC150>, and 5-substitution of 4-bromo-1-methylimidazole <92H(33)21>. 2-Aminoimidazole is readily 4-hydroxyalkylated by aldehydes <93TL6981>, and there are other examples <86JFC(32)329, 88CL981>. When formaldehyde is used in the presence of HCl chloromethyl products are formed with imidazoles <82S1103> and benzimidazoles <88JMC260>. Combined hydroxymethylation and decarboxylation occur when imidazole carboxylic acids or esters are treated at $90\text{--}100^\circ\text{C}$ with formalin in aqueous sodium hydroxide. Presumably the carboxylate ester is hydrolyzed first, and the anionic species is then attacked by formaldehyde before

or after decarboxylation. The observation the *N*-methylimidazoles require higher temperatures can be explained by their inability to form the anion (70) (Scheme 24).



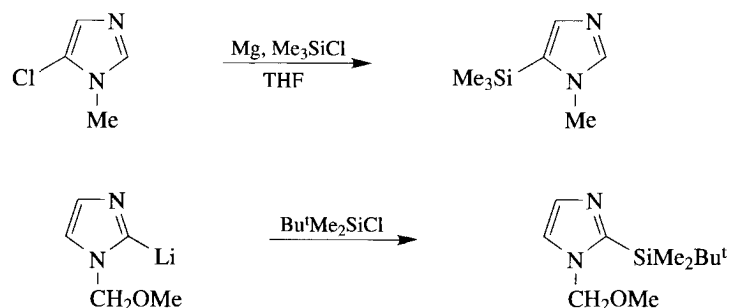
Scheme 24

The related Mannich reaction seldom occurs because *N*-substitution takes place under the usual acidic conditions (see CHEC-I) <89JHC409>. In basic media, though, this is a reversible process and *C*-substituted products accumulate. Since 1-substituted imidazoles will not react one can assume that the imidazole anion is again the reactive species. Aminomethylation of imidazole-4-carboxylic acid or imidazole-4,5-dicarboxylic acid gives either 5-dimethylaminomethylimidazole-4-carboxylic acid or 2,4,5-tris-dimethylaminomethylimidazole, depending on the ratio of reagents. A tenfold excess of dimethylamine and formaldehyde at 80–100°C leads to the trisubstituted product. 4-Nitroimidazole and its 5-carboxylic acid will not react, presumably because they exist in aci-nitro forms <89CHE165>. 2-Nitroimidazole (azomycin), however, has been reported to react with secondary amines under Mannich conditions to give such products as 4-pyrrolidinomethyl-2-nitroimidazole <83IJC(B)157>. In contrast to the behavior of alkylimidazoles, imidazole carboxylic acids undergo Mannich reactions more readily at *C*-4(5) than at *C*-2. Possible pathways are *ipso*-replacement of carboxyl or initial thermal decarboxylation. The fact that no carbon dioxide is lost on prolonged heating with dimethylamine in the absence of formaldehyde points to *ipso*-substitution <89CHE165>.

The most common reactions with aldehydes and ketones reported have been those of lithio-imidazoles. The products are usually alcohols, but sometimes ketones are formed on aerial oxidation of the primary products. Access to 2-, 4-, and 5-carbinols is now readily available <94H(38)2487>.

3.02.5.3.10 Silylation

Introduction of a *C*-silyl group is best accomplished by silylation of the azole anion, whether by reaction with a Grignard reagent or lithiated derivative (Scheme 25) <90JCS(P1)1645, 91CB1639, 94JMC332>.

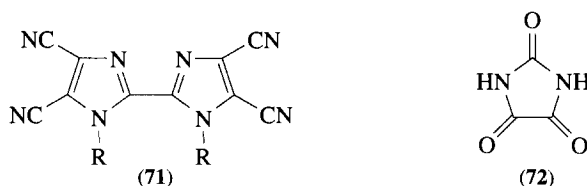


Scheme 25

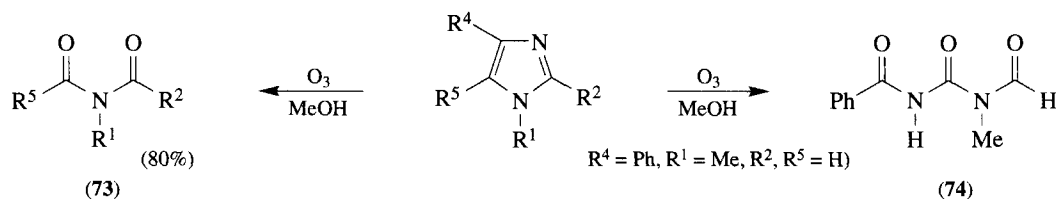
3.02.5.3.11 Oxidation

Although the imidazole ring is not always very susceptible to oxidation, substituents can modify this general behavior. Certainly *N*-oxidation is quite uncommon (if not absent), but oxygen transfer to imidazole nitrogen has been implicated in the epoxidation of some alkenes by *t*-butylhydroperoxide catalyzed by an imidazole-ligated manganese(II) complex. Peracids usually seem to disrupt the ring <87JA1456>, but with manganese porphyrin catalysts the imidazole seems only to function as a ligand and base catalyst <87RTC332>.

Oxidative dimerization of the lithium derivatives of 1-substituted 4,5-dicyanoimidazoles give (71) <91JA6178>. Chromium trioxide in acetic acid converts 5-chloro-1-methyl-4-nitroimidazole into the 1-methyl derivative of parabanic acid <89IJC(B)391>, while 2-imidazolone forms parabanic acid (72) itself when treated with nitric acid <82JOC474>, and lead tetraacetate oxidizes 2-amino-1-methyl-4(5H)-imidazolone into the 4,5-dione <87BCJ4115>.



Ozone in methanol ring opens 1-substituted imidazoles. Thus, 1-methylimidazole forms *N*-methyl-*N*-formylformamidine (73; R¹ = Me; R², R⁵ = H); 2-substituted and 2,5-disubstituted analogues give similar products; 1-methyl-4-phenylimidazole forms (74). Hence, 4-substituted imidazoles are converted into *N,N*-diacylureas. The others give *N*-substituted *N*-acylamides. Ozonolysis of the 4,5-bond appears to be occurring (Scheme 26) <92H(33)385>.



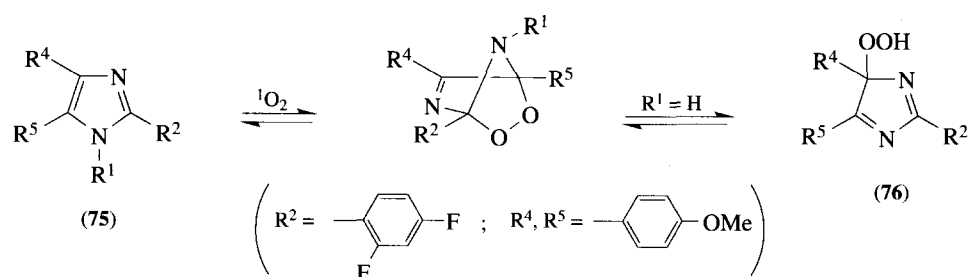
Scheme 26

Treatment of benzimidazoles with 30% hydrogen peroxide in acetic acid gives 22–57% yields of 2-benzimidazolones <83KPS121>, and lead tetracetate slowly converts benzimidazole into a mixture of 2-benzimidazolone, its *N*-acetyl derivative, and 1,2-diacetylaminobenzene. With excess oxidant there is also some oxidation at C-5 <86AJC295>. Neither selenium dioxide nor mild permanganate treatment affect benzimidazole <82CHE833>. 1-Aminobenzimidazoles are oxidized by lead tetraacetate or active manganese dioxide to give good yields of 3-aminobenzo-1,2,4-triazine via an intermediate nitrene <89CHE1241>.

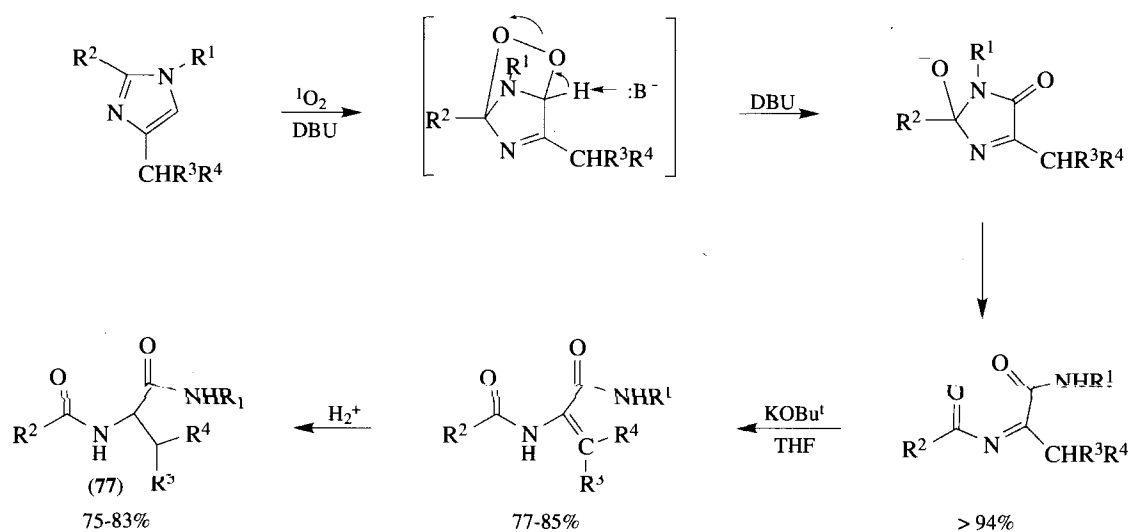
A review of photolytic oxidation states that singlet oxygen cleaves the imidazole ring, probably through intermediate endoperoxides or hydroperoxides. Endoperoxides are probably formed in aprotic media. In solvents like methanol solvent inclusion products are common <86CRV795>. Fenflumizole (75) reacts quantitatively with singlet oxygen to form 2-(2,4-difluorophenyl)-4-hydroperoxy-4,5-bis(4-methoxyphenyl)-4*H*-imidazole (76) in a reversible reaction. In ethanol at ambient temperature the peroxide regenerates fenflumizole and singlet oxygen together with minor quantities of other products. Although C-2 is the thermodynamically favored position for the hydroperoxide group in alkylimidazoles, C-4(5) is preferred in perarylated species (Scheme 27) <91ACS627>.

A novel photooxidative cleavage of trisubstituted imidazoles using singlet oxygen has been used to prepare chiral dipeptides (77). The singlet oxygen induces a 1,4-dicarbonyl insertion by a Diels–Alder reaction which initially forms an endoperoxide. The final hydrogenation step utilizes a rhodium salt or chiral phosphine complex to induce chirality (Scheme 28) <84JA457>.

Photochemical oxidation of 4,5-dibromo(chloro)-1,3-dimethyl-2-imidazolone converts it into 1,3-dimethyl-2,4,5-imidazolidinetrione. The bromo derivatives are quite unstable to light and moisture <81AG(E)612>. Singlet oxygen ring opens 1,3-disubstituted-4,5-diphenyl-2-imidazolones to form diacylureas. It has been suggested that this photooxidation may involve dioxetanes (78) rather than

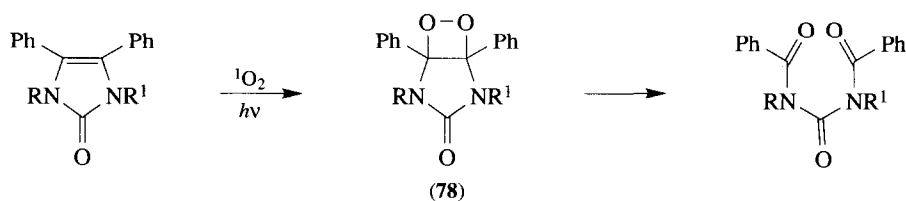


Scheme 27



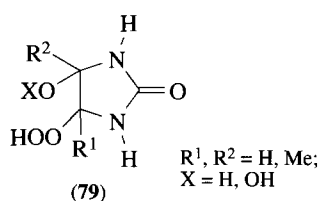
Scheme 28

hydro- or endo-peroxide intermediates, but zwitterionic intermediates cannot be ruled out (Scheme 29) <90T1331>.

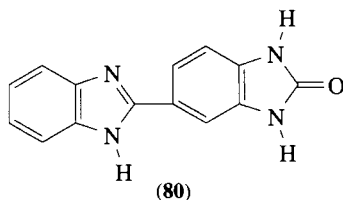


Scheme 29

Stable hydroperoxyimidazolidin-2-ones (79) are formed by a radical pathway when 2-imidazolones are treated with 2.25 equivalents of hydrogen peroxide at 25°C <85JHC1675>.

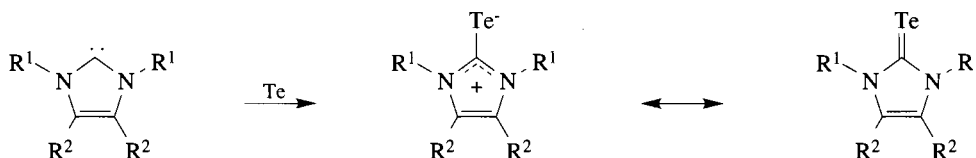


Photooxidation of benzimidazole with singlet oxygen in methanol gives 2,4'-bibenzimidazole (10%), 2,5'-bibenzimidazole (22%), 2-benzimidazolone (10%), and the benzimidazo-benzimidazolone (**80**) (10%) <85CZ231>.



3.02.5.3.12 Reactions of carbenoid imidazoles with electron-deficient species

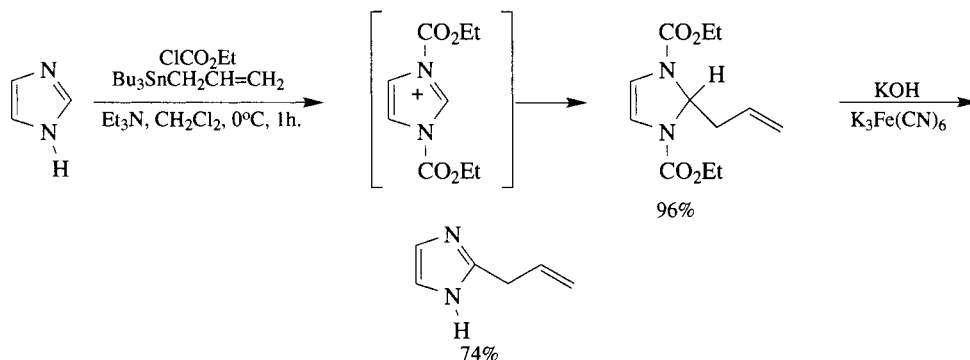
Good yields of 2-telluroimidazoles can be obtained when imidazol-2-ylidenes react with tellurium (Scheme 30) <93CB2047>. Similar mesoionic adducts are formed with boron trifluoride or hydride <93CB2041>, or aluminum hydride <92JA9724>.



Scheme 30

3.02.5.4 Nucleophilic Attack at Carbon

Unactivated imidazoles and benzimidazoles are seldom sufficiently electron deficient for nucleophilic substitution, but electron-withdrawing substituents or quaternization can facilitate reaction. For example, 1,3-bis(alkoxycarbonyl)imidazolium salts, formed *in situ*, react with organotin reagents to form 2-alkenyl products (Scheme 31) <92TL5399>.



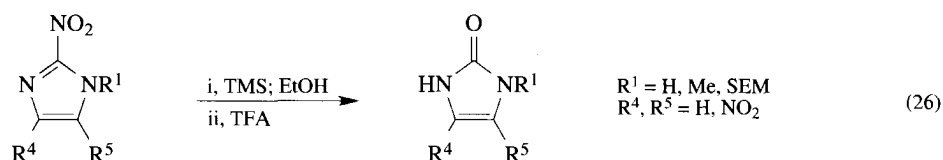
Scheme 31

In activated imidazoles and benzimidazoles nucleophilic substitution probably involves the usual addition-elimination mechanism. The 2-position or the 5-position of imidazole are usually preferred to 4-substitution, although there are exceptions. There are few examples of hydrogen replacement, and in benzimidazole *N*-oxides and *N*-alkoxybenzimidazoles nucleophilic substitution at C-2 is accompanied by loss of the oxygen function <93CHE127>.

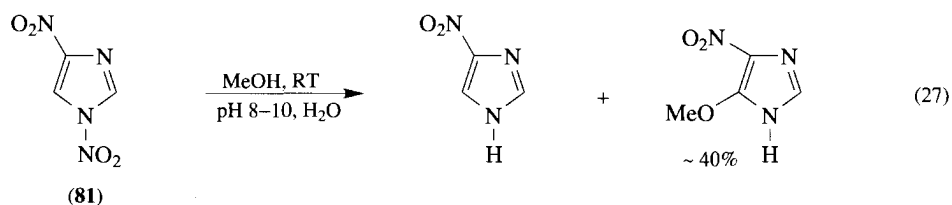
3.02.5.4.1 Hydroxide and other O-nucleophiles

(i) Neutral imidazoles

Only rarely does reaction of an imidazole with hydroxide ion lead to hydroxylation (see CHEC-I). Displacement of an activated halogen is much more common. Adjacent nitro groups assist 4(5)-bromo- and -iodoimidazoles to react with methoxide or phenoxide ions, and the 1-methyl analogues react similarly, with the 5-halogeno species proving the more reactive because of better delocalization of the developing negative charge in the transition state. Surprisingly, though, in the 1,2-dimethyl analogues only the 5-nitro-4-halogeno isomers give alkoxy products. Steric problems may be responsible for this apparent anomaly $\langle 87AJC1399 \rangle$. When 4,5-dinitroimidazole is treated with methoxide or ethoxide there is considerable evidence of ring cleavage and around 10% of reductive denitration both at elevated temperatures and with excess reagent. The major imidazole products are 5-alkoxy-4-nitro- and 4-nitro-imidazoles ($\approx 9:1$). An anion-radical mechanism has been proposed to account for this. With aqueous sodium hydroxide the 4,5-dinitroimidazole ring is destroyed even at room temperature. In common with other hard reagents such as azide or acetate, phenoxide ion will not react with the sodium salt of 4-nitroimidazole-5-sulfonic acid even when heated $\langle 83CHE650 \rangle$. Alkoxide displacements on 2,4- and 2,5-dinitroimidazoles occur preferentially in the 2-position giving nitroimidazolones as the ultimate products (Equation (26)) $\langle 92H(34)1385 \rangle$.



Sodium isopropoxide replaces the 2-bromo atom of 1-substituted 2,4,5-tribromoimidazole by an isopropoxy group $\langle 87JCS(P1)1437 \rangle$. In 1,4-dinitroimidazole (**81**) reaction with methanol leads to “*cine*”-substitution, the reaction being first order with respect to both reactants and also to hydroxide ions. The yield is not affected by increasing the concentration of methanol from 10 to 40%, and only slightly by raising the pH from 8 to 10. Above that level the product is not formed (Equation (27)) $\langle 84PJCS11 \rangle$.



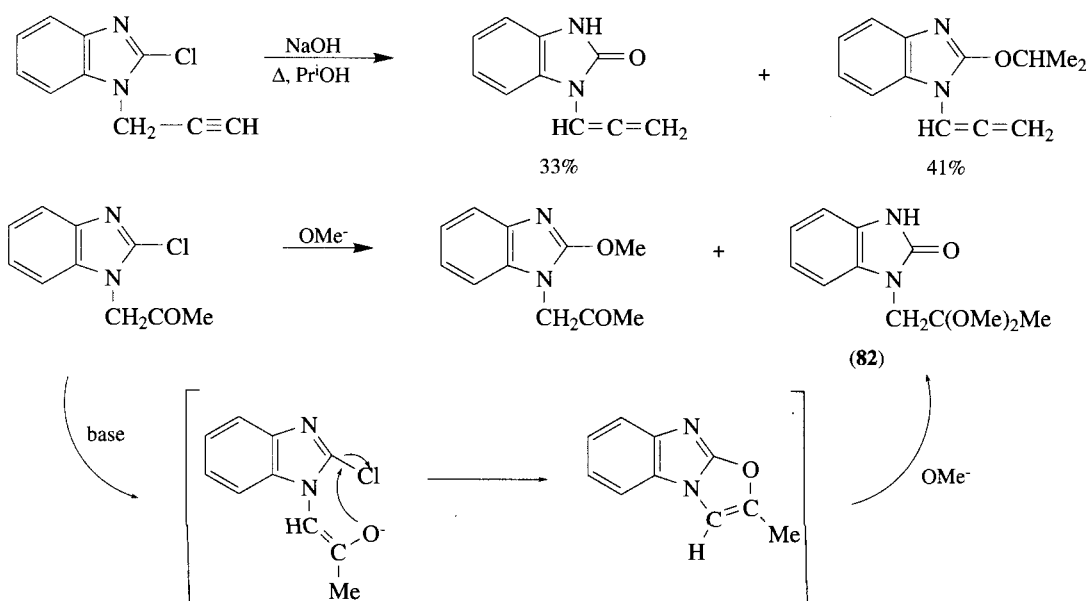
When 1-substituted 2-chlorobenzimidazoles are heated with sodium hydroxide in isopropanol mixtures of 2-oxygenated products are formed. The acetal (**82**) seems to form as a consequence of intramolecular displacement of chloride (Scheme 32) $\langle 88BSF139 \rangle$.

Condensation of tetraaminopyrimidine with 1-arylsulfonyl-4-methylimidazolin-2-ones gives pteridines by way of hydrolytic cleavage of the imidazole species to *N*-arylsulfonylaminoacetone $\langle 82BAU1700 \rangle$.

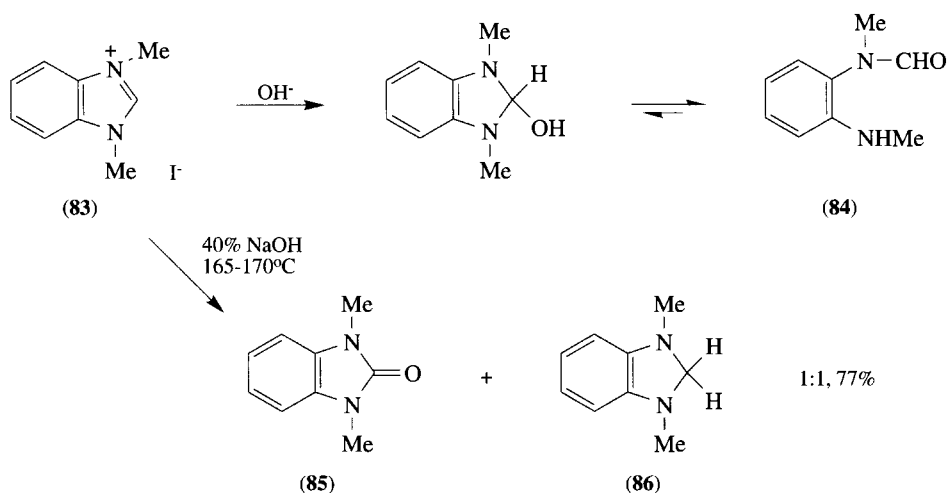
(ii) Azolium ions

The ring cleavage reactions and formation of pseudo bases have been described in detail in CHEC-I. Under more severe conditions the quaternary salt (**83**) can be converted directly into the benzimidazolone (**85**) and the reduced benzimidazole (**86**). Structures (**85**) and (**86**) are also disproportionation products of heating (**84**) in an inert atmosphere or in the absence of solvent (Scheme 33) $\langle 85CHE1398 \rangle$.

There are a number of examples also of the formation of 2-imidazolones and 2-benzimidazolones from reaction of 2-halogeno salts with dilute sodium hydroxide $\langle 81AG(E)612, 82CHE830 \rangle$. With

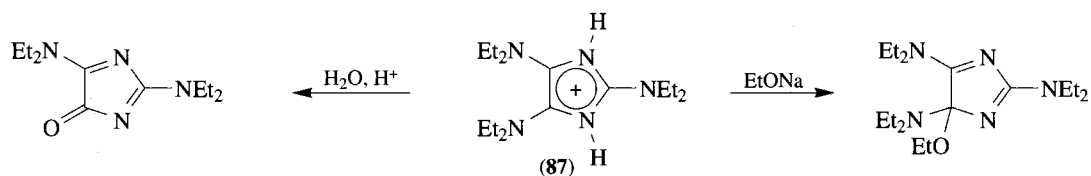


Scheme 32



Scheme 33

sodium ethoxide the imidazolium salts (87) form 4-ethoxy-4H-imidazoles (Scheme 34) <83BSB781>. Benzimidazolium salts (1-methoxy-3-methyl) lose the oxygen function while forming the 2-ethoxy product <93CHE127>.



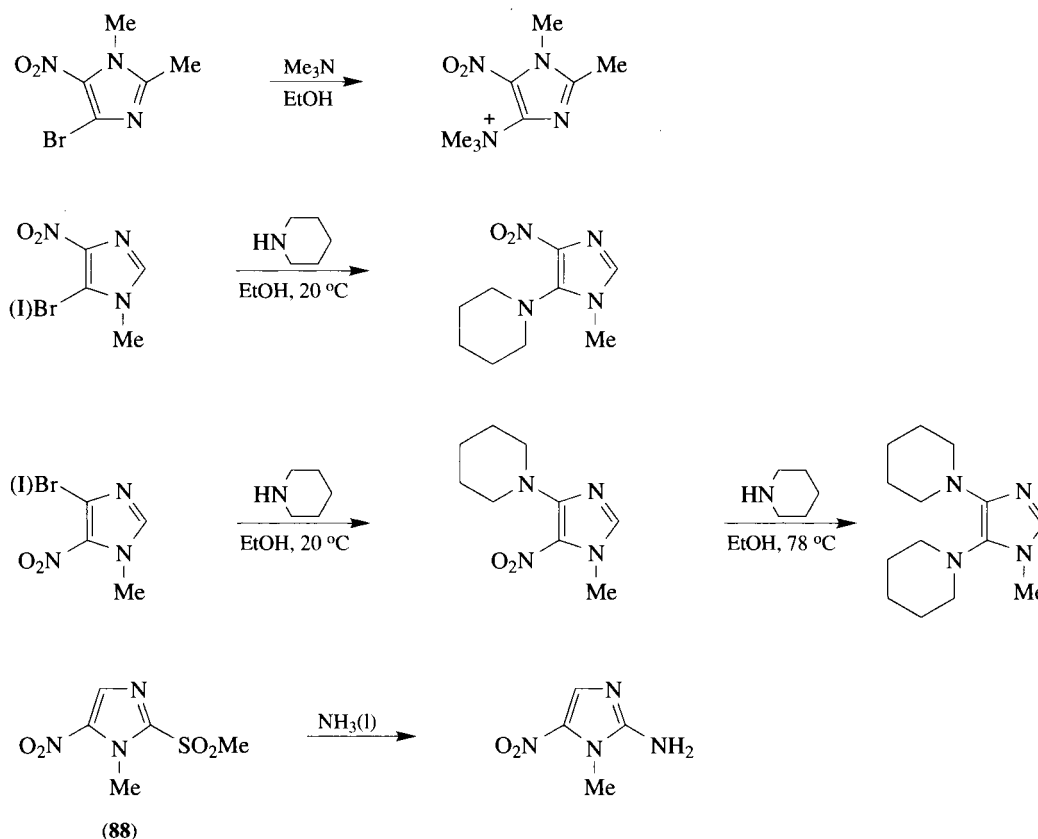
Scheme 34

3.02.5.4.2 Nitrogen nucleophiles

As discussed in CHEC-I amination of the unactivated species will not generally occur, and replacement of halogen by amino is almost unknown in uncondensed imidazoles. Nevertheless, in

sodium methoxide-DMSO 4-amino-1,2,4-triazole converts 2-methyl-4-nitroimidazole into its 5-amino derivative. With hydroxylamine in the presence of potassium hydroxide or sodium methoxide no amination products are formed. Instead, 4-acylamino-2-aryl-1-oxy-2*H*-1,2,3-triazoles result, probably by an intramolecular process. Amination, which may go via initial deprotonation of the triazole amino group, occurs readily only with 1-arylimidazoles more reactive than the *meta*-chlorophenyl derivative <92TL7941, 93T5339>. With sodamide 1-benzylimidazole is converted into its 2-amino derivative <83S861>. A wide variety of groups, including amino, have been introduced into the 5-position of mesomeric 4-triphenylphosphoniumimidazoles <85T2239, 89CHE593>, and 1-methoxy-3-methylbenzimidazolium chloride reacts at -78°C with liquid ammonia to give 2-amino-1-methylbenzimidazole in 65% yield <82CHE830>.

Reactions with amines and their anions have been used frequently to displace a halogen <82CHE649, 85CHE1303, 87AJC1399, 87JMC150, 89H(29)1325, 89JCS(P1)95, 94SC341>, nitro <83CHE650, 86MI 302-05, 87AJC1399>, or sulfonic group <82IJC(B)928, 82IJC(B)989> from an imidazole which bears at least one electron-withdrawing group. Again C-2 and C-5 displacements are more facile than those at C-4. Both 5-bromo(iodo)-1-methyl-4-nitro imidazole and the 4-bromo(iodo)-1-methyl-5-nitro isomers are subject to halogen displacement by ethanolic piperidine at 20°C . With excess ethanolic piperidine at 78°C the nitro group of the 5-nitro isomer is also replaced (Scheme 35) <87AJC1399>.

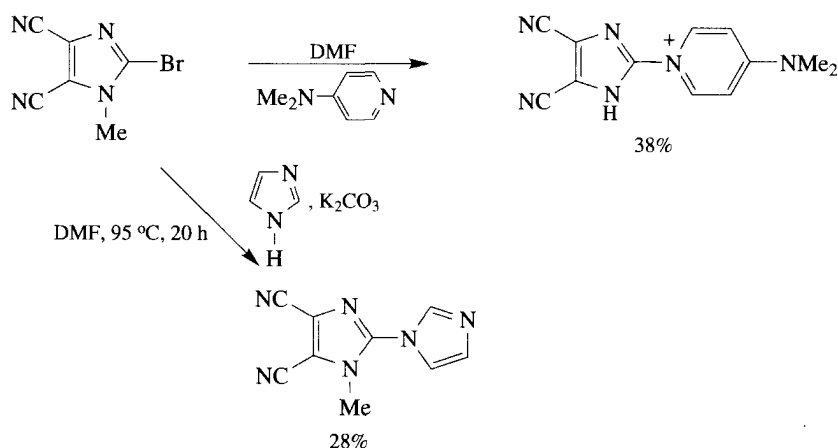


Scheme 35

When 2-bromo-4,5-dicyano-1-methylimidazole is treated at reflux with 4-dimethylaminopyridine the initial nucleophilic substitution product loses its *N*-methyl group because 4,5-dicyanoimidazole anions are such good leaving groups (Scheme 36) <89H(29)1325>.

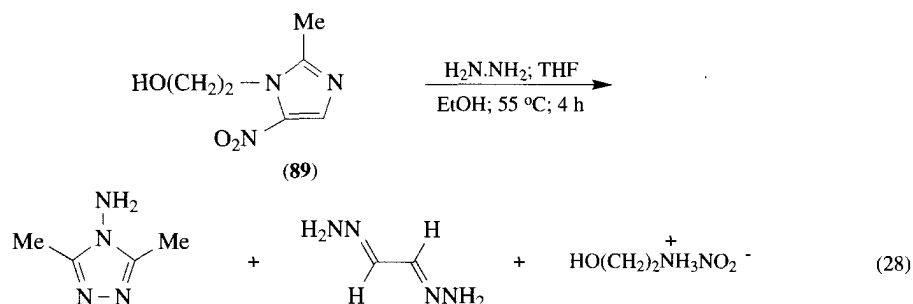
Other examples include reactions of 2-halogenobenzimidazoles with primary and secondary amines <87JHC31>, alkaline dimethylformamide <88BSF139>, and also with hydrazine <83S861>. Benziimidazole-2-sulfonic acids react similarly <88CHE880>. Azide ion or amine replaces the sulfone group of (88) <82IJC(B)989>.

When metronidazole (89) and other 4(5)-nitroimidazoles are treated with hydrazine the products include 4-amino-4*H*-1,2,4-triazole and ring-opened species. The 4-nitro isomers are less reactive than the 5-nitro compounds (which are also known to be more biologically active). A proposed rationale for the reactions (Equation (28)) involves initial nucleophilic addition of hydrazine at C-



Scheme 36

4. The triazole forms by combination of ring-fission products with hydrazine. Similar reactions of hydrazine with 2-nitroimidazoles in the presence of palladium-carbon result in reduction of the nitro group <84JOC932>, while 1-methylbenzimidazole-3-oxide gives 2-hydrazino-1-methylbenzimidazole <93CHE127>.

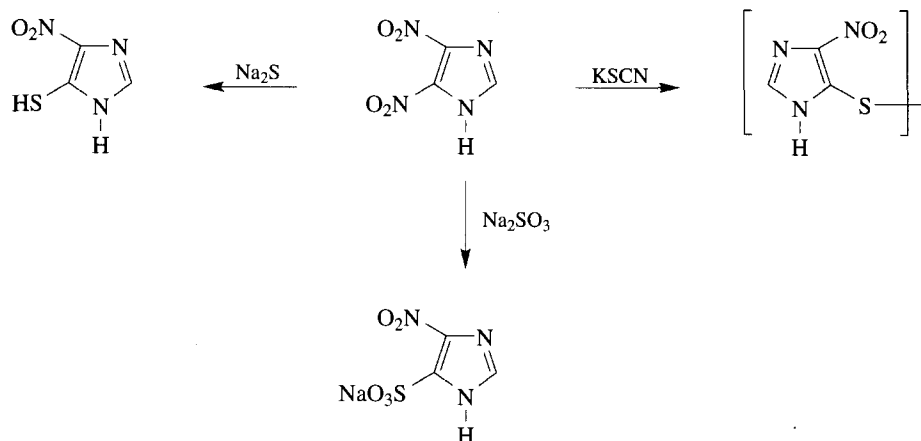


3.02.5.4.3 Sulfur and related nucleophiles

Imidazoles with a nitro group in the ring are readily subject to halide displacement by thiolate anions with 5-halogeno-4-nitro compounds being three to ten times more reactive than the 4-halogeno-5-nitroimidazoles. Bromide is substituted slightly more readily than iodide, perhaps because of the greater capacity of bromine to help stabilize a Meisenheimer complex, or there could be steric reasons <82CHE616, 84JHC155, 86JHC1087, 87AJC1415, 87JCS(P1)1437, 91JHC577>. Both 2,4,5-tribromo- and 2,4,5-triiodoimidazoles undergo reductive dehalogenation by phenylthiolate to the 4,5-dihalogenated products. 1-Protected derivatives though tend to undergo substitution of the 2-halide group by the sulfur nucleophile <87JCS(P1)1437>. With the sodium salt of 2,4,6-trimethylbenzenesulfonic acid 5-chloro-1-methyl-4-nitroimidazole forms the 5-sulfone <91JHC577>. When 4,5-dinitroimidazole is treated with sulfide, sulfite, or thiocyanate one of the nitro groups is replaced by the sulfur function (Scheme 37) <83CHE650>.

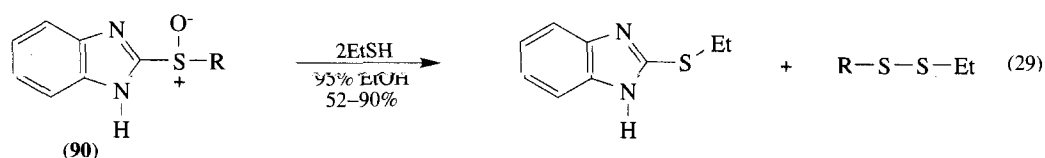
Reaction of 4-bromo-1-methyl-2-nitroimidazole with cysteamine preferentially replaces the nitro group; with the 5-bromo isomer a mixture of 2-cysteamino and 2,5-dicysteamino products is observed. Certainly the 4-bromo group is not strongly activated for nucleophilic displacement, but the preference for nitro substitution in the 5-bromo isomer is surprising <93CJC427>. In some 1,2-disubstituted 5-nitroimidazoles (ronidazole and dimetridazole) cysteine reacts under neutral aqueous conditions to give 5-S-cysteinyl products. Rate enhancements resulting from raising the pH suggest attack by thiolate isomers, although a mechanism in which the alkylthio radical reacts with the radical anion of the substrate cannot be excluded <93CJC1349>.

Methylsulfonyl groups activated by an adjacent nitro substituent are readily displaced in reaction with thiophenol and thiocresol anions <87AJC1415>. In a reaction believed to involve an intermediate

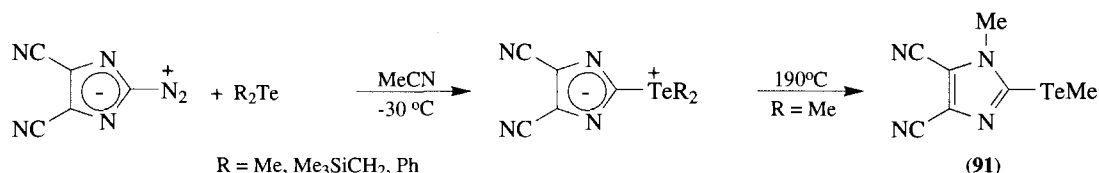


Scheme 37

sulfonic acid, 2-sulfinylbenzimidazoles (**90**) are converted by ethanethiol into a mixture of thioether and disulfide. The benzimidazole becomes protonated, and the sulfonic acid is eliminated after the *ipso*-substitution by thiolate (Equation (29)) (<87JOC4620, 90AHC(48)1>).



There are a number of examples in which 1-alkoxybenzimidazoles, 1-alkoxy-3-methylbenzimidazolium salts, and 1-alkylbenzimidazole 3-oxides react with anionic sulfur species to give 2-substitution with simultaneous deoxygenation (<93CHE127>). The most useful general approach to the preparation of imidazolethiols and thioethers now appears to be via lithiated derivatives (see Section 3.02.5.5.1). Dialkyl- and diaryl-tellurides react with 2-diazo-4,5-dicyanoimidazole to give stable ylides which undergo a modified Stevens rearrangement to form (**91**) (Scheme 38) (<91CB699>).

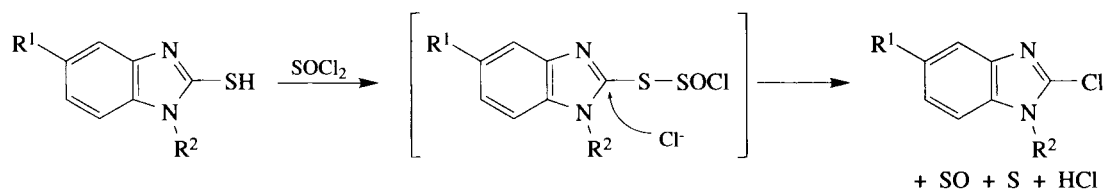


Scheme 38

3.02.5.4.4 Halide ions

The common nucleophilic substitution reaction which comes under this heading is the conversion of a 2-(benz)imidazolone into the 2-chloro species, usually with phosphoryl chloride (<87JHC31, 91MI 302-03, 93AHC(57)291, 94AHC(59)245>). 2-Thiobenzimidazoles react similarly with thionyl chloride, perhaps by the pathway in Scheme 39. To be successful, the substrate needs an electron-attracting group in the 5-position (<85CHE872>).

Conversions of diazonium salts into halogenoimidazoles are quite common (<88CPB2730, 93AHC(57)291>), with applications to the synthesis of fluoroimidazoles of particular interest. The Balz-Schiemann method, in which the diazonium fluoroborate is photolyzed, has been used to prepare 2,4-difluoroimidazole (<84JOC1951>). The limiting factor in these reactions is the difficulty of preparing aminoimidazoles. With ethyl 4-diazoimidazole-5-carboxylate the Sandmeyer reaction fails, perhaps



Scheme 39

because of the great stability of the 4-diazo compound, but 1-substituted 4-diazonium salts show the expected reactivity (Equation (30)) <90AHC(48)65, 93AHC(57)291>.



Fluoride converts 1,2-dimethyl-4-trimethylammonio-5-nitroimidazole into the 4-fluoro derivative <87JMC150>. The 2-nitro group of 1-methyl-2,4-dinitroimidazole is replaced by bromine or chlorine when treated with 2-bromoethanol or 2-chloropropanenitrile respectively <84IJC(B)363>. When benzimidazole-2-nitrosamine is treated with dry HCl or HBr with copper metal in acetonitrile the corresponding 2-halogenobenzimidazoles are formed in 71% and 63% yields respectively <87CHE1090>.

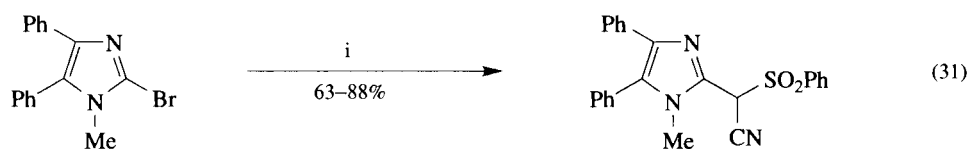
3.02.5.4.5 Hydride sources

The fully aromatic species are usually quite resistant to hydride reduction. Attempted reduction of 1,2-dimethyl-5-nitroimidazole with tributyltin hydride failed to yield 1,2-dimethylimidazole <90JCS(P1)919>, but the apparent reduction of 5-iodo-1-methylimidazole to 1-methylimidazole by phenylsulfonylacetonitrile and sodium hydride with tetrakis(triphenylphosphine)palladium(0) as catalyst may be an example <92S552>. Lithium aluminum hydride (but not diborane) is able to convert 2-(but not 4-)fluoroimidazoles into the hydrogen species <84JOC1951>.

3.02.5.4.6 Carbanions

(i) Activated methyl and methylene carbanions

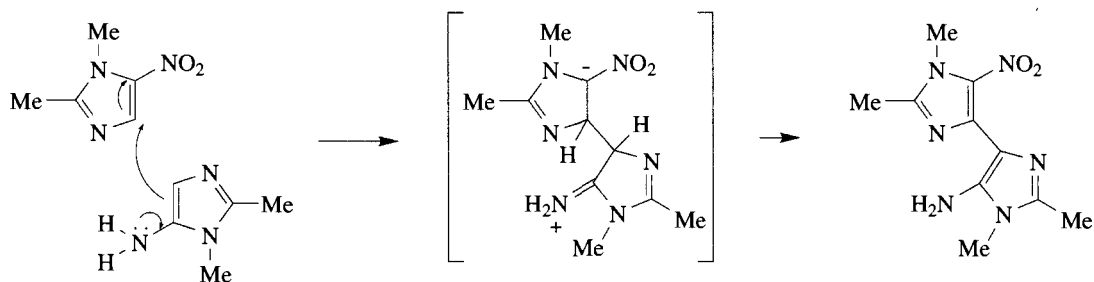
Few examples exist, but palladium-catalyzed cross-coupling of halogenoimidazoles with phenylsulfonylacetonitrile under basic conditions appears to provide examples of active methylene nucleophiles. As mentioned above (see Section 3.02.5.4.5), 5-iodo-1-methylimidazole is only reductively dehalogenated under the conditions, but 5-bromo-1-methyl-, 4-iodo-1-methyl-, and 2-bromo-1-methyl- (but not 2-chloro-1-methyl)imidazoles react successfully with the carbanion (Equation (31)) <92S552>.



i, $\text{PhO}_2\text{SCH}_2\text{CN}$, NaH, $\text{Pd(PPh}_3)_4$, $(\text{MeOCH}_2)_2$, reflux 1.5–24 h

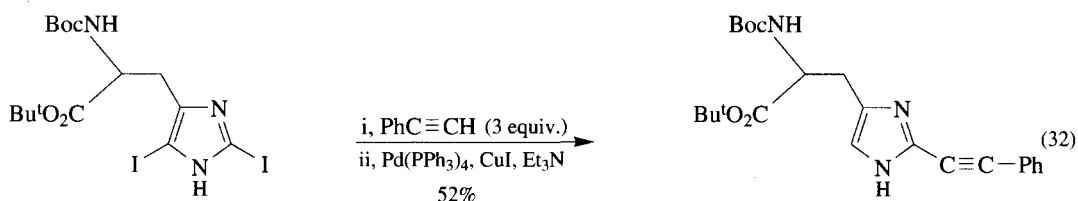
During the catalytic reduction of nitroimidazoles, diimidazole products are observed, presumably as a consequence of nucleophilic substitution. Nitroimidazoles have low energy LUMOs (they are

soft electrophiles) and should be reactive towards the ring carbons of 4- and 5-aminoimidazoles (Scheme 40) <92JCS(P1)2789>.



Scheme 40

Reaction of protected 2,5-diiodohistidine with phenylacetylene in the presence of palladium(0) complexes can lead to displacement of the 2-iodo group by arylalkynyl, but in a competing reaction the alkyne reduces the 5-iodo function (Equation (32)). Careful choice of ligand can lead to preferential coupling at C-2. Alkylzinc iodides in the presence of palladium(0) also replace a 2-iodo group by alkyl <93AG(E)1326>. Alkylation at C-2 of imidazoles has been achieved via the unstable 1,3-dialkoxycarbonyl salts in the presence of allyltributyltin. The initially formed imidazolines are rearomatised by oxidation with potassium ferricyanide in basic medium <94JOC1319>.



(ii) Cyanide

The use of CuCN with diazonium salts is well known <89H(29)1325>. Provided activation is present, a suitably orientated halogen substituent (5-iodo(bromo)-1-methyl-4-nitro, but not 4-iodo(bromo)-1-methyl-5-nitro-), can be displaced by nitrile when heated with KCN and KI in ethanol. 4-Halogenoimidazoles are resistant unless boiled in DMF when they give the 5-nitriles, perhaps via a transmethylation reaction. The observation that neither DMF nor KI are absolutely necessary renders the 'rearrangement' mechanism unclear <87AJC1399>. A nitro group, too, can be displaced by cyanide as in the preparation of 5-cyano-1-methyl-4-nitroimidazole from the 1-methyl-4,5-dinitro precursor <90EUP348803>. Cyanation of halogenoimidazoles in the presence of nickel(0) complexes has not yet been reported <93BCJ2776>. Nor has the palladium-catalyzed reaction with zinc cyanide <94SC887>.

A number of examples of 2-cyanation of benzimidazolium or benzimidazole *N*-oxides have been reported <93CHE127>, but with benzimidazole itself, although an attempted Reissert reaction introduced a nitrile function at C-2, the attempted rearomatization failed when a retro-Reissert reaction regenerated starting material <87JHC1349>.

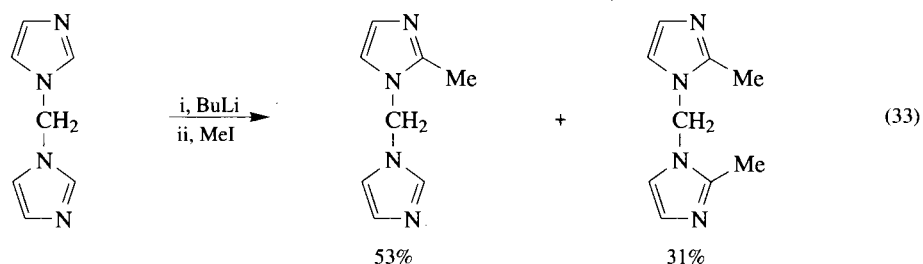
3.02.5.4.7 Azide ions

Most such reactions involve diazonium salts, but reaction of a group of 5-fluoro-4-trifluoromethylimidazoles with azide was found to give 5-azido products <90S352, 90S360>.

3.02.5.5 Nucleophilic Attack at Hydrogen

3.02.5.5.1 Metallation at a ring carbon atom

There have been a number of reviews of this topic <85H(23)417, 88CHE117, 94H(38)2487>. Provided that the annular nitrogen is substituted, imidazoles can be lithiated at ring carbon atoms with reactivity order C-2 > C-5 > C-4 <93RTC123, 94H(38)2487>. A number of suitable *N*-protecting groups has been developed having regard to ease of attachment and removal, steric, and electronic properties <84JCS(P1)481, 88JOC1107, 88JOC5685, 89JCS(P1)1139>. Whereas butyllithium is frequently the reagent of choice for making lithioimidazoles, LDA has advantages when there are substituents susceptible to nucleophilic attack. Carbon-2 is commonly lithiated at -78°C without the need for any chelating agents (e.g., TMEDA) to enhance the basicity of the reagent (Equation (33)) <93JCS(P1)1079, 94H(38)2487, 94JMC332>.



Careful choice of reaction conditions allows 2-lithiation even in the presence of groups susceptible to attack by the reagent. At -100°C in THF 4,5-dicyano-1-methylimidazole forms the 2-lithio compound; at -80°C butyllithium attacks one of the nitrile functions <92JHC1091>. Even 4- and 5-chloroimidazoles can be 2-lithiated, as can 4-bromoimidazole, but when the 2-position is blocked halogen-metal exchange and direct lithiation can occur elsewhere <94JMC332>.

An *N*-methyl group is able to withstand extreme metallation conditions, but it is difficult to remove <83JCR(S)196>. Benzyl groups are labile under reductive or oxidative conditions, but they are susceptible to lateral metallation <84JCS(P1)481, 85S302, 90JHC673, 91JA6178>. It is not clear which of the anions (2-yl or *N*-C α) is kinetically preferred even though the former is thermodynamically favored <90JHC673>. While the trityl protecting group is readily removed by mild acid hydrolysis, solubility and steric problems sometimes restrict its applicability <84JCS(P1)481>. Alkoxy- and aryloxy-methyl groups are stable under metallation regimes, but deprotonation may be difficult in that boiling with acid is necessary to remove the groups <90JCR(S)58, 94H(37)673>. The SEM group can be cleaved by 0.5 molar hydrochloric acid at 50°C or with 1 molar tetrabutylammonium fluoride in refluxing THF <86JOC1891, 86TL4095>. In contrast, dialkoxymethyl and trialkylsilyl groups are quite labile, normally being removed during workup procedures <89JCS(P1)1139>. An *N*-dialkylamino protecting group, introduced under Mannich conditions, is readily removed by acid <88JOC5685>.

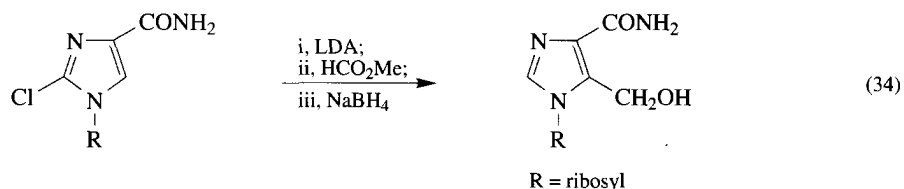
Sometimes 2-lithio derivatives of 1-protected imidazoles give poor yields when the anion is quenched with hindered electrophiles. Thus, although arylsulfonyl protecting groups permit facile 2-lithiation, quenching with carbonyl electrophiles is often unsatisfactory because the arylsulfonyl group has decreased the nucleophilicity of the 2-anion <88JOC1107, 94H(37)673>.

When 1-methylimidazole is quaternized at *N*-3 by 4-methoxybenzyl chloride, the salt deprotonates readily in the presence of sodium hydride in DMF. 1,3-Dimethylimidazolium salts react analogously, allowing access to 2-chloro-, 2-bromo-, 2-deutero-, and various 2-substituted phosphorus- and sulfur-containing imidazoles <88T7413>.

Direct 4-lithiation of imidazole can only be achieved in the presence of a large substituent at *N*-1, or in activated imidazolium salts where the adjacent site is occupied, for example, 2-phenylthio-1-tritylimidazole gives a low yield mixture of 4- and 5-substituted products when treated with *t*-butyllithium in THF <89JCS(P1)1139>, and 5-chloro-3-(4'-methoxybenzyl)-1-methyl-2-phenylimidazolium chloride is deprotonated at C-4 by sodium hydride, potassium amide, or butyllithium <94H(38)2487>. It is well known that the adjacent lone pair effect makes imidazol-4-yl *sp*² anions less stable than their 5-yl counterparts <85JHC57>.

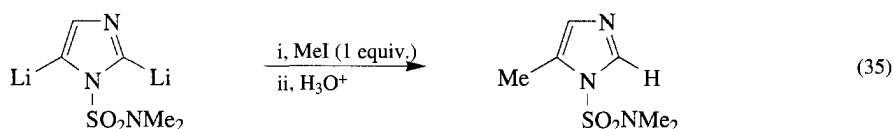
Lithiation at the 5-position is possible when C-2 is blocked, a reaction of use in introducing functionality to imidazole nucleosides (Equation (34)) <87CPB4056>. When the 2-position is blocked by trialkylsilyl, however, 5-deprotonation becomes more difficult with *s*-butyllithium the reagent of

choice. These silyl groups are quite labile, with *t*-butyldimethylsilyl the most stable, and they are usually introduced immediately prior to lithiation. Workup commonly causes desilylation <84JCS(P1)481, 86T2351, 88TL3411, 91SI021, 93RTC123, 94JMC332>. In *N*-protected 2-phenylthioimidazoles LDA metallates C-5; butyllithium is also useful, but carbon–sulfur bond cleavage can be a problem <83JCS(P1)279, 88TL3411, 88TL5013, 89JCS(P1)1139, 92CPB2681>. Other examples of 5-lithiation of 2-substituted imidazoles include 2-dimethylamino-1-methyl- <91TL5325>, and 1,2-dimethyl-imidazole <83JCS(P1)271, 90JCS(P1)1645>, but a number of bases failed to deprotonate *N*-protected 2-nitroimidazoles <89JCS(P1)95>.



When it is necessary to remove the 2-protecting group after 5-lithiation and quenching, although phenylthio groups survive workup (they can be removed later using Al–Hg), trialkylsilyl groups are much more labile (see above). An alternative is tertiary amido which is later removed in alkaline conditions <90JCS(P1)1645>.

Polyolithiation at both 2- and 5-positions gives access to 1,2,5-trisubstituted imidazoles in yields dependent on the ability of the 2-anion to further deprotonate at C-5 <83JCR(S)196>. As the 5-anion is the more reactive, sequential quenching by different electrophiles becomes possible (Equation (35)) <84JCS(P1)481>.

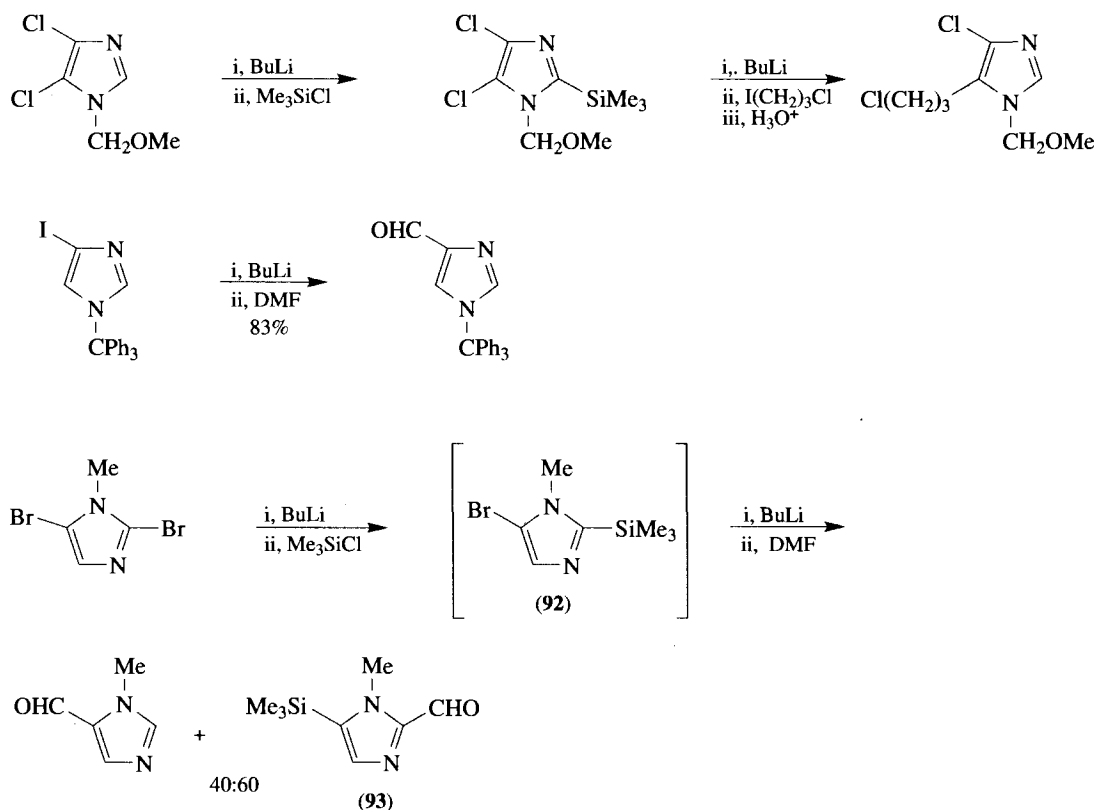


Although halogen–lithium exchange cannot be classified under this heading, it is convenient to discuss it here. Bromine and iodine groups at any position in *N*-substituted imidazoles will exchange. In 1-substituted 2,4,5-tribromimidazoles exchange in excellent yields at low temperatures is in the order 2 > 5 > 4, making selective exchange possible <86TL1635, 87JCS(P1)1445, 87JCS(P1)1453, 91JOC4296, 92JOC3776, 92TL5865>. Double bromine–lithium exchange in 1-methyl-2,5-dibromimidazole gives the 2,5-dianion which selectively forms the aldehyde at C-5 when treated with DMF <85JHC57>. With only one equivalent of butyllithium the resulting 2-anion can be converted into the 2-trimethylsilyl derivative (**92**) which, on subsequent lithiation disproportionates to give 1-methyl-2,5-di(trimethylsilyl)imidazole and 1-methyl-2,5-dilithioimidazole. Further disproportionation of these products gives 2-lithio-1-methyl-5-trimethylsilylimidazole which reacts with DMF to give (**93**) (Scheme 41) <93TL3401>. Complications may arise from transmetallation <94H(38)2487>. 5-Chloro groups are less prone to exchange than bromo or iodo unless the 2-position is blocked <90EUP365030>.

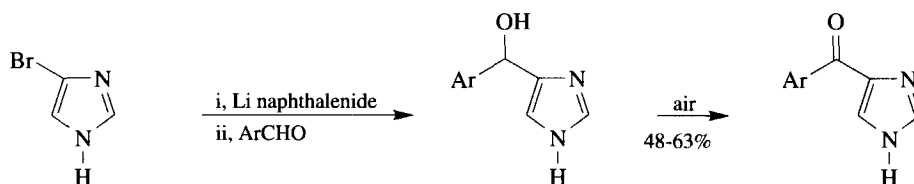
Attention is also drawn to the metallation of *N*-unsubstituted imidazoles. The *N*-lithio species (or *N*-Grignard reagent) is formed initially, but halogen–metal exchange can occur with excess metallating reagent (Scheme 42) <82JOC2196, 87JCS(P1)1445, 91CHE556>. All of these reactions are of value for modification of the substituent pattern in the imidazole ring.

Treatment of *N*-protected 4-iodoimidazoles in dichloromethane with ethylmagnesium bromide gives 4-anions which react smoothly with a variety of electrophiles. There are the usual problems of a 4-anion rearranging to the more stable 2-anion <85JHC57, 91JOC4296>, but at room temperature the former is relatively stable <91JOC5739, 93SL748>.

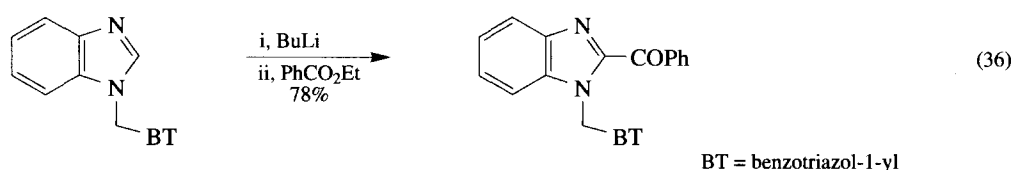
In benzimidazole, 1-protected compounds are readily lithiated in the 2-position, and 1-methyl-benzimidazole-2-magnesium bromide is also a source of carbanions at C-2 <86JOU384>. The benzotriazol-1-ylmethyl group can act as both protecting and activating group when it increases the acidity of H-2 (Equation (36)) <89JHC829>. Other protecting groups which have been used include diethoxymethyl <82JCS(P1)287>, hemiaminals <89JOC2949>, *p*-fluorobenzyl <90JOC1399>, phenylthiomethyl <87JCS(P1)775>, and dialkylamino (see also Section 3.02.7.1.11) <92CHE1009>.



Scheme 41

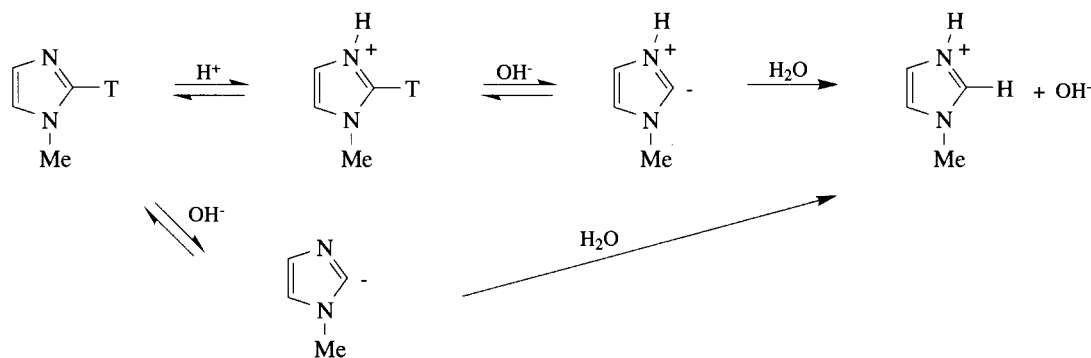


Scheme 42



3.02.5.5.2 Hydrogen exchange at a ring carbon in neutral imidazoles

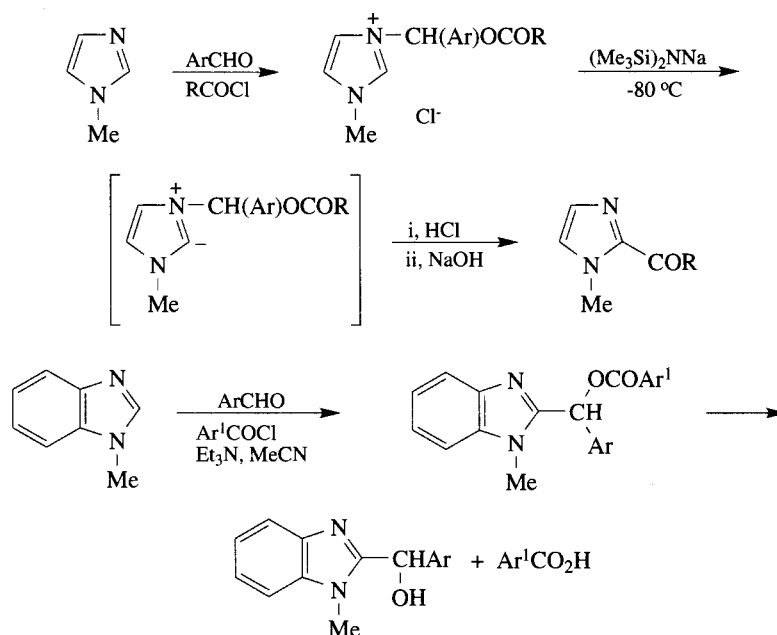
Most of the features of hydrogen and deuterium exchange in imidazoles were detailed in CHEC-I. A study in 1989 of base-catalyzed hydrogen exchange determined the rate-pH profile for detritiation from carbon-2 of aqueous 1-methylimidazole. The profile was found to be consistent with a mechanism involving hydroxide ion attack on the conjugate acid of the substrate to form an ylide in the rate-determining step. At higher pH values, hydroxide ion catalyzed exchange of the neutral molecule becomes increasingly important. Comparison of the second order rate constants derived from the rate-pH profiles of imidazole, benzimidazole, and their 1-methyl derivatives demonstrate that methyl substitution doubles or triples the rate, while benzannulation increases it 10 to 20 fold. An FMO analysis of the reaction schemes for proton transfer has been used to explain the accelerating effects of the methyl and benzo substituents (Scheme 43) <86CJC1240>.



Scheme 43

3.02.5.5.3 C-Acylation via deprotonation

Acylation of 1-methylimidazole at C-2 takes place via the azolium salt which deprotonates to form an ylide, and then rearranges $\langle 84TL1715, 86CHE587 \rangle$. This reaction has similarities to the Regel acylation process (see CHEC-I). In the presence of excess aromatic aldehyde, instead of the usual 2-acylation, esters, alcohols, and benzoic acids are formed (Scheme 44) $\langle 83CHE916 \rangle$.

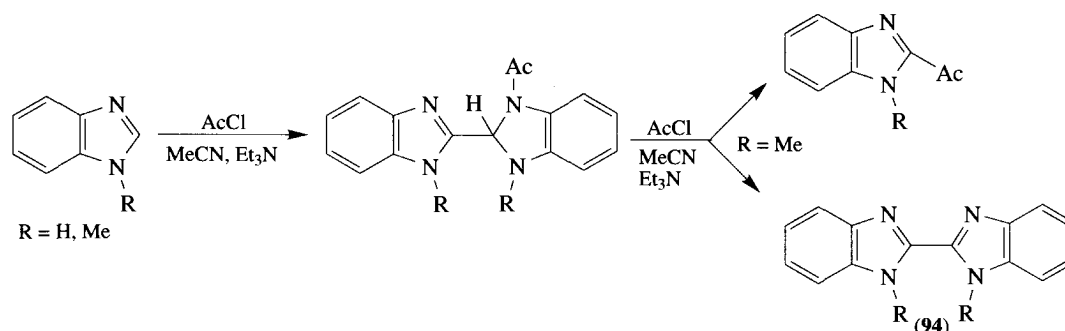


Scheme 44

Similar imidazolium ylides are implicated as catalysts in the aroylation of *N*-phenylbenzimidoyl chlorides $\langle 92CPB2627 \rangle$, and in reactions of 1-substituted imidazoles with cyanogen bromide to form 2-cyano- or 2-bromo-imidazoles $\langle 88S470 \rangle$.

Direct acylation of benzimidazole and its 1-methyl derivative under Regel–Buechel conditions mainly gives coupling products which can be converted into 2-acylbenzimidazoles by heating with an acyl halide in acetonitrile containing triethylamine. Some 1,1'-dimethyl-2,2'-dibenzimidazolyl (**94**) is also isolated (Scheme 45) $\langle 87CHE284 \rangle$.

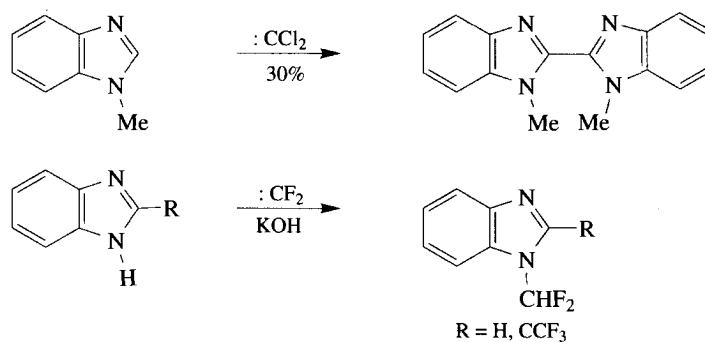
Acid chlorides convert 1-methylbenzimidazol-2-yl-silanes and -stannanes into 2-acylbenzimidazoles. The reaction also works with imidazoles, with the stannanes being more reactive than the silanes. The mechanism is believed to involve initial *N*-acylation, then loss of the silicon or tin substituent to give a zwitterion, and finally *N* → *C*-migration of the acyl group. As in Regel acylation, acetyl chloride will not induce the reaction $\langle 83JHC1011 \rangle$.



3.02.5.6 Reactions with Radicals and Electron-deficient Species

3.02.5.6.1 Carbenes

Imidazoles react with chloroform at high temperature to form azines by carbene insertion (see CHEC-I) and trichloromethyl radicals do much the same thing (91MI 302-04), but carbenes do not always induce ring expansion. In alkaline medium, chlorodifluoromethane converts benzimidazole and its 2-methyl analogue into the 1-difluoromethyl derivatives (62%, 70%) (82CHE1314). Dichlorocarbene in basic conditions had earlier been shown to *N*-alkylate benzimidazole (78CI(L)126), and later 1-methylbenzimidazole was shown to couple under the influence of the same reagent (Scheme 46). Initial attack of the carbene at N-3 has been proposed (87H(26)1161). Examination of the reactions of *N*-unsubstituted imidazoles and benzimidazoles with difluorocarbene shows that 1-difluoromethyl products (37–87%) are formed. The yields increase in line with the lipophilicity of the 2-substituent even though a large substituent might be expected to hinder reaction. As with dichlorocarbene there is evidence for interphase catalysis. As it is difficult to imagine an imidazole anion reacting easily with a carbene one might suspect that it is the free base species in the organic layer which is involved (sodium salts are, however, known to react (92MI 302-04)). The reaction of 2-trifluoromethylbenzimidazole appears anomalous, but presumably the substituent is hydrolyzed to carboxyl and decarboxylated after incorporation of the difluoromethyl group (Scheme 46) (84CHE422).

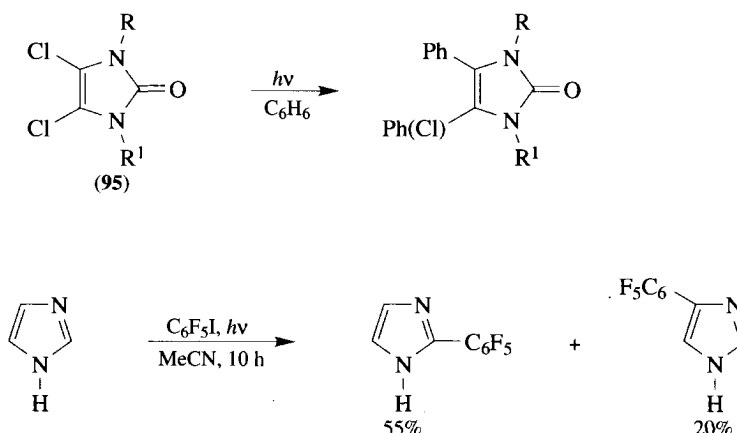


3.02.5.6.2 Free radical attack at ring carbon atoms

(i) Aryl radicals

Common sources of phenyl radicals are *N*-nitrosoacetanilide, diazoaminobenzene, or benzoyl peroxide which induce 2-phenylation of imidazoles and benzimidazoles. The 2-position is frequently the most susceptible to nucleophilic attack (CHEC-I). Most photochemically induced arylations also probably involve radical substitution, for example, photolysis of 1,3-dialkyl-4,5-dichloro-2-imidazolone (95) in benzene (Scheme 47) (81AG(E)612). Under photolytic conditions pentafluoro-

iodobenzene converts imidazole into both 2- and 4-pentafluorophenyl derivatives, while 2-methylimidazole substitutes at C-4 (74%) in a reaction believed to be an electron-transfer process, occurring via formation of the aryl radical and the imidazole radical cation (Scheme 47) <93JCS(P1)1705>.

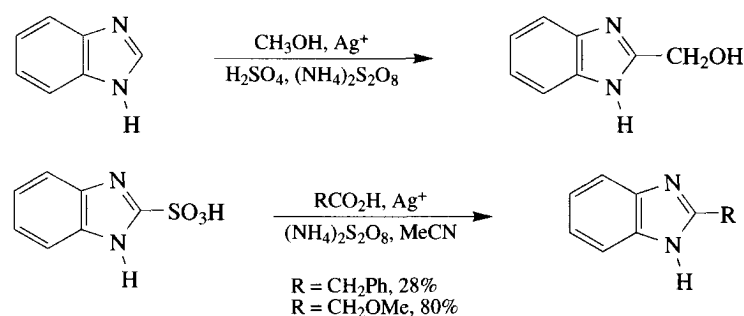


Scheme 47

When benzimidazole couples under photochemical conditions there is a mixture of products coupled between C-2 of one benzimidazole molecule and C-4 and C-5 of the other. Coupling with 2-acetyl-5-iodothiophene, though, occurs only at C-4 <91H(32)1059>. Prolonged heating of 1-methylbenzimidazole-2-nitrosamine in benzene yields 86% of 1-methyl-2-phenylbenzimidazole <87CHE1090>.

(ii) Alkyl and other carbon radicals

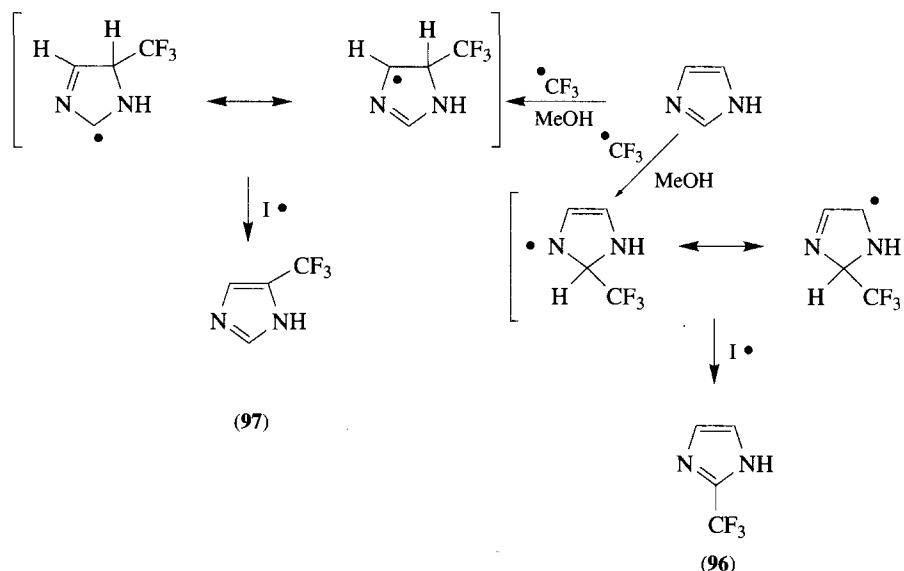
Silver-catalyzed oxidative decarboxylation of aliphatic carboxylic acids has continued to be used for the homolytic 2-alkylation of imidazoles and benzimidazoles in spite of indifferent yields <82CHE1299, 85AP(318)393>. Similar oxidative processes include the use of alcohols or cyclic ethers in the presence of acidic persulfate, iron(II) sulfate and hydrogen peroxide, or iron(II) sulfate and *t*-butyl peroxide. Substitution of a hydrogen (but unexpectedly not sulfonic acid) occurs at C-2 <88CHE646, 88JOU1215>. It had been reported earlier that alkyl radicals are able to displace a sulfonic acid group in the same way that conventional nucleophiles do (Scheme 48) <84CHE1401>.



Scheme 48

Although the use of *t*-butyl peroxide with alkyl iodides has yet to be reported for imidazole alkylation <89ACS(B)995>, it has been used to initiate the photoaddition of 1-heptene to benzimidazole and its 1-benzyl derivative <91IZV106, 91IZV108>. Among the photochemical alkylations are those which generate a trifluoromethyl or perfluoroalkyl radical. Radical dissociation of trifluoroiodomethane by γ - or UV-irradiation forms trifluoromethyl radicals which preferentially attack the 4-position of imidazole with a lesser amount of 2-substitution (2 to 3 : 1 ratio). Total yields of (96) and (97) can be high. The reactions are aided by electron-donating substituents and retarded by electronegative groups. 1-Alkylimidazoles mainly substitute at C-5, and benzimidazole reacts at the

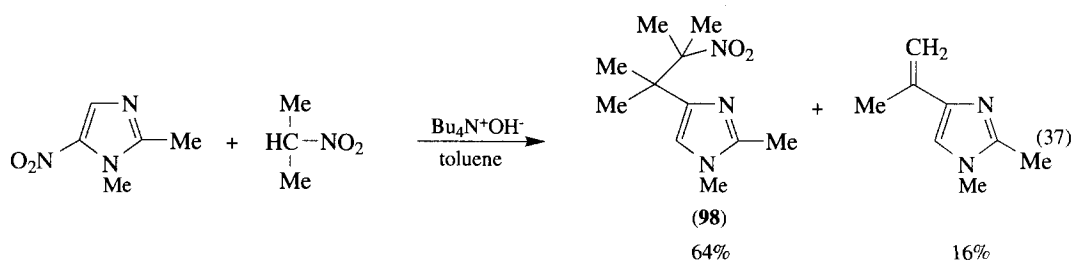
4-position initially, but some disubstitution can occur (Scheme 49) <82JOC2867, 84JOC1060, 86MI 302-06, 90TL5705, 93JCS(P1)645>.



Scheme 49

With *N*-acylhistidine esters and *N*-acylhistamines the radicals also substitute at the 2- (13–27%) and 4-positions (23–34%). Imidazole is 20 times more effective than pyridine at trapping trifluoromethyl radicals <84JOC1060>. Even though generation of these radicals by photochemical or electrochemical methods or from trifluoroacetyl peroxide are mild methods, they invariably give mixtures of isomers. More selective trifluoromethylation utilizes methylthio blocking groups <91BCJ2255>. Indirect electrochemical reduction by means of aromatic anion radical mediators (e.g. 4-nitropyridine 1-oxide) of perfluoroalkyl halides in the presence of imidazole anions gives perfluoroalkylimidazoles by an $S_{RN}1$ process (Scheme 50) <87CC1240, 90TL1279>.

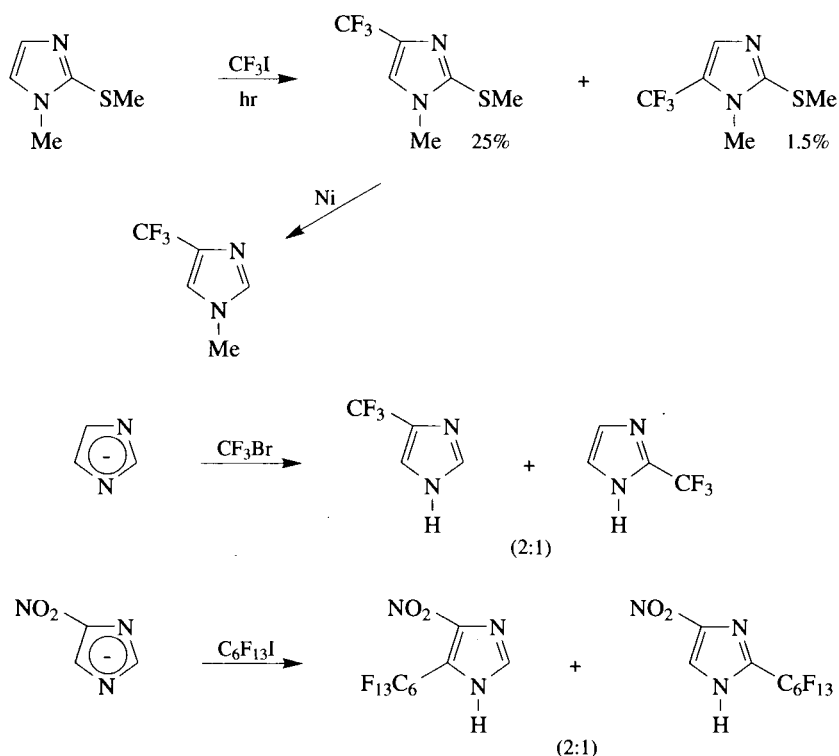
Alkyl radicals formed from secondary nitroalkanes are known to substitute at C-4 of 1,2-dimethyl-5-nitroimidazole. The mechanism involves initial electron transfer from nitronate anion to give a 2-nitropropyl radical and the radical anion of the 5-nitroimidazole. Combination of these species at C-4 to form a Meisenheimer complex ultimately leads to *cine*-substitution products. Subsequent $S_{RN}1$ reaction gives (98) (Equation (37)) <89H(28)849>.



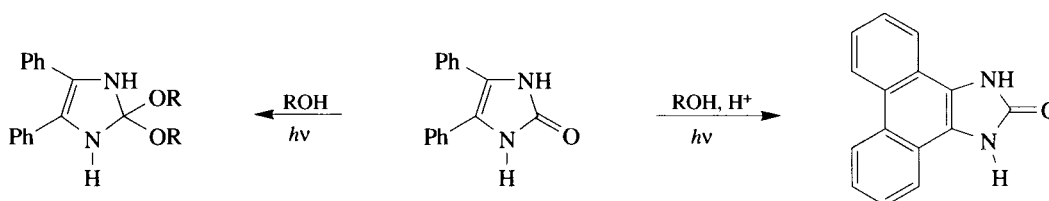
Iodoimidazoles couple with (π -allyl)nickel halide complexes under irradiation in toluene to give 2-allyl products <93JOC997>. Photolysis of 1,2-dimethyl-5-nitroimidazole in aqueous cyanide gives the 5-cyanoimidazole. With other 1-substituents the 5-carbamoyl products are formed <89OPP105>. Direct homolytic carbamoylation procedures have yet to be used on imidazoles <93H(36)2687>.

(iii) Other radicals

When alcoholic solutions of 4,5-diphenylimidazolone are photolyzed the acetals form, but in acidic media oxidative dehydrogenation to a phenanthroimidazolone was reported (Scheme 51) <89PIA391>.



Scheme 50



Scheme 51

3.02.5.6.3 Electrochemical reactions and reactions with free electrons

Rather than giving the expected π^* radical anions, electron addition (using ^{60}Co γ -rays) to halogenoimidazoles has been found to form σ^* radical anions, the SOMO being primarily the carbon-halogen σ^* orbital with little delocalization. Seemingly the imidazole ring stabilizes the C—Cl and C—Br σ^* radical ions in a like manner to iodouracil and iodopentafluorobenzene. Liquid solution studies have further demonstrated that radical ions are present when 5-bromo- and 5-iodoimidazoles are reduced by sodium and liquid ammonia in *t*-butanol. Tributyltin hydride similarly reduces halogenoimidazoles, probably via the imidazole radical $\langle 89\text{TL1409} \rangle$.

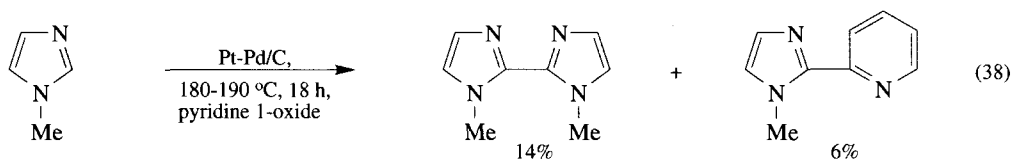
When nitroimidazoles and -benzimidazoles are subjected to electrochemical reduction, the initially formed unstable radical anions subsequently decompose with elimination of hydrogen. Thus, in acetonitrile, 2-substituted 5(6)-nitrobenzimidazoles generate hydrogen as a result of bimolecular reaction of two primary radical anions $\langle 85\text{CHE688} \rangle$.

Electrochemical reduction of 1-vinylazoles in acetonitrile or DMF is also a one-electron process in which the radical anions which are generated dimerize $\langle 86\text{CHE253} \rangle$.

3.02.5.6.4 Catalytic hydrogenation and reduction by dissolving metals

So resistant are imidazoles and benzimidazoles to catalytic hydrogenation that 1-methylimidazole, benzimidazole, and its 1-methyl derivative condense dehydrogenatively in the presence of platinum-

or palladium-carbon catalyst and pyridine 1-oxide. Imidazole itself does not appear to dimerize to any extent under the same conditions (Equation (38)) <89CPB1987>.

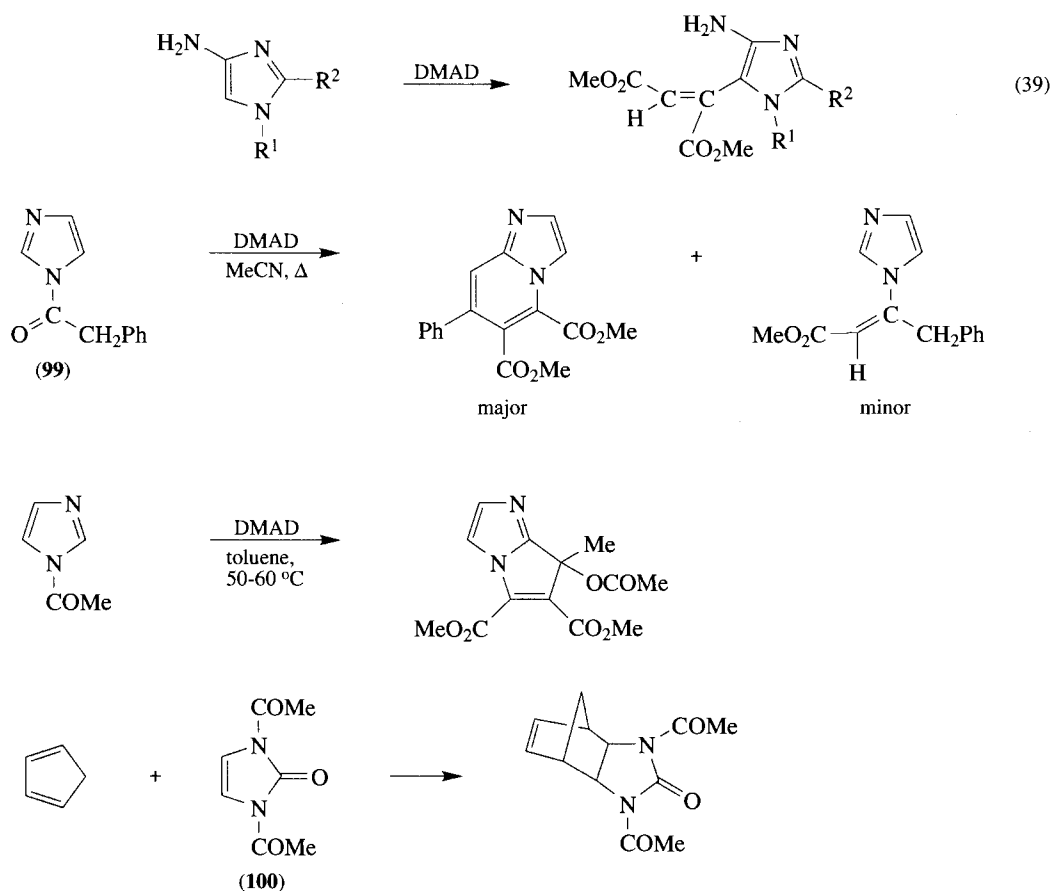


Catalytic hydrogenation conditions applied to 2-furylbenzimidazoles merely reduce the furan ring in ethanol, but in acidic medium the fused benzene ring is also hydrogenated <86MI 302-07>. Reduction of 4-fluoroimidazoles has been accomplished by catalytic hydrogenolysis <84JOC1951>.

3.02.5.7 Reactions with Cyclic Transition States

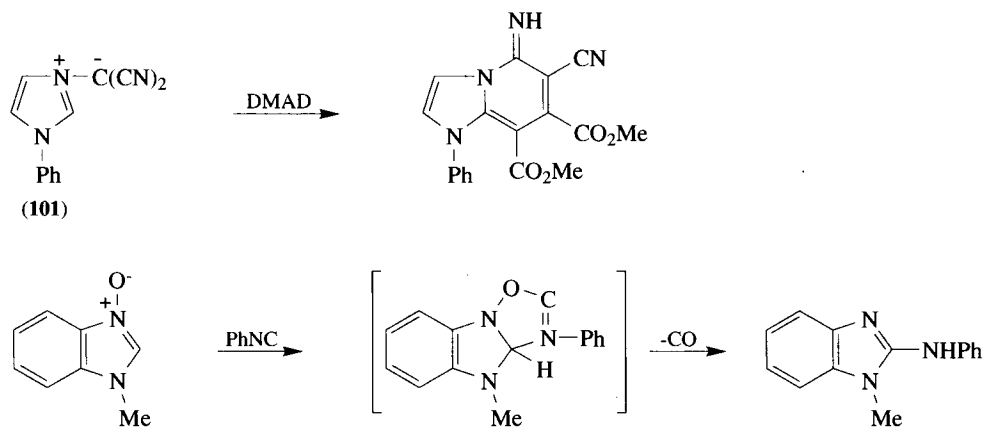
3.02.5.7.1 Diels-Alder reactions and 1,3-dipolar additions

These reactions have been reviewed (CHEC-I) <83T2869, 93CHE127>. Most reactions of imidazoles with dienophiles such as DMAD give only *N*-alkylation products (see Section 3.02.5.2.6), and sometimes *C*-alkylation products (Equation (39)) <92JCS(P1)2779>. But examples of cycloaddition are known, for example, the reaction of 1-phenacetyl-imidazole (**99**) with DMAD <88CC1151, 90CB327>, and the novel transacylation of 1-acetyl-imidazole with the same reagent <90JCS(P1)1821>. The latter reaction involves initial electrophilic alkylation of the nitrogen, and subsequent intramolecular transacylation. In neither example does imidazole act as a diene (Scheme 52). However, 1,3-diacetyl-2-imidazolone (**100**) reacts with cyclopentadiene in what appears to be a Diels-Alder reaction <93JOC3387>.



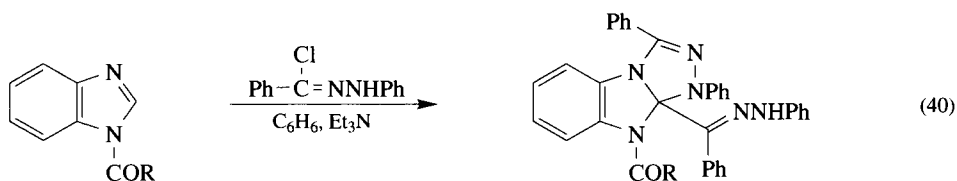
Scheme 52

The 1,3-dipolar addition of azolium *N*-dicyanomethylides (**101**) (which have an azomethine ylide structure) to acetylenic dipolarophiles forms azolopyridines <83JCS(P2)1317>. Cycloadditions of 2-diazoimidazoles are discussed later under functional group properties (see Section 3.02.7.1.6). In imidazole *N*-oxides the oxide group, in combination with the adjacent ring carbon, has 1,3-dipolar properties. The cyclic adducts which form are usually unstable and subject to further transformations involving oxygen transfer, ring opening, and formation of 2-substituted derivatives (Scheme 53) <93CHE127>.



Scheme 53

In the 1,3-dipolar addition of silver and copper acetylides to 1-amino-benzimidazolium salts, the initial tricyclic product ring-opens to yield a 1,3-diarylpyrazole <84JGU1493>. Chloronitrilimines react with 1-acylbenzimidazoles by 1,3-dipolar addition. Benzimidazole and 4,5-disubstituted imidazoles, though, tend to be *N*-alkylated by these reagents (Equation (40)) <85H(23)2183, 93CRV2731>.



3.02.5.7.2 Photochemical cycloadditions

Photoadditions of this type frequently give rise to four-membered rings initially <80AHC(27)241>. Photooxidations, which probably proceed by cycloaddition of singlet oxygen, have been discussed earlier (see Section 3.02.5.3.11).

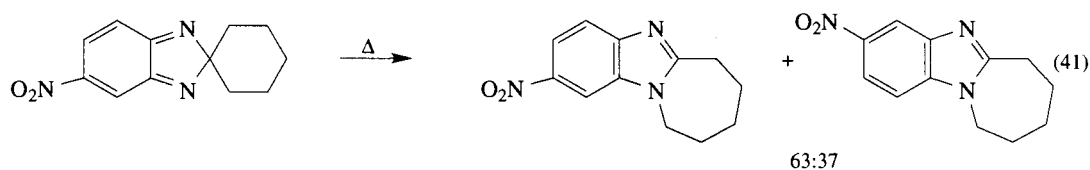
3.02.6 REACTIONS OF NON-AROMATIC COMPOUNDS

3.02.6.1 Isomers of Aromatic Derivatives

3.02.6.1.1 Compounds not in tautomeric equilibrium with aromatic derivatives

(i) 2*H*-Imidazoles and -benzimidazoles

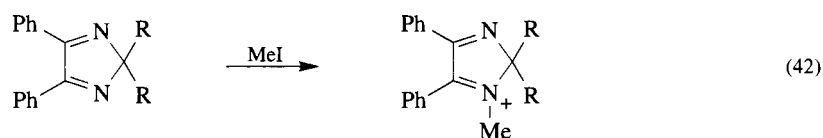
2*H*-Imidazoles (**3**) have properties which are considerably different from those of their 1*H*-counterparts into which they can rearrange thermally by 1,5-sigmatropic rearrangement <84AHC(35)375>. Migratory aptitudes in a series of 4,5-diphenyl-2*H*-imidazoles has been found to be in the order PhCH₂ > Ph > Et > Me, while spiro-2*H*-imidazoles and -benzimidazoles form bi- and tricyclic species when the C → N rearrangement takes place (Equation (41)) <88JCS(P1)991>.



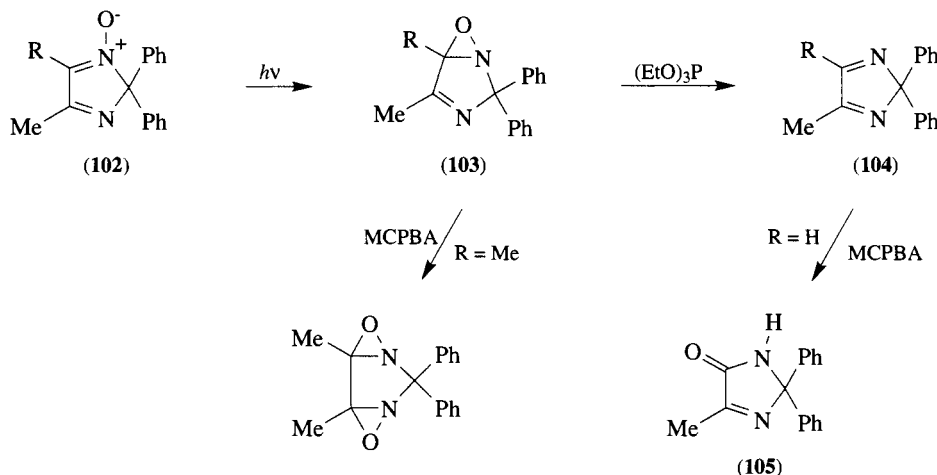
Attempts to rearrange 4-alkylthio-5-aryl-2-spiro-2*H*-imidazoles in boiling acetic acid were, however, unsuccessful $\langle 87S547 \rangle$. A 2-chloro-2-phenyl-2*H*-benzimidazole is implicated as an intermediate in the synthesis of 1*H*-benzimidazoles from *ortho*-amidoarylazides $\langle 84CI(L)222 \rangle$, while a 2-methoxycarbonyl-2*H*-imidazole is an intermediate in the thermal ring contraction of oxygenated pyrazines to 1*H*-imidazoles (see Section 3.02.8.2.3.ii) $\langle 83CC399 \rangle$.

2-Ethoxy-2*H*-imidazoles are converted into 4-ethoxy-4*H*-imidazoles by acid catalysis, suggesting that the latter are more stable with an oxygen substituent at the tetrahedral carbon atom $\langle 84AHC(35)375 \rangle$. The 1,2-proton shift barriers for 1*H* to the 2*H*- or 4(5)-*H* non-aromatic tautomers, determined by INDO calculations, suggest that the 2*H*- and 5*H*-imidazoles have similar energies $\langle 86BSF(2)429 \rangle$.

Although acid treatment may cleave the ring, alkyl halides readily quaternize 2*H*-imidazoles. The resulting quaternary salts have sufficiently acidic methyl groups to exchange readily with deuterium (Equation (42)) $\langle 83JCS(P1)2065 \rangle$, and methyl 2-alkyl-3-imidazolin-5-one carboxylates (which are tautomers of 2*H*-imidazoles) can be *N*- or *O*-alkylated depending on the reaction conditions $\langle 89JCS(P1)279 \rangle$.



Peracids can oxidize 2*H*-imidazoles to *N*-oxides and *N,N'*-dioxides, and sometimes to imidazolinones. Ultraviolet irradiation of the *N*-oxide (**102**) probably converts it into the oxaziridine (**103**) which may be reduced to the non-oxygenated compound (**104**) with triethylphosphite. Peracid epoxidizes (**103**) (*R* = Me), and converts (**104**) (*R* = H) into a mixture of the 5-imidazolinone (**105**) and a little *N,N'*-dioxide (Scheme 54) $\langle 92JHC803 \rangle$.

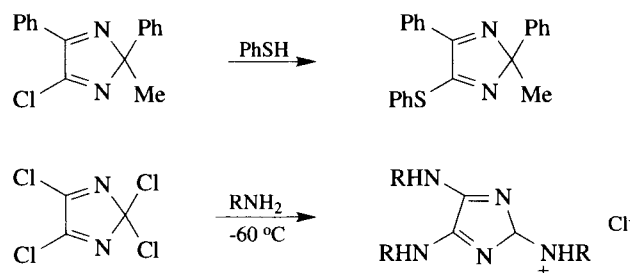


Scheme 54

Lead dioxide in methanol converts 2*H*-imidazole 1,3-dioxides into stable nitroxide radicals $\langle 91IZV2113, 91IZV2122 \rangle$ (see Section 3.02.7.2.8).

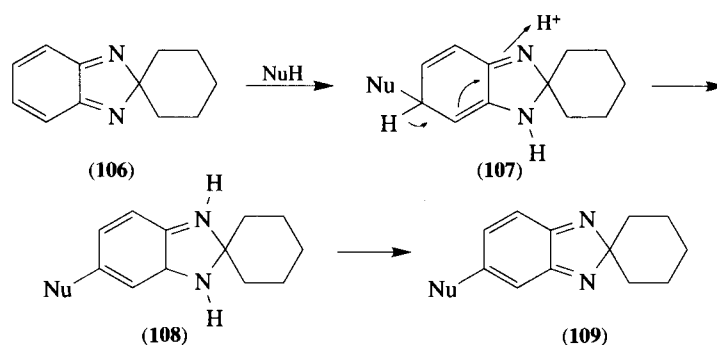
Nucleophilic attack at ring carbon atoms is well known with suitably substituted 2*H*-imidazoles; chlorine atoms at C-4 or C-2 can be replaced by nucleophiles (Scheme 55) $\langle 83BSB781, 84AHC(35)375 \rangle$.

Studies of the nucleophilic substitution of 2*H*-benzimidazole-2-spirocyclohexane (**106**) indicate that sulfur nucleophiles attack via an initial Michael-type 1,4-conjugate addition, followed by a prototropic shift in the adduct (**107**). When the nucleophile is electron withdrawing (e.g., phenyl-



Scheme 55

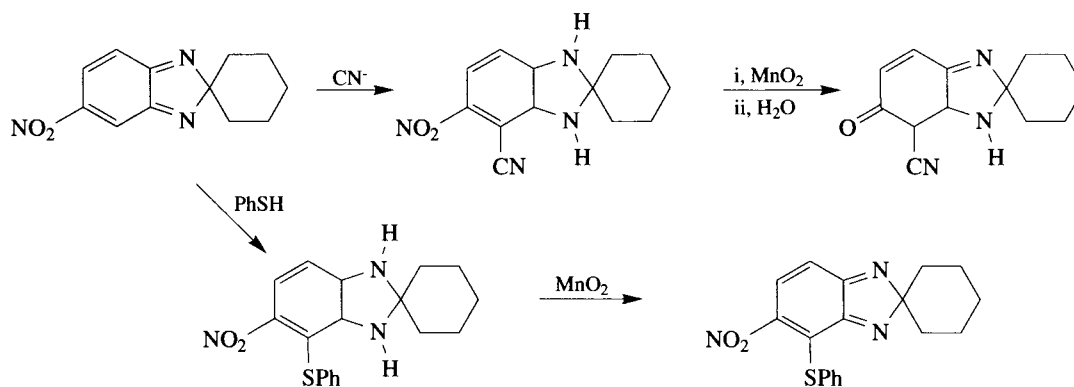
sulfonyl) 1,3-dihydro products (**108**) are isolated. If the nucleophile is electron donating the adducts are oxidized *in situ* (Scheme 56).



Scheme 56

The parent compound is so reactive towards thiols that up to four sulfur groups can be introduced. In isopropanol at -10°C , however, the monosubstituted compounds (**109**) ($\text{Nu} = \text{PhS}$) can be made in reasonable yield. Further nucleophilic substitution of 5-nitro and 5-phenylsulfonyl derivatives occurs at the 4- and 6-positions; the 1,3-dihydro products are isolated <92JCS(P1)685>. Conditions have been devised for substitution of one or two chlorines in 5,6-dichloro-2*H*-benzimidazoles using amines, thiolate, or oxyanionic nucleophiles in ethanol <88S871>. Indeed nucleophilic displacements of hydrogen are not uncommon (Scheme 57) <90HCA902>.

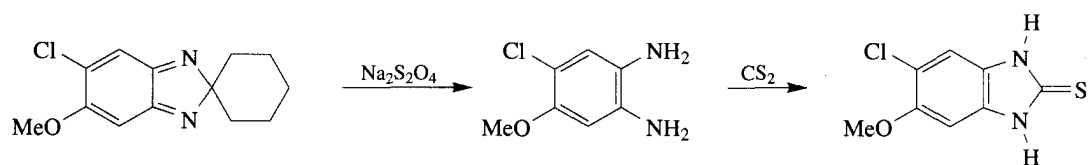
2*H*-Benzimidazoles can also be converted into 1*H*-benzimidazoles by a ring-opening–ring-closure sequence (Scheme 58) <92JCS(P1)3129>.



Scheme 57

(ii) 4*H*-Imidazoles

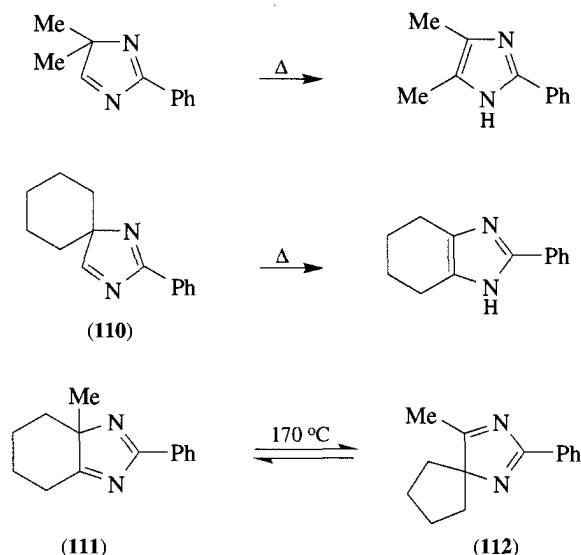
A review devoted to these compounds has appeared <84AHC(35)413>. 4*H*-Imidazoles (**4**) also include the diazafulvenes which are designated as intermediates in some reactions of 1*H*-imidazoles



Scheme 58

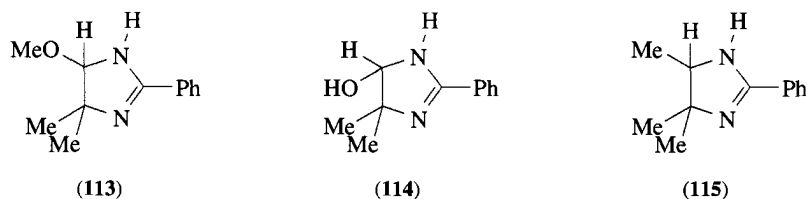
<86JOC3228, 86TL159>. Difluorodiazafulvene is an intermediate in the conversion of 4-trifluoromethylimidazole into the nitrile <86JOC3228>.

Like 2*H*-imidazoles, the 4*H*-isomers rearrange thermally to give the more stable 1*H*-compounds, but migration is to carbon in this instance <83CC1082, 87JCS(P1)1389, 91JCS(P1)335, 92PHC107>. When heated, 4,4-dimethyl-4*H*-imidazole rearranges quantitatively to the 4,5-dimethyl-1*H*-isomer by successive (1,5)-methyl and -hydrogen shifts. There is better orbital overlap in the transition state for migration to carbon than to nitrogen <87JCS(P1)1389>. Similarly the 2-phenyl-4-spiro compound (**112**) rearranges cleanly when warmed in DMSO. The shift is much more facile than in the 4,4-dimethyl-2-phenyl analogue <83CC1082>. The reverse thermal rearrangement of (**111**) to (**112**) was able to be followed by NMR methods but less than 20% of the spiro compound was formed, and the level remained the same when the mixture was cooled to room temperature (Scheme 59) <91JCS(P1)335>.

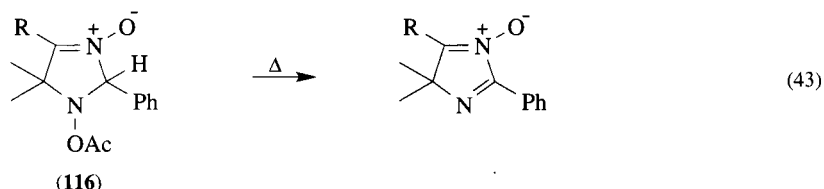


Scheme 59

When heated in methanol 4,4-dimethyl-2-phenyl-4*H*-imidazole does not rearrange; instead (**113**) is formed. Aqueous acid treatment or chromatography on alumina cleaves the ether function <83CC1082>. Certainly, in accord with MNDO calculations, 5-unsubstituted 4*H*-imidazoles are prone to nucleophilic attack in the 5-position. The hydrate (**114**) is formed when 4,4-dimethyl-2-phenyl-4*H*-imidazole is adsorbed on alumina, and addition across the 1,5-bond also occurs with methylmagnesium bromide (giving (**115**)) <87JCS(P1)1389>. In 5-amino-4*H*-imidazoles both water and aqueous acid replace the amino group to give the 4*H*-5-imidazolone. Methyl iodide and acetic anhydride react specifically at the exocyclic nitrogen <85JHC537>.

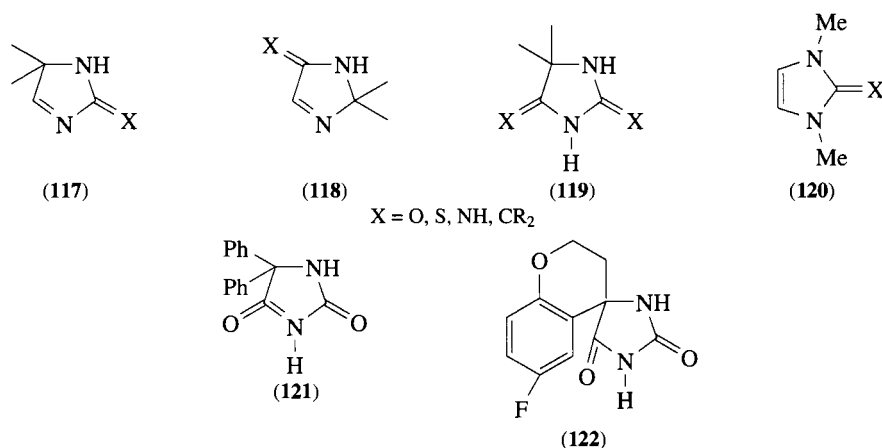


4*H*-Imidazole *N*-oxides and *N,N'*-dioxides, which are made by oxidation of 1-hydroxy-3-imidazoline 3-oxides or 1-hydroxy-3-imidazolines with lead or manganese dioxides, undergo facile covalent hydration and oxidation to nitroxyl radicals (see Section 3.02.7.2.8). Oxidation of 5-ethyl-4*H*-imidazole 1,3-dioxide converts the ethyl group into acetyl. The 1-acetoxy-3-oxide (**116**) eliminates acetic acid when heated (Equation (43)). Although 2- and 5-aryl-4*H*-imidazole 1,3-dioxides are stable, the 5-alkyl analogues are less so because of the lability of their alkylnitron groups <88CHE1355>.

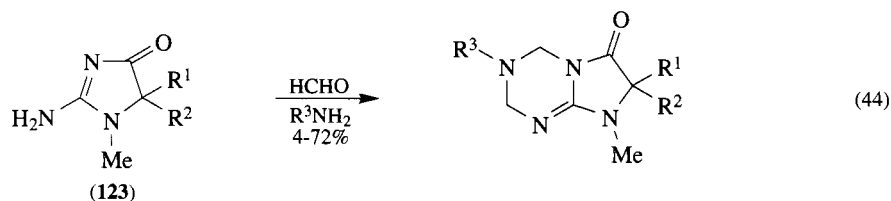


(iii) Others

A number of other structures fall under the heading of isomers of aromatic derivatives (**117**)–(**120**). Of these, the most important are the 5,5-disubstituted hydantoin (**119**) (*X* = O). Hypersensitivity to the 5,5-disubstituted hydantoin drugs, dilantin (**121**) and sorbinol (**122**) is believed to be due to the formation of *N*-chloro metabolites. It is known that hypochlorite converts these compounds into mono- and di-*N*-chloro derivatives, and intermolecular chlorine exchange is possible between a 1,3-dichloro derivative and hydantoin to give 1-chlorohydantoin <90JHC1793>. In alkaline medium 5,5-disubstituted hydantoin is ring opened to give α -aminoamides <85JOC267>.

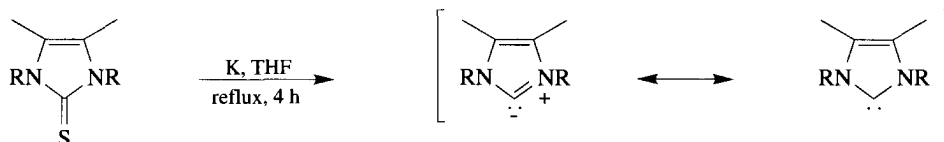


The 2-amino analogues of (**119**), (**123**), react with paraformaldehyde in the presence of primary amines to form the imidazo[3,2-*a*][1,3,5]triazines (Equation (44)) <91CHE601>. 3-Substituted-5-methoxyhydantoin eliminate methanol when heated to form the 2,5-diones <84S270>.



Imidazol-2(3*H*)-thiones are reduced by potassium metal in THF forming stable carbenes (imidazol-2-ylidenes) which react very readily with electrophiles <93S561> (Scheme 60). Bromine oxidizes

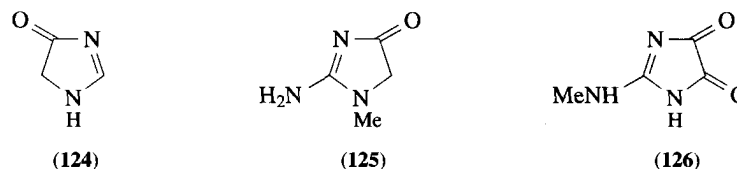
the compounds to disulfides, while iodine merely forms charge transfer complexes. Chlorine, IBr, and cyanogen chloride all react at the sulfur <88JA2586>. Oxidation of 2-allyl-1,3-dicarbethoxy-4-imidazoline (related to (120)) gave a 74% yield of the aromatic 2-allylimidazole <92TL5399>.



Scheme 60

3.02.6.1.2 Compounds in tautomeric equilibrium with aromatic derivatives

Such compounds include 2- and 4(5)-imidazolinones, usually much more stable than the aromatic 2- and 4-hydroxy-imidazoles with which they are in tautomeric equilibrium. The same can be said for the analogous thiones. 2-Imidazolin-4-one (124) is a high boiling, dense liquid which darkens in air <84LA831>. Creatinine (125) also exists mainly as the imidazolinone. Oxidation with mercury(II) acetate converts it into creatone (126) in a reaction which must also involve a Dimroth rearrangement. In aqueous acid 2-amino-1-methylimidazole-4,5-dione also rearranges to (126) <87BCJ4115>.



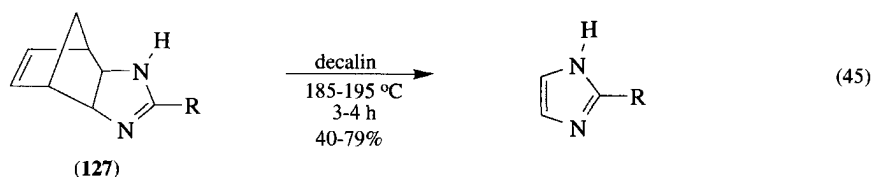
3.02.6.2 Dihydro Compounds

3.02.6.2.1 Tautomerism and interconversion

Imidazolines can exist as the 2-, 3-, or 4-isomers ((5)–(7)), and whereas (5) can exist as a pair of tautomers, any proton shift in (6) will give (7) by rearrangement. Hydrolysis of *N*-unsubstituted 3-imidazolines (6) to α -aminoketones presumably occurs via (7). “Nickel boride”, prepared *in situ*, transforms 3-imidazolines into 2-imidazolines by double-bond migration <86H(24)2871>.

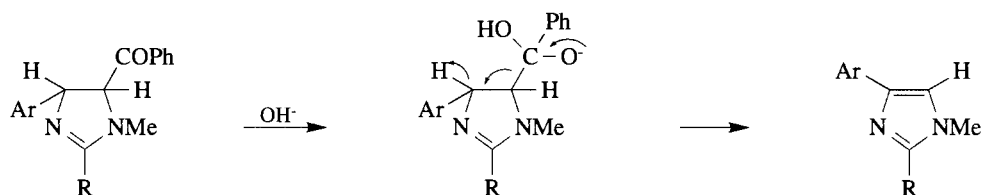
3.02.6.2.2 Aromatization

The 3- and 4-isomers are more readily aromatized than 2-imidazolines which are cyclic amidines and hence resonance stabilized (see CHEC-I) <80AHC(27)241>. Heating in decalin, however, transformed (127) into a 2-substituted imidazole by a retro-Diels–Alder sequence (Equation (45)) <93JOC3387>.



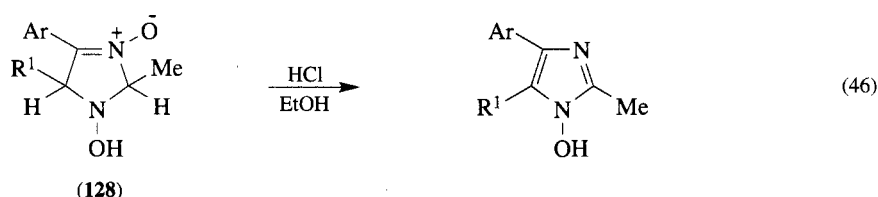
Oxidative methods have also been successful (e.g., barium permanganate) <90JA3452>. Heating in the presence of nitrogen can be successful, but a solvent like chloroform can insert to form a pyrimidine <80JCS(P1)1431>. Palladium and carbon dehydrogenates 2-mono- and 2,4-di-substituted

imidazolines, but results are mixed with 4-mono-substituted compounds <90SC2683>. Reaction with alkali may be fruitful if there is a group capable of elimination present (Scheme 61) <85CHE1296>.

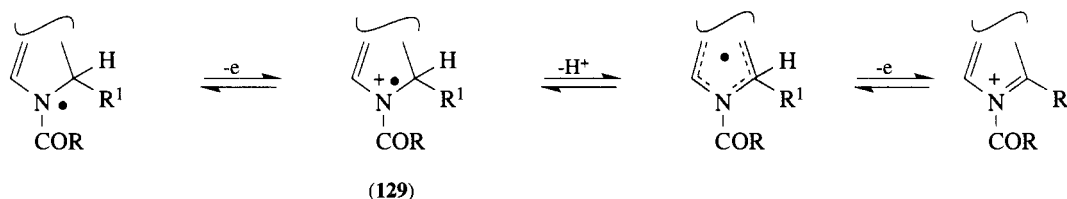


Scheme 61

Ethanolic HCl aromatizes 4-aryl-3-imidazoline 3-oxides (**128**), and heating *in vacuo* or with 10% sodium hydroxide may also be effective (Equation (46)) <86S704>.



4-Imidazolines and 1,2-dihydrobenzimidazoles can be aromatized electrochemically. The main pathway is probably by loss of a proton from the cation radicals (**129**) followed by loss of another electron (Scheme 62) <82CHE272>.

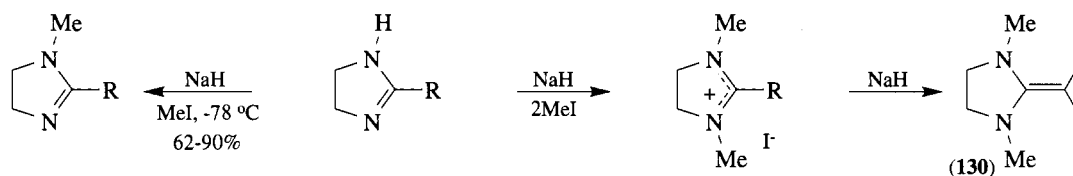


Scheme 62

3.02.6.2.3 Other reactions

(i) 2-Imidazolines

2-Imidazolines (**5**) are quite strongly basic compounds, and they are also readily *N*-alkylated or *N*-acylated to form 1-alkyl or -acyl derivatives or 1,3-disubstituted salts. With nonyl bromide 2-methyl-2-imidazoline gives 2-methyl-1-nonyl-2-imidazoline and *N*-acetyl-*N,N'*-dinonylethylenediamine, formed as a consequence of hydrolytic decomposition of the hydrobromide salt <92KFZ48, 94H(37)689>. Improved alkylations involve pre-generation of the imidazoline anions. With excess alkyl halide the quaternary salt is formed, but suitable 2-substituents allow deprotonation by sodium hydride to give 2-alkylideneimidazolidines (**130**) (Scheme 63) <87CB2053>.



Scheme 63

(131)

(131a)



Scheme 65

It is known that imidazolines are quite susceptible to ring cleavage by aqueous acids or alkalis. The acidic reagents protonate a nitrogen thereby activating C-2 to attack by water; hydroxide ion attack at C-2 or at the 1,2-bond takes place in basic media $\langle 81JHC933 \rangle$. Lithium aluminum hydride, or borane in THF, reduces 1,3-dialkyl-2-imidazolinium salts to imidazolidines by hydride attack at the 2-position. Alkaline borohydride, however, induces partial or total over-reduction to give ring-

opened products <92JHC1725>. Nucleophilic substitution reactions have been reported for 2-chloro- <84S170, 91CB2145> and 2-methylthio-2-imidazoline <88JIC296>.

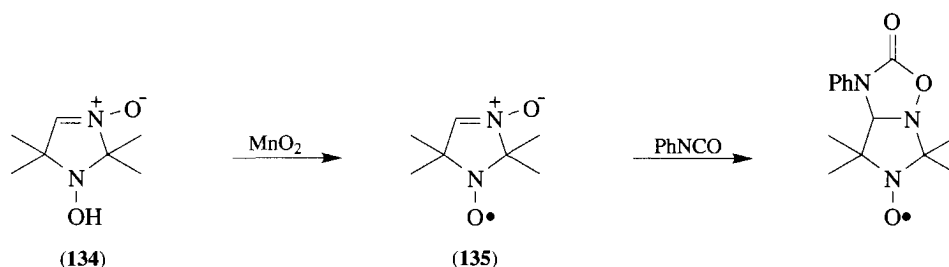
The greater reactivity of 2-ethoxy-2-imidazoline-1-carboxylic acid over 1-carboxy-2-imidazolidinone in aqueous alkali to decarboxylation has been ascribed to tautomeric protonation of N-3 in the former <82TL659>. Irradiation of either the *cis* or *trans* forms of 2,4,5-triphenyl-2-imidazoline gives a mixture in which the *trans* form (**131a**) predominates <75BCJ3669>.

(ii) 3-Imidazolines

3-Imidazolines (**6**) are sufficiently basic to form hydrochloride salts in anhydrous media, but these salts readily hydrolyze with ring opening. Alkylation and acylation occur; 1-acyl derivatives of (**6**) are readily hydrolyzed by aqueous acid to form an aldehyde or ketone and an α -aminoketone (see CHEC-I). On lithiation, 1,2-disubstituted 4-methoxy-3-imidazoline rearranges to the 3-lithio-4-imidazoline which can react with an alkyl halide to form a 5-alkyl-3-imidazoline <93AG(E)1765>.

Most research since the mid-1980s has focussed on the reaction of 3-imidazoline *N*-oxides <84IZV2565, 84TL5809, 85IZV161, 85TL4801, 89MI 302-02, 90CHE643>. 1-Hydroxy-3-imidazoline 3-oxides (**134**) are in tautomeric equilibrium with open chain nitrones. Electron-withdrawing 2-substituents and a donor group in the 4-position favor the cyclic form <89MI 302-02>. Oxidation gives stable radicals (**135**) which form cycloadducts with dipolarophiles (Scheme 66) <85TL4801>. Radicals formed from 3-imidazoline 1-oxides or 1-hydroxy-3-imidazolines can be formylated on nitrogen under Vilsmeier conditions and exocyclically brominated or chlorinated by NBS or NCS on a 4-methyl group <84IZV2565, 85IZV161>. The 4-phenyl derivatives are *ortho* nitrated <84TL5809>, and a nitrile group in the 4-position reacts normally with nucleophiles <84MI 302-02>.

3-Imidazolines (**120**) ($X = CH_2$), which couple readily with 2-methoxythioimidazolium salts, can be made by deprotonation of a suitable 2-methylimidazolium salt by methyllithium <93LA1149>.



Scheme 66

(iii) 4-Imidazolines

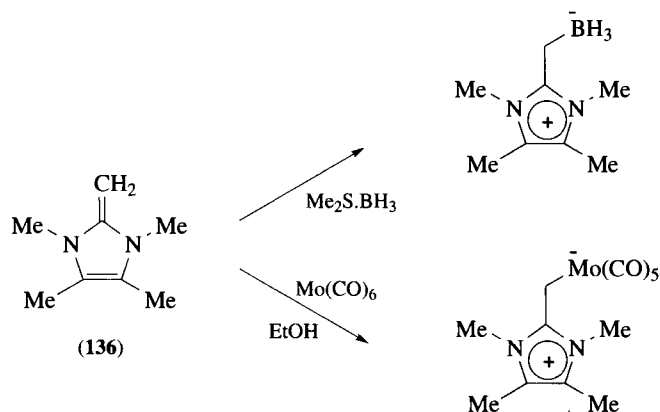
4-Imidazolines (and isomers) can act as dienophiles in Diels–Alder reactions (see CHEC-I). The ylide properties of 1,3,4,5-tetramethyl-2-methylene-4-imidazoline (**136**) are demonstrated by the reactions of Scheme 67. This compound has the π -electrons delocalized over the whole ring and the exocyclic double bond which shows characteristic shortening <93CC1136>.

3.02.6.3 Tetrahydro Compounds

Imidazolidines can be regarded as aldehyde ammonias which resist aromatization.

3.02.6.3.1 Ring fission

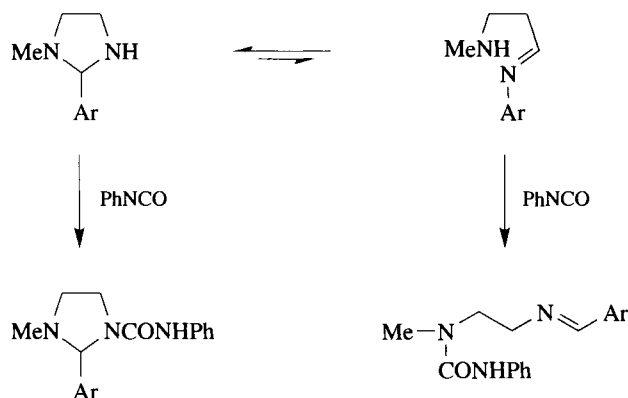
The range of acidic reagents which cleave imidazolidines has been summarized in CHEC-I. The compounds are resistant to cold dilute alkali. Although they are subject to ring-chain tautomerism, the cyclic form is usually dominant. Indeed, with 2-isopropyl-1-methyl- and 1-methyl-2-(*p*-nitrophenyl)-imidazolidines only the cyclic forms exist. In some other analogues evidence of both



Scheme 67

tautomeric forms can be gleaned from their reactions with isocyanates (Scheme 68) $\langle 80\text{H}(14)1313, 90\text{JOC}1772 \rangle$.

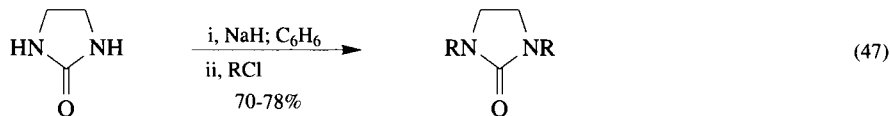
Thermal fragmentation of imidazolidines in the presence of dipolarophiles causes a tandem cycloreversion–cycloaddition reaction which leads to cycloadducts $\langle 89\text{T}4649 \rangle$.



Scheme 68

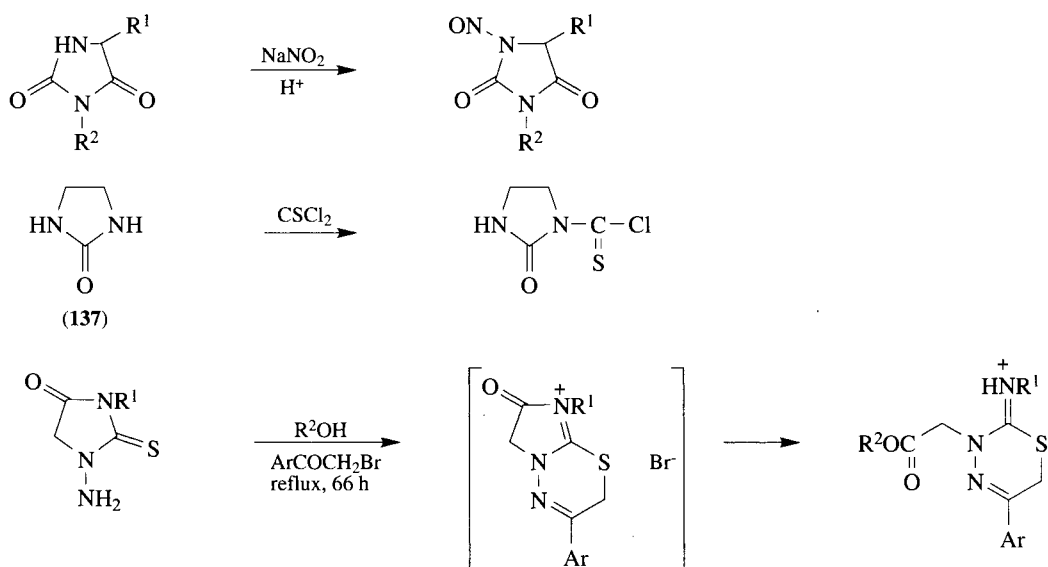
3.02.6.3.2 Other reactions

Alkylation of imidazolidines (and their oxo and thio derivatives) is usually carried out in the presence of a strong base such as sodium hydride $\langle 86\text{JOC}2228, 91\text{JA}8546, 91\text{PHA}670 \rangle$, potassium carbonate in DMF $\langle 89\text{S}38 \rangle$, or potassium hydroxide in DMSO (Equation (47)) $\langle 82\text{JOC}2787 \rangle$.



Initial *N*-silylation followed by reaction with an alkyl halide has also been reported $\langle 91\text{PHA}670 \rangle$. *N*-Acylation is achieved similarly $\langle 90\text{TL}6763, 91\text{JHC}41, 91\text{TL}4791 \rangle$, and *N*-halogenation $\langle 84\text{MI} 302-03, 90\text{JHC}1793 \rangle$, *N*-nitrosation $\langle 84\text{CHE}1160, 93\text{JCS(P}2)1561 \rangle$, and *N*-cyanation $\langle 85\text{JHC}1025 \rangle$ are also known.

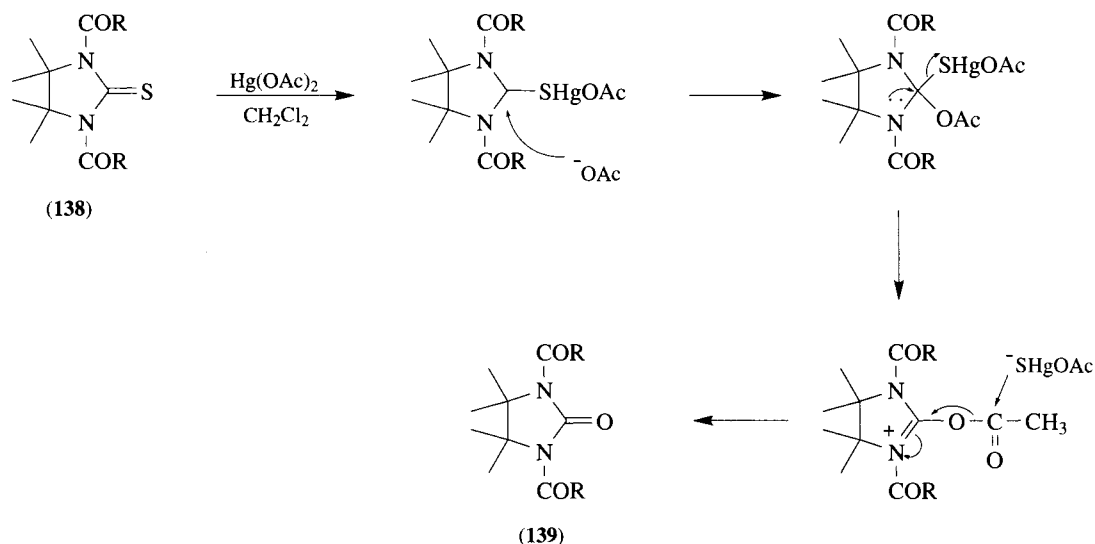
Alkylating and acylating agents, however, can frequently react with a substituent such as amino, oxo, or thione (Scheme 69) <89S518, 91CHE1221, 91JHC41, 92SC145>.



Scheme 69

Oxo functions can be reduced to hydroxy by sodium borohydride <84JOC4745, 89JHC1523> or lithium aluminum hydride <82JOC2787>. With excess reagent the hydrocarbon may form even though cyclic ureas like (137) reduce much less readily than other carbonyl compounds. For *N*-substituted derivatives the ease of reduction increases in the order $\text{Ph} > \text{PhCH}_2 > \text{Me} > \text{Et}$ <86JOC2228>. Deacylation of *N*-acyl derivatives is achieved by hydrogenolysis <86H(24)25>.

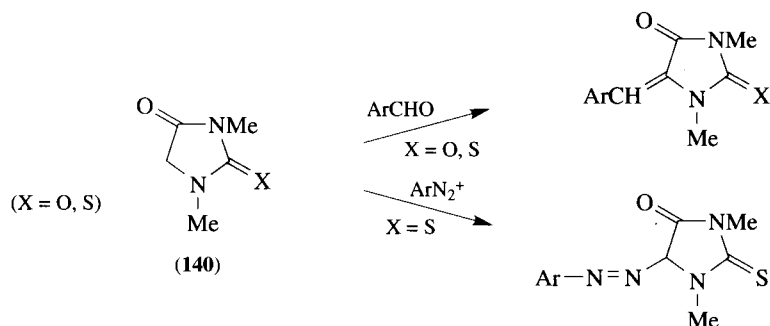
Acid hydrolysis will often convert thione, thioalkyl, and imino derivatives into the oxy analogues, and sulfur functions can also be directly oxidized to oxo <85PS(22)49, 91TL4791>. When mercuric acetate was used to convert the 1,3-diacylimidazolidin-2-thione (138) into the corresponding imidazolidinone (139) the process was believed to proceed as in Scheme 70.



Scheme 70

The hydrogen atoms at C-5 of hydantoins (140) ($\text{X} = \text{O}$) and some other imidazolidinones are sufficiently acidic for the compounds to form benzylidene derivatives at that position. The thione

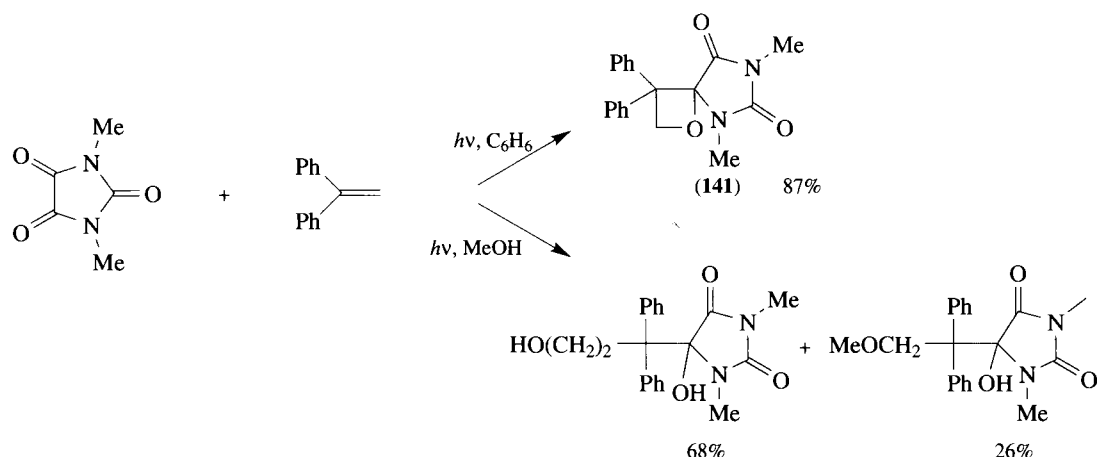
(**140**) ($X = S$) reacts with diazonium salts to form 5-arylhydrazones, and is 5-aminomethylated under Mannich conditions. The dioxo analogue, however, does not take part in the second two reactions <87MI 302-01> (Scheme 71). 2-Alkylideneimidazolidines take part in inverse Diels–Alder synthesis <87TL2681, 87TL6027>, and they are *C*-alkylated by alkyl halides in neutral media <94H(37)1233>.



Scheme 71

Chiral imidazolidinones have been kinetically resolved with the aid of homochiral lithium amide bases <91SL515>.

Photolysis of 1,3-dimethylimidazolidinetetriones (parabanic acid derivatives) in the presence of alkenes in benzene solution results in the formation of spiroketones (**141**). In protic solvents, however, solvent is incorporated into the products (Scheme 72) <89JOC2359>.



Scheme 72

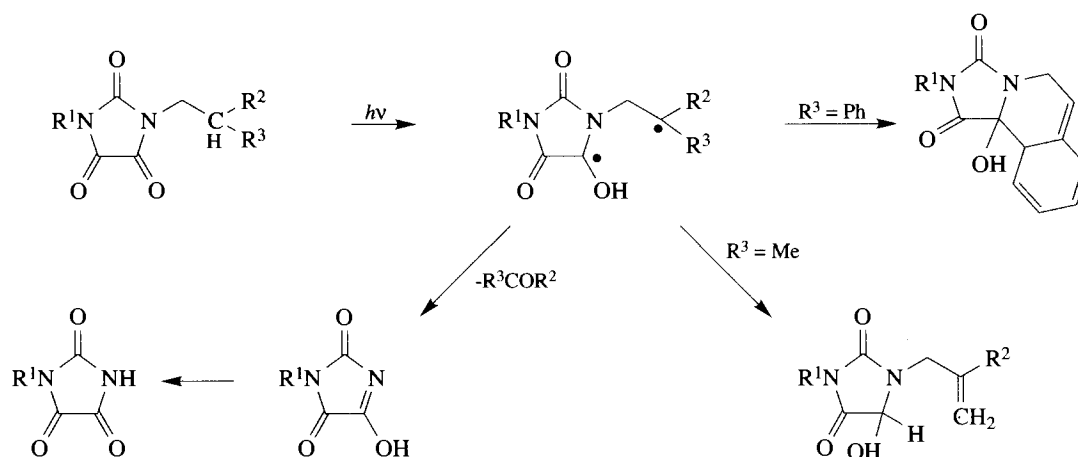
When the *N*-alkyl side chain is sufficiently long intramolecular cyclization can occur on irradiation. Intramolecular hydrogen abstraction may lead to products of elimination, disproportionation, and cyclization with the product composition dependent on the substituents present (Scheme 73) <84TL3327>.

3.02.7 REACTIONS OF SUBSTITUENTS

3.02.7.1 Substituents on Carbon

3.02.7.1.1 Reactions of substituents involving ring transformations

Dimroth rearrangement seems to be almost unknown for the fully aromatic compounds (but see Sections 3.02.5.1.2 and 3.02.7.1.6(i)).



Scheme 73

3.02.7.1.2 Fused benzene rings

(i) Unsubstituted

Benzimidazole is subject to *N*-alkylation, *N*-acylation, etc. in much the same way as imidazoles, but the fused benzene ring reduces reactivity as it does the basicity of the compound. The electron-withdrawing properties of the fused homocyclic ring increase the facility with which nucleophilic substitution occurs at C-2. Electrophilic substitution reactions tend to occur preferentially in the 5(6)-positions. As most electrophilic substitution reactions involve Lewis acids it is the benzimidazolium species which is substituted; in this substrate the annelated benzene ring is by far the more reactive, but substituents can modify this general regiochemistry and ease of attack. Chlorination, bromination, and nitration of 2-aminobenzimidazole take place initially at C-5, and subsequently at C-6 <83S861>. Attempted nitration of 1-picrylbenzimidazole using 100% nitric acid and 96% sulfuric acid gave a mixture of products (initially 5,6-dinitro) but the compounds proved to be unstable <88BSF356, 92AJC525>. With oleum at elevated temperatures benzimidazole is 5(6)-sulfonated. With solutions of sulfur trioxide in dichloromethane (cf. see Section 3.02.5.3.3) yields of 60–83% are possible, but at low sulfur trioxide concentrations charge-transfer compounds form <87CHE1084>.

Only a few electrophilic substitutions will take place in the 2-position of benzimidazole, for example, acylation in the presence of triethylamine. Brief heating with excess acid chloride and triethylamine, or reaction at elevated temperatures gives 2-acyl products in 75–94% yields, but the reaction conditions which are suitable for imidazole failed, leading to the formation of dimers <83CHE37>. Treatment of 1-tributystannylbenzimidazole with very reactive alkyl halides also yields 2-substituted products <84TL5555>. The most fruitful method for introducing electrophiles into the 2-position of benzimidazole is to treat the 2-anion (generated by lithiation of the 1-protected species) with an electrophile <87JCS(P1)775, 89JHC829, 89JOC2949, 90JOC1399>.

Nucleophilic attack at C-2 or H-2 is also enhanced by benzannellation (e.g., lithiation takes place there). The 2-proton is quite acidic as is a 2-methylene group. Indeed 2-methylbenzimidazole may be metallated at the methyl group <86CHE868>, and in the presence of base 2-cyano-methylbenzimidazole is both *N*- and *C*-alkylated (exocyclically) <88CHE281>. Detritiation at the 2-position of benzimidazole occurs 10 to 20 times faster than in imidazole <86CJC1240>.

1-Benzylbenzimidazole (especially when quaternized) can be 2-aminated, and a 2-chloro group is readily replaced by hydrazino, oxo, and other groups <82CHE830, 88BSF139>. Radicals also attack the 2-position of benzimidazoles <82CHE1299> (see also Section 3.02.5.6.2). Benzimidazole quaternary salts form pseudo bases which may be in equilibrium with ring-opened structures (see Section 3.02.5.4.1) <85CHE1398>.

Benzimidazoles are oxidized by 30% hydrogen peroxide in acetic anhydride to give benzimidazolones <83KPS121>. A more powerful oxidizing regime such as acid dichromate can cleave

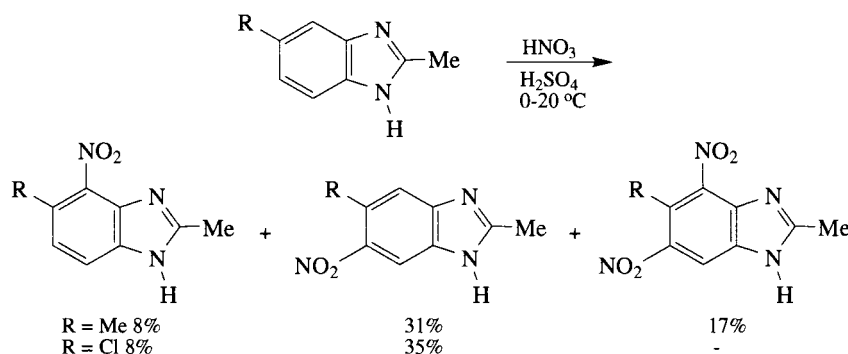
the benzene ring giving imidazole-4,5-dicarboxylic acid. The success of this reaction, however, is dependent on the amount of oxidant, the concentration of the sulfuric acid, and the redox potential of the medium <85MI 302-02>.

(ii) *Substituted*

Although their effects may be modified or offset by the ring itself, substituents usually play an important role in directing electrophilic substitution reactions. As noted above reaction usually occurs at the 5- and/or 6-positions of benzimidazole. When these positions are blocked 4- and 7-substitution can occur, for example, nitration of 2,5,6-trimethylbenzimidazole occurs at the 4- and 7-positions <88JMC260>.

The effects of 5-substituents on basic deuterium exchange at the 2-methyl groups in series of 1,2-dimethyl-5-substituted benzimidazoles appear to be dominated by resonance effects. Donor groups such as amino and methoxy slightly weaken the methyl acidity; acceptor groups such as nitro have pronounced acid-strengthening effects <84CHE1011>.

When electrophilic substitution in the same ring is considered, 5-substituents do not universally control the regiochemistry. 5-Methyl-, 5-methoxy-, and 5-nitrobenzimidazoles are all 6-nitrated, but strong donor groups at C-5 (amino, hydroxy) overcome the usual preference for 6-nitration and favor formation of the 5-nitro products. Earlier suggestions that 2-methyl-5-chloro-, -methoxy-, or -methylbenzimidazoles are 4-nitrated have now been corrected. 5-Chloro-2-methylbenzimidazole gives a mixture of 6- (35%) and 4-nitro (8%) products; the dimethyl substrate gives 4-nitro (8%), 6-nitro (31%), and 4,6-dinitro (17%) products (Scheme 74) <92S1283>. In sulfuric acid 2-(*p*-acetamidophenyl)-5- and -4-chlorobenzimidazoles are 6- and 5-nitrated respectively <91JOU2132>. Mononitration of 5-hydroxybenzimidazole gives 41–94% of the 4-nitro product; subsequent treatment with nitric–sulfuric acids results in the formation of the 4,6-dinitro derivative in 67–89% yield <89IZV2329>.



Scheme 74

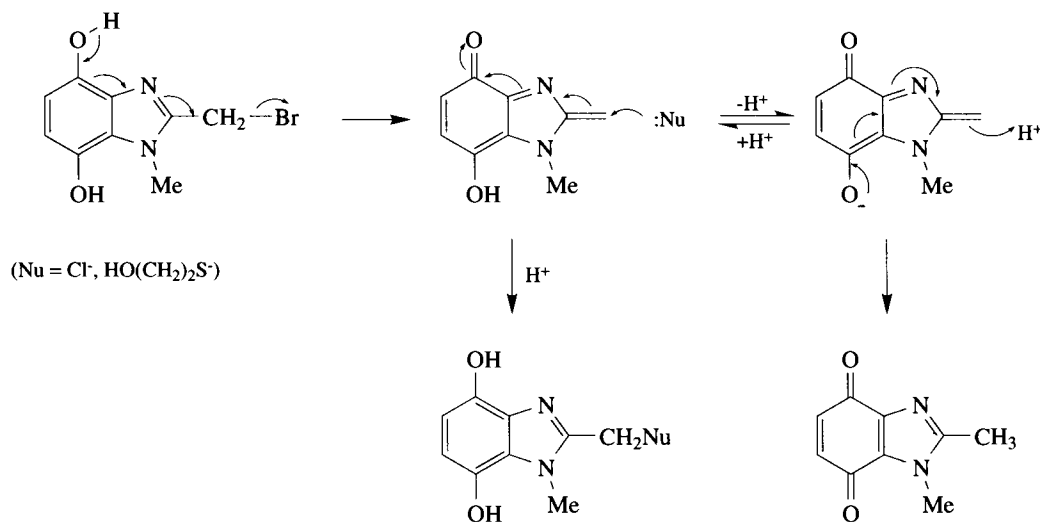
1,2-Disubstituted-5-hydroxybenzimidazoles couple at C-4 with diazonium salts <90IZV662>, while 5-hydroxybenzimidazole is halogenated to give a mixture of 4-mono- and 4,6-dihalogeno products <89IZV1630>. Mannich reaction of 5-hydroxybenzimidazole, too, is at the 4- and 6-positions <85BAU1705>. Chloromethylation of 4,7-dimethoxybenzimidazole at the 5-position is as expected <88JMC260>.

Deuterium exchange in 5-methoxy-1,2-dimethylbenzimidazole is believed to occur at the 4-position, but this regiochemistry was inferred from CNDO/2 calculations of localization energies and π -electron charges and may be incorrect <86CHE557>.

Friedel–Crafts acylation of 2-benzimidazolone and its 5-methyl derivative with aliphatic acid chlorides occurs at the 5(6)-positions. It is necessary to use a large excess of aluminum chloride catalyst because it binds at the oxygen function <84CHE658>.

Electron-withdrawing groups in the 5-position of benzimidazole-2-thiones assist replacement of the sulfur group by chloride when the compounds are treated with thionyl chloride. Neither unsubstituted benzimidazole-2-thione, nor the 1,5,6-trimethyl derivative react <85CHE872>.

In anaerobic aqueous buffer the hydrolysis of 2-bromomethyl-4,7-dihydroxy-1-methylbenzimidazole is believed to follow the pathway of Scheme 75 <86JOC522>.



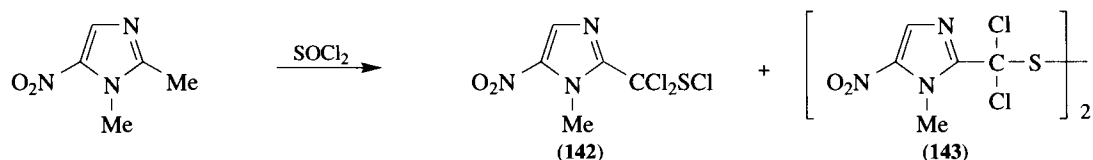
Scheme 75

3.02.7.1.3 Alkyl groups

(i) Reactions similar to those of toluene

The usual oxidation reactions of alkylimidazoles were discussed in CHEC-I. Reactions can sometimes be controlled to form either the aldehyde or the carboxylic acid.

Radical halogenation of methyl groups with such reagents as bromine (in the presence of light), NCS and NBS are known, but not common <84BAU2349, 93ZOB1879>. Treatment of 1,2-dimethyl-5-nitroimidazole with thionyl chloride gives a mixture of the 2-dichlorochlorothiomehyl compound (**142**) and the thioether (**143**) (Scheme 76) <89JHC1819>. Conversion of a 2-methyl group into formyl has been accomplished by successive reactions with NCS and potassium hydroxide <88JCS(P1)2541>.



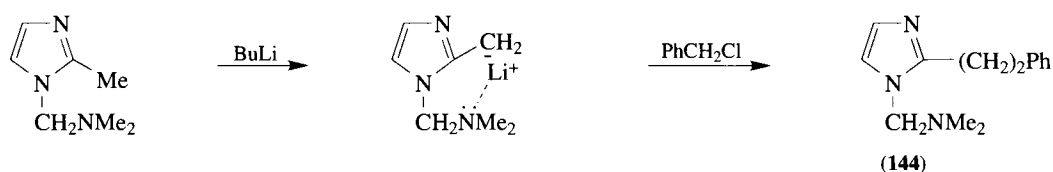
Scheme 76

(ii) Reactions involving "complete" anion formation

Organolithium reagents will sometimes extract a proton from the α -position of a 2-alkyl group <94H(38)2487>. Treatment of 1,2-dimethylimidazole with LDA at -78°C gave a surprising 84% of 2-methylithiation and 18% 5-lithiation <90JCS(P1)1645>, and 1-dimethylaminomethyl-2-methylimidazole was converted by butyllithium into a stabilized anion which reacted with benzyl chloride to form (**144**) (Scheme 77) <90TL5779>. Such metallation reactions also occur quite readily with 1-substituted 2-methyl-2-imidazolines <90JCS(P1)375, 92T5213> and 1-hydroxy-4-methyl-3-imidazoline <82JOU1881>.

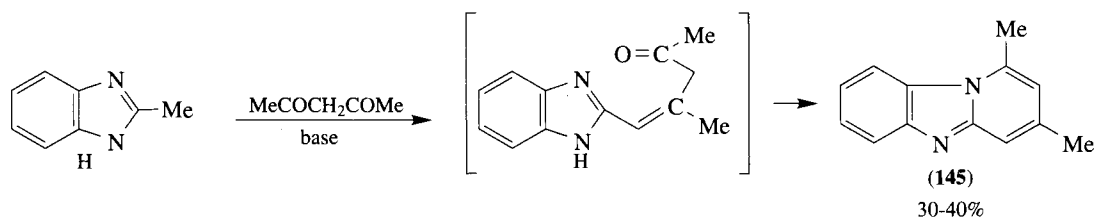
(iii) Reactions involving traces of reactive anions

In aqueous or alcoholic solutions of bases 2-alkylimidazoles give transient anionic species which can react irreversibly with electrophiles such as aldehydes and ketones. A series of 1-substituted



Scheme 77

2-methylimidazoles was found to form the 2-benzylacetic esters when treated with benzyl chloroformate in the presence of triethylamine $\langle 90\text{JMC}781 \rangle$. Similar base-induced condensation of acetylacetone with 2-methylbenzimidazole has been used to prepare 1,3-dimethylpyrido[1,2-*a*]benzimidazole (145) (Scheme 78) $\langle 89\text{CHE}1413 \rangle$. A 4-methyl group adjacent to a nitro function is also active $\langle 85\text{JOC}5892 \rangle$.



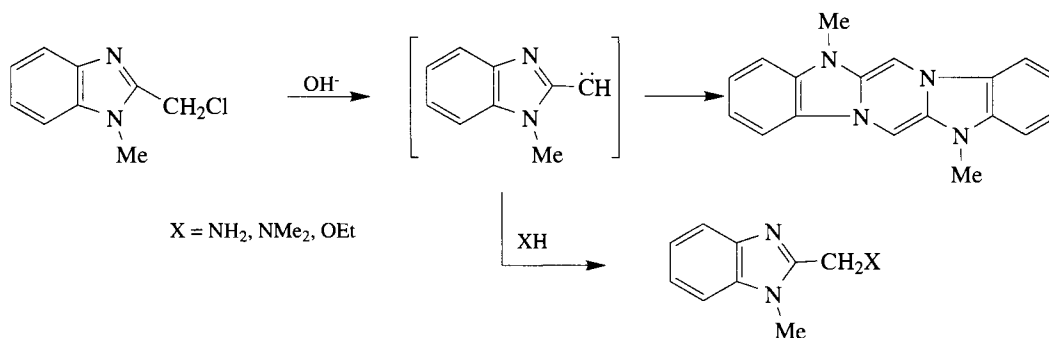
Scheme 78

In ethanolic sodium deuteroxide, metronidazole (1-hydroxyethyl-2-methyl-5-nitroimidazole) exchanges all of its methyl protons for deuterium $\langle 82\text{JHC}659 \rangle$. The kinetics of such base-catalyzed deuterium exchange reactions have been studied for a range of *N,C*-dimethylimidazoles showing the greatest kinetic acidity in 1,5-dimethyl-2-nitroimidazoles. Resistance to exchange in these latter compounds is a function of weak resonance stabilization of the “carbanions”. These kinetic acidities roughly parallel the reactivities in aldol condensations $\langle 81\text{JOC}4717 \rangle$.

3.02.7.1.4 Substituted alkyl groups

(i) Haloalkyl

Chloromethyl and other alkyl halide side-chains on imidazole are able to take part in nucleophilic substitution and elimination reactions. This makes the groups valuable precursors for extending or modifying side chains on the heteroring. The most common transformation is to hydroxyalkyl by reaction with alkali $\langle 89\text{CJC}1139 \rangle$. The hydrolysis of 2-chloromethyl-1-methylimidazole has been shown to be an $\text{S}_{\text{N}}1$ process of the neutral molecule $\langle 89\text{CJC}1139 \rangle$. In contrast, the action of 40% sodium hydroxide on 2-chloromethyl-1-methylbenzimidazole involves initial formation of a carbene by abstraction of HCl from the chloromethyl group. This carbene is rapidly trapped by nucleophiles such as ammonia, amines, and alcohols, but under phase transfer conditions in the absence of a nucleophile, cyclodimerization takes place (Scheme 79) $\langle 89\text{CHE}1192 \rangle$.



Scheme 79

Other nucleophiles which have been used to displace the halogen of halomethyl groups on imidazoles include azide $\langle 89CJC1139 \rangle$, nitronate anions $\langle 85TL1023, 90TL1269, 91EJM167 \rangle$, alcohols $\langle 88JOC1256 \rangle$, amines $\langle 82S1103 \rangle$, thiols $\langle 88CL981 \rangle$, and seleniols $\langle 88JCS(P1)1033 \rangle$. Dehydrobromination of the bromoethyl precursor generates 4-vinylimidazole $\langle 88JHC915 \rangle$. Alkenyl side chains can also eventuate when the substitution products of $S_{RN}1$ reaction between a haloalkylimidazole and nitronate undergo base-induced nitrous acid elimination (see also Section 3.02.5.6.2(ii)) $\langle 85TL1023, 89CR(C)1341 \rangle$.

When heated with 5% aqueous ammonia 2- and 4-trifluoromethylimidazoles are converted into the cyano derivatives, the reactions proceeding via difluorodiazafulvenes. Although yields are high (4-cyano- 87%; 2-cyano-, 99%) the reaction fails for 1-substituted imidazoles which cannot generate the fulvenes $\langle 86JOC3228 \rangle$. This method complements the synthetic approach to cyanoimidazoles from *N*-cyanoimidazolium ylides $\langle 85TL6273 \rangle$.

(ii) Hydroxyalkyl

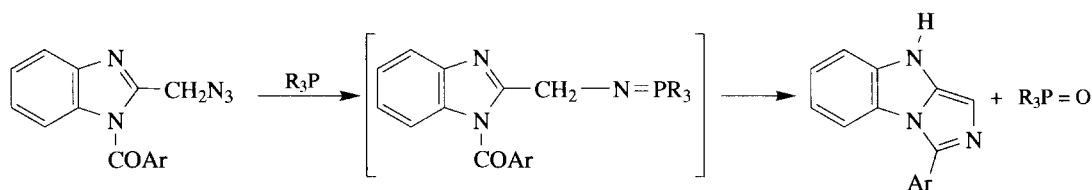
Hydroxyalkyl groups are convenient sources of the aldehyde function, usually by oxidation with active manganese dioxide $\langle 81PJC1055, 83JOC3605, 92H(33)21, 92JHC1021, 92SC2971 \rangle$, or treatment with phosgene in DMSO in the presence of triethylamine $\langle 91JHC1941 \rangle$. The late access to imidazolecarbaldehydes from lithiated derivatives will probably reduce the use of oxidative procedures (see Section 3.02.5.5.1). 2-(1'-Hydroxyalkyl)imidazoles can be oxidized to the ketones with such reagents as pyridinium chlorochromate $\langle 84TL3251 \rangle$, or by autoxidation $\langle 87H(26)1877 \rangle$.

Conversion of hydroxyalkyl into haloalkyl requires acidic conditions, for example, thionyl chloride $\langle 82S1103, 88CL981 \rangle$. The compounds are readily converted into esters with acid chlorides or anhydrides $\langle 82CJC723 \rangle$. Hot acetic anhydride, though, was found to induce elimination in 2-(1'-hydroxyalkyl)-1-methylimidazoles giving the 2-ethenyl products $\langle 90S78 \rangle$. With thiols in acetic acid, thioethers are formed $\langle 88SC1581 \rangle$, while alkyl halides react in the usual way to give ethers $\langle 92EJM551 \rangle$. Nitrate esters can be prepared and converted by one equivalent of a non-nucleophilic base into aldehydes $\langle 82JOC2661 \rangle$.

(iii) Other substituted alkyl substituents

The methylene of 2-cyanomethylbenzimidazole is sufficiently acidic to be nitrosated and alkylated in the presence of base $\langle 88CHE281 \rangle$. It is possible to convert 5-(1'-cyanoalkyl)-4-nitroimidazoles into the 5-keto derivatives $\langle 86JHC913 \rangle$.

With tertiary phosphines 1-aryl-2-azidomethylbenzimidazoles form condensed derivatives (Scheme 80) $\langle 89T1823 \rangle$. Mixed nitric and sulfuric acids oxidize the Mannich base, 2,4,5-tris(dimethylaminomethyl)imidazole, to imidazole-4,5-dicarboxylic acid $\langle 89CHE165 \rangle$.



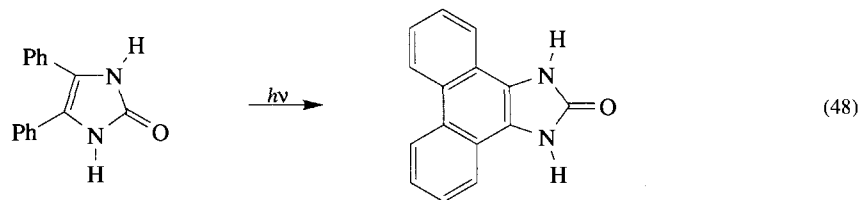
Scheme 80

3.02.7.1.5 Other C-linked substituents

(i) Aryl groups

Electrophilic substitution in *C*-arylimidazoles usually occurs in the *ortho*- and *para*-positions. In most instances the imidazolium species is involved, rendering the aryl substituent by far the more reactive site. Electron-withdrawing substituents in the imidazole ring may alter the usual tendency for *ortho*-*para* attack by electrophiles (see CHEC-I).

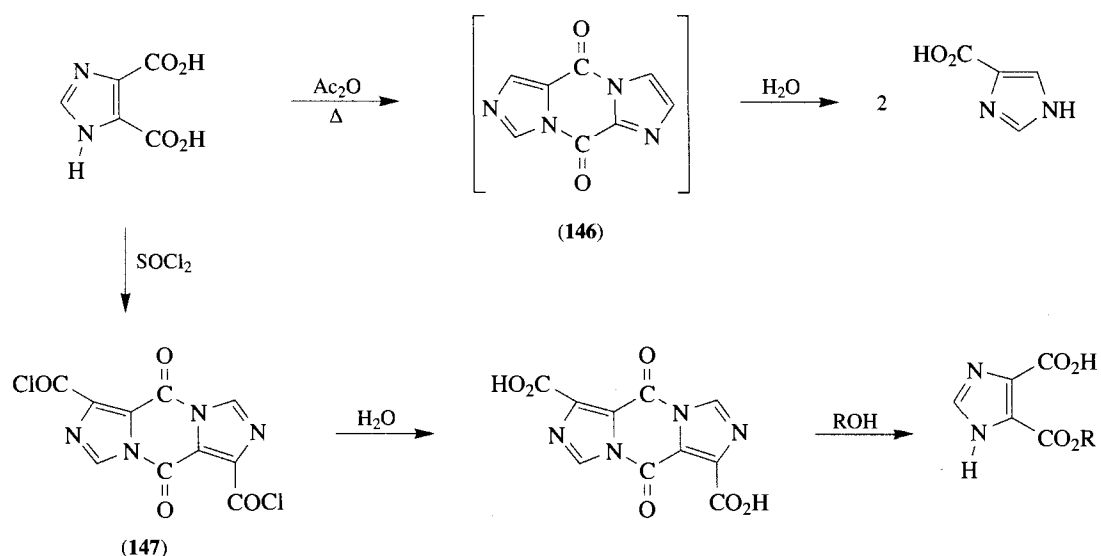
Depending on the substituents on the imidazole or benzimidazole moiety, electrocyclic ring closure can be induced, leading to dihydrophenanthrene and dihydroisoquinoline derivatives (<86JOC3420, 89PIA391>). Oxidative dehydrocyclization is favored under acidic conditions (Equation (48)). The corresponding thiones give the disulfides in similar conditions (<90IJC(B)18>).



(ii) Carboxylic acids and derivatives

The acids are stable compounds which readily form salts, and are subject to decarboxylation and conversion into acid derivatives with the usual reagents. Acid chlorides are usually made with phosphoryl chloride (<82JHC561> or thionyl chloride (<84SC251, 85JHC413>).

When imidazole-4,5-dicarboxylic acid is heated with acetic anhydride, the bis-azolidine (**146**) which is formed readily hydrolyzes in water to give the monocarboxylic acid. This is a novel method of removing one carboxyl group (<82JHC253>), which has been modified to broaden its applicability to the synthesis of mono- and diesters and -amides. Replacement of the acetic anhydride by thionyl chloride forms the related azolidine (**147**) which forms the unstable carboxylic analogue which reacts with nucleophiles such as alcohols and amines (Scheme 81) (<84SC251, 85JHC413>).



Scheme 81

Heating imidazole-4,5-dicarboxylic acid at 180°C with dimethylacetamide also gives the monocarboxylic acid (<88S767>). Although heating failed to decarboxylate 2,4-difluoroimidazole-5-carboxylic acid (<84JOC1951>), it was successful when 4-cyanoimidazole-5-carboxylic acid was heated for 20 hours in nitrobenzene (<83JHC1103>).

Mannich reactions of imidazole-4-carboxylic or the 4,5-dicarboxylic acid gave mixtures of 5-dimethylaminomethylimidazole-4-carboxylic acid and 2,4,5-tris(dimethylaminomethyl)imidazole depending on the reagent ratio. 4-Nitroimidazole-5-carboxylic acid is, however, inert to these aminomethylation conditions. It is more likely that the Mannich reaction involves *ipso*-replacement of carboxy than prior thermal decarboxylation (cf. *ipso*-hydroxymethylation (<83JHC1417>)) (<89CHE165>).

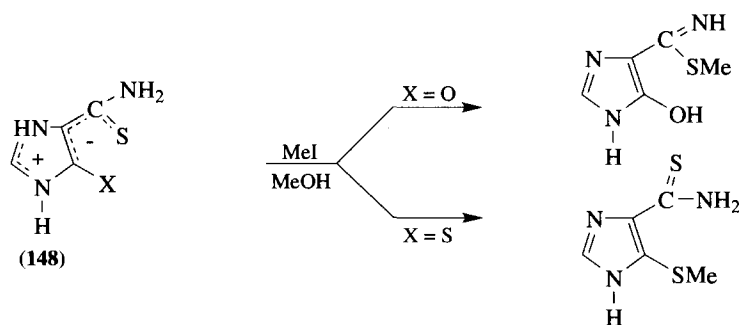
The disodium salt of 1-hydroxybenzimidazole-2-carboxylic acid can be decarboxylated merely by heating in acid (<88JCS(P)1681>). In a Borodin-Hunsdiecker-type reaction alkaline bromination of 4-

nitroimidazole-5-carboxylic acid bromodecarboxylates the substrate <82CHE539>. A 4-dithio-carboxylic acid function can be converted into nitrile (70%) by treatment with lead and ammonium acetates in DMSO at 95–100°C <92JAP(K)05294941>.

Ester groups are converted in the usual ways to amide <82CJC723, 84JOC1951, 85H(23)2247, 85JHC753, 87SC1409> and hydrazide <82CJC723, 87JHC165>, reduced by metal hydrides to hydroxymethyl <84JOC1951, 91JOC4058>, and by dibal-H to carbaldehyde <87CPB4056>. There is a novel synthetic approach to acyl cyanides involving reaction of 1-substituted imidazole-4-carboxylates with diethyl phosphorocyanidate <85CC459>.

Imidazole acid halides are very reactive and are easily converted into other acid derivatives <82JHC561, 84JOC1951>. They cannot, however, be used as precursors of acetyl functions in reaction with lithium dimethylcopper <92JHC1021>.

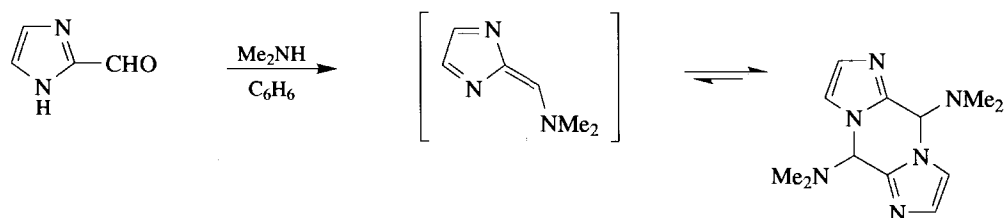
Amides are quite unreactive, but may be converted into nitriles by dehydration using phosphoryl chloride <86JHC679>, the triphenylphosphine-carbon tetrachloride complex in THF, or with dichlorophenylphosphine oxide <87SC1409>. In solution 2-hydroxy(or 2-mercapto)imidazole amides (or thioamides) exist as zwitterions. The thioamides can be made from the amides by reaction with P_4S_{10} . Methylation takes place readily at exocyclic sulfur atoms, and although one would expect harder reagents like dimethylsulfate to attack oxygen and nitrogen centres, this is not observed. Presumably the zwitterionic structures (148) control the selective methylation (Scheme 82) <82CHE731>. The imidazolidine formed when the acid chloride of 1-methyl-5-nitroimidazole-2-carboxylic acid is treated with imidazole reacts with the magnesium salt of a β -ketoacid to form the β -diketone at C-2 <94H(38)503>.



Scheme 82

(iii) Aldehydes and ketones

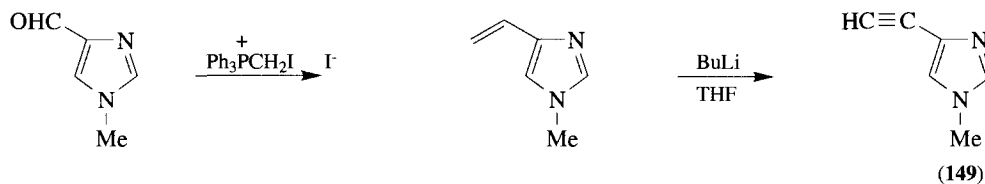
Among the usual reactions that imidazolecarbaldehydes undergo are formation of acetals <82JOC2196, 91JMC1368>, oximes <83AQ99, 91JMC1368>, and Schiff's bases <93JOC974>. When imidazole-2-carbaldehyde is treated with dimethylamine in benzene a dimeric species forms in equilibrium with the monomer (Scheme 83) <93JOC974>.



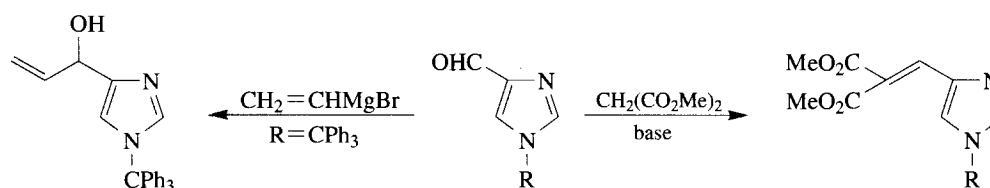
Scheme 83

Wittig reactions are common methods of elaboration of the side chain <83JOC3605, 87CPB4056, 87SC223, 91CI(L)801>. When 1-methylimidazole-5-carbaldehyde is heated with iodomethyl-

triphenylphosphonium iodide, and the iodoethenyl product is treated with butyllithium in THF, the ultimate product is the highly toxic 5-ethynyl-1-methylimidazole (**149**) (Scheme 84) <91CI(L)801>.



An aldehyde function can be reduced to hydroxyalkyl by sodium borohydride <93JOC4642> and other organometallic hydride sources <92LA317>, and will usually take part in condensation reactions with active methylene reagents <91JHC1941, 92H(33)21> or carbanionic species such as Grignard reagents (Scheme 85) <90TL3871, 92LA317>.



Treatment of 2-chloro-1-ribosylimidazole-4-carbaldehyde with sodium cyanide and manganese dioxide gives the 4-carboxamide <87CPB4056>. When synthesizing purine derivatives one strategy is to build the pyrimidine ring on to the preformed suitably 4,5-disubstituted imidazole. The most appropriate 4- and 5-substituents are combinations of amino carboxamide and amino nitrile. Thus reactions which can convert an aldehyde group into nitrile or amide are valuable. Another approach is to heat the aldehydes at 60°C for 2 hours with hydroxylamine to give the corresponding nitrile (via the oxime) in high yield <93JOC4642>. As yet the one-pot reaction using hydroxylamine hydrochloride, magnesium sulfate, and *p*-toluenesulfonic acid as catalyst does not appear to have been used with imidazole carbaldehyde <83SC219>.

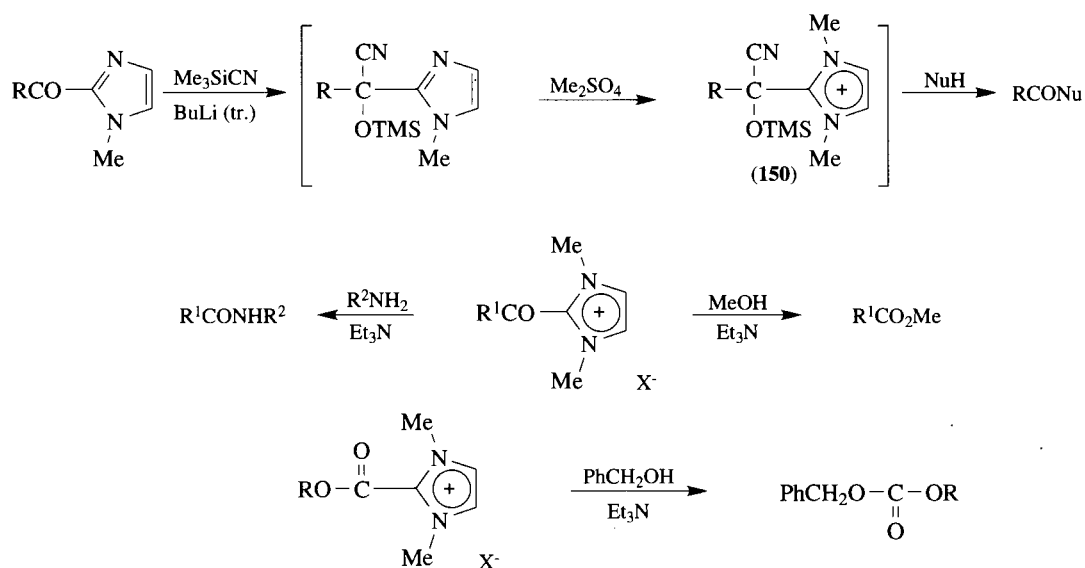
Ketone functions on imidazole can be reduced to secondary alcohols by sodium borohydride, and converted into tertiary alcohols with lithium acetylides or Grignard reagents <88CPB22, 88H(27)457>. They form the usual carbonyl derivatives (e.g., oximes <82JCB(10)27>), and can be chain extended by aldol condensations <91JCS(P1)2691, 94H(38)503>.

Access to 2- and sometimes 4-acylimidazoles is from the hydroxalkyl precursors <80AHC(27)241> (see Section 3.02.7.1.4(ii)), from carbanions derived from *N*-protected imidazoles (see Section 3.02.5.3.6), by photochemical or thermal rearrangement of *N*-acylimidazoles (see Section 3.02.7.2.4), by direct acylation (see Section 3.02.5.3.6), and by ring synthetic methods <83JOC3605, 83S47, 83S576, 84JOC566, 84JOC3494>. Metallation procedures are only useful for making 4-acylimidazoles when C-2 is blocked <85H(23)417, 85JHC57, 86T2351, 94H(38)2487>.

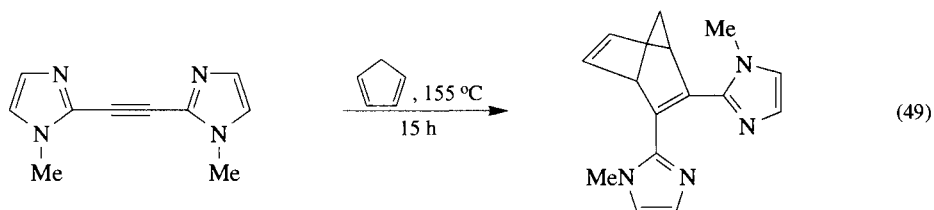
The observation that 2-benzoyl-1-methylimidazole was unchanged on heating with propylamine, 20% sulfuric acid, or 5% potassium hydroxide for ten hours, whereas ethanolic sodium hydroxide converted it into benzoic acid and 1-methylimidazole, indicates a tendency (as in the azolides) to revert to the original imidazoles. Obviously the *C*-acyl bond is much stronger than an *N*-acyl bond, but reactivity towards nucleophiles can be enhanced markedly by quaternization, especially in the quaternary salt of the *O*-silylated cyanohydrin (**150**) <86CPB4916>. A number of examples are shown in Scheme 86. Similarly, 2-ester and 2-amide groups on imidazolium are susceptible to nucleophilic substitutions in which the imidazole moiety is the leaving group. Whereas alcohols and amines react, carbanions are usually unsuccessful reagents (Scheme 86) <94JCS(P1)239>.

(iv) Unsaturated alkyl groups

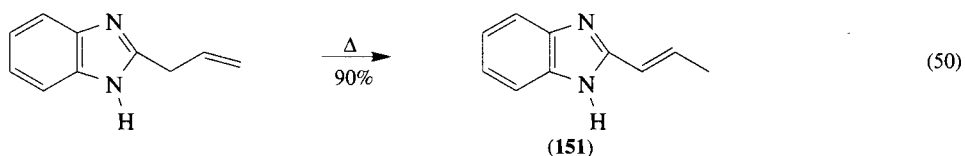
Vinyl and ethynyl groups conjugated to an imidazole ring may not react like aliphatic alkenes and alkynes. They can be catalytically reduced to the saturated (or less unsaturated) species <87SC223, 88JA5571> and cleaved by oxidation <90JHC2189, 93JCS(P2)1511>. The corresponding 4-carbaldehyde is



formed in 71% yield when 1-methyl-2,5-diphenyl-4-styrylimidazole is oxidized with osmium tetroxide (93JCS(P2)1511). Although addition reactions do not always occur normally, Michael additions are known (see CHEC-I), and the compounds can act as dienophiles in Diels–Alder reactions (Equation (49)) (82CHE835, 88JA5571).



Among the photochemical transformations of *C*-alkenylimidazoles is the *cis-trans* isomerization of urocanic acid. In the mixture of (*E*)- and (*Z*)-isomers the latter is stabilized by intramolecular hydrogen bonding (92JHC1621). When 2-allylbenzimidazole is heated the more stable (conjugated) vinyl isomer (**151**) is formed (Equation (50)) (92TL5399).



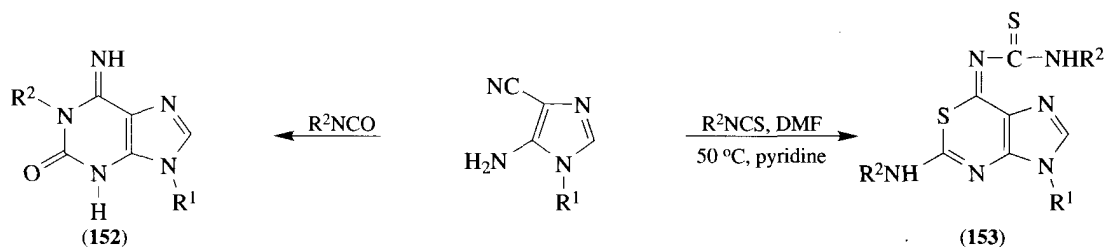
(v) Nitrile groups

Most of the interest in cyanoimidazoles has focussed on the synthesis of 4-amino-5-cyanoimidazoles as precursors to purines. These are available by ring synthetic methods (see CHEC-I) (89H(29)1325, 89JMC119, 91JMC1187), but nitrile groups can be introduced by transformations of amide (see Section 3.02.7.1.5(ii) above), aldehydes (see Section 3.02.7.1.5(iii) above), trifluoromethyl groups (see Section 3.02.7.1.4(i)), diazonium salts (89H(29)1325), oximes (see Section 3.02.7.1.5(iii) above), from lithioimidazoles (90SL277), and by direct reaction with cyanogen chloride or bromide (85TL6273, 88S470).

A nitrile function can be hydrolyzed to amide or carboxylic acid (88S767, 89JMC119), catalytically reduced to the primary amine (91JMC1187), and is subject to addition across the carbon–nitrogen

system <89JMC119, 91JMC1187>. Butyllithium is also able to add to a nitrile group, thereby complicating ring lithiation of cyanoimidazoles <92JHC1091>.

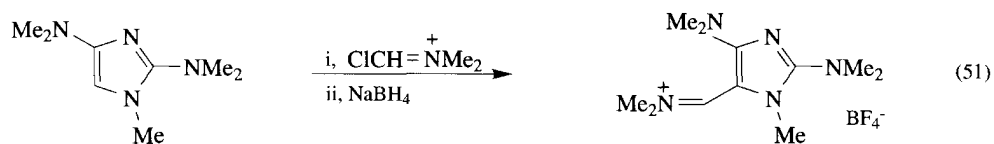
Typical cyclizations of aminocyanoimidazoles are exemplified by the syntheses of the isoguanosine (**152**) <88JHC495>, and the chalcogen, imidazo[4,5-*d*][1,3]thiazine (**153**) (Scheme 87) <88CPB1283, 88JHC495>. There are other examples <91HCA1742>.



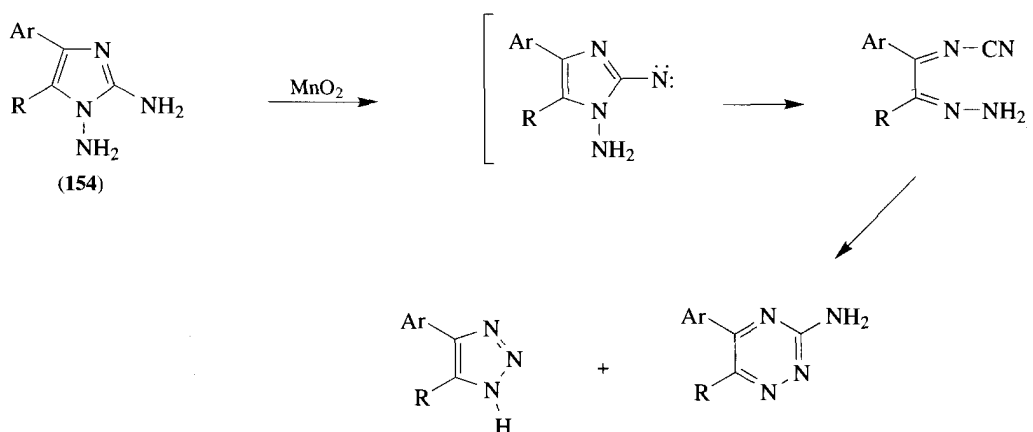
Scheme 87

3.02.7.1.6 Amino and related groups

Aminoimidazoles, usually prepared by ring synthesis or by reduction of the nitro compounds, are not particularly stable in air with the 5-isomers being more stable than 4-aminoimidazoles. 2-Aminoimidazoles are more stable than either of the 4- or 5-isomers <81JOC4717>. The prototropic tautomerism of 4(5)-aminoimidazole has been discussed earlier (see Section 3.02.4.3.2). Amino groups activate adjacent carbons towards electrophilic substitution (Equation (51)) <83TL3563>.



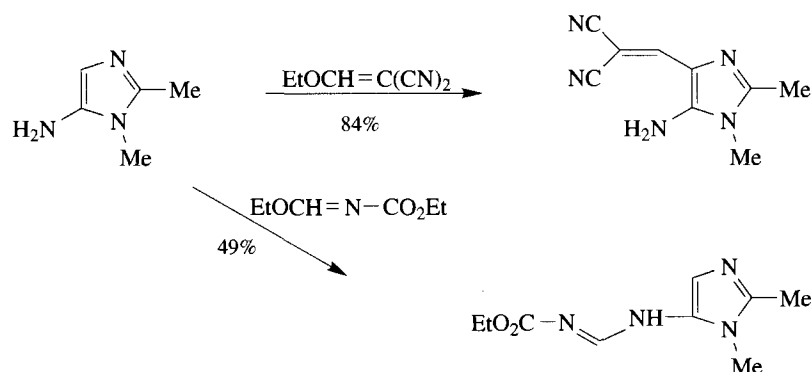
The Dimroth rearrangement is almost unknown in imidazole chemistry <82BCJ1912, 84JHC627, 87BCJ4115> (see also Section 3.02.8.1.1(ii)). Oxidation of 4-aryl-1,2-diaminoimidazoles (**154**) causes ring opening and ultimate rearrangement to a mixture of 1,2,3-triazoles and 1,2,4-triazines, presumably through a common nitrene intermediate. Under the same conditions 1,2-diaminobenzimidazole gives only the analogous benzotriazine and 1-aminobenzimidazole (Scheme 88) <93ACS244>.



Scheme 88

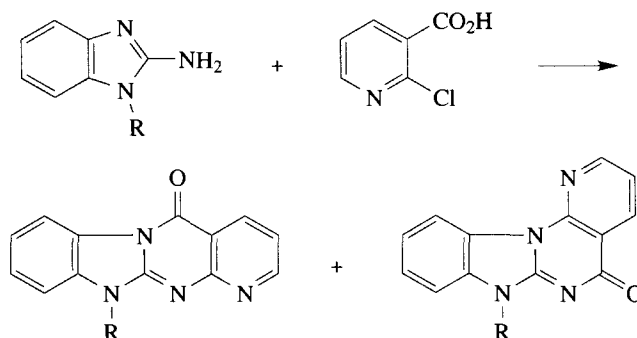
The C-amino substituents possess reduced reactivity towards electrophiles in comparison with an annular nitrogen. Reactions which result in exocyclic substitution may be a consequence of primary annular substitution followed by rearrangement (see CHEC-I). A frontier orbital analysis of elec-

trophilic addition reactions of 5-aminoimidazoles has been used to rationalize the preferences of certain reagents for *N*- or *C*-addition. Isocyanates, isothiocyanates, and diketene all give *N*-addition products with 4- and 5-aminoimidazoles, while DMAD reacts at a ring carbon site $\langle 92\text{JCS(P1)2779} \rangle$. 5-Aminoimidazoles seem to act as soft nucleophiles, hence soft electrophiles favor reaction at the 4-position. Reagents with higher LUMO energies are less likely to react at carbon due to smaller frontier orbital interactions $\langle 92\text{JCS(P1)2789} \rangle$. Frequently, though, mixtures of *N*- and *C*-addition products are formed (Scheme 89) $\langle 89\text{CC551} \rangle$.



Scheme 89

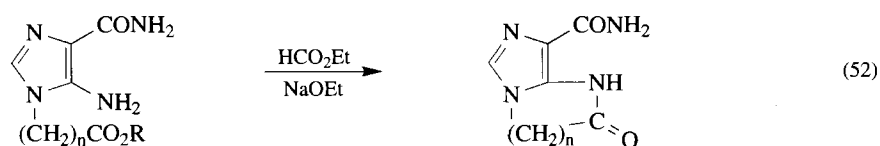
2-Aminobenzimidazoles undergo copper-catalyzed Ullman-type reaction with 2-chloropyridine-3-carboxylic acid $\langle 87\text{G263} \rangle$. Here the exocyclic amino group has been both arylated and acylated (Scheme 90).



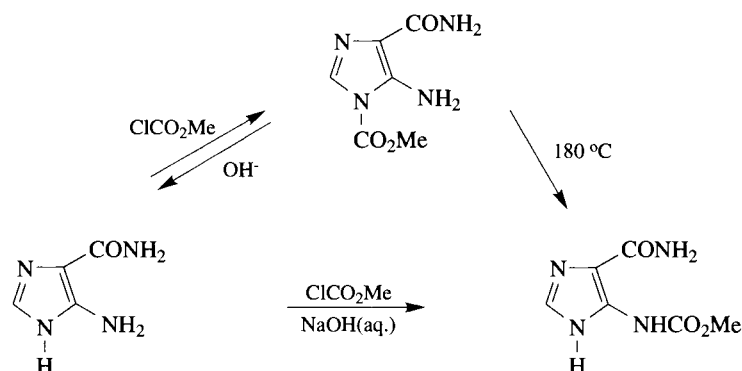
Scheme 90

The reactions of 2-aminobenzimidazoles have been reviewed $\langle 83\text{S861} \rangle$. The compounds form Schiff's bases with carbonyl compounds, with isocyanates and isothiocyanates they give ureas and thioureas, they are subject to 1,3-dipolar addition reactions, and to the formation of carbamates on acylation and aroylation. When aminoimidazoles are acylated there is frequently competition between the annular and exocyclic nitrogen (see above). Acid chlorides and anhydrides (soft) acylate the amino group; chlorocarbonic acid esters (hard) are specific for the heteroatom $\langle 84\text{CHE204} \rangle$. When heated, the *N*-acyl products isomerize (Scheme 91).

Thermal rearrangement of 2-amino-1-methoxycarbonylbenzimidazole to the 2-amido species is believed to proceed through an intermediate imine with concurrent *intra*- and *inter*-molecular rearrangements $\langle 84\text{DOK32, 84ZC57} \rangle$. There are many examples of amino acylation which often result in cyclization (Equation (52)) $\langle 87\text{JHC1155, 90ACS67, 90S360} \rangle$.



Schiff's base formation with aldehydes, ketones and orthoesters is common $\langle 83\text{S861, 88S242} \rangle$ as are similar condensations with isocyanates and isothiocyanates $\langle 88\text{CPB1283, 88JHC495, 91HCA1742,} \rangle$



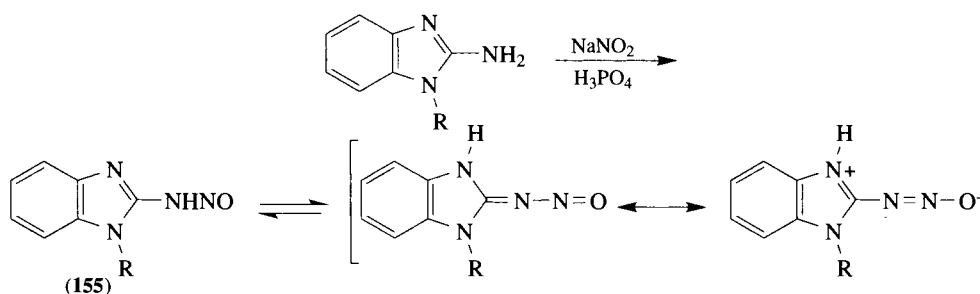
Scheme 91

91JOC2139). These reactions are of value in the synthesis of purine analogues and isomers (85JHC753, 88CPB1283, 91HCA1742). Both 2-amino-imidazoles and -benzimidazoles give iminophosphoranes in aza-Wittig reactions (94H(37)997).

Exocyclic *N*-bromination has been suggested as intermediate in the formation of the unexpected bromination products of 2-amino-1-methylimidazole (93CJC427). Electrochemical oxidation of 2-aminobenzimidazole involves initial formation of a free radical species (at physiological pH) which rapidly dimerizes to a hydrazo intermediate. Further oxidation of this gives an azobenzimidazole (91BSF654).

Primary amino groups on imidazole react with nitrous acid to give diazonium salts by way of primary nitrosamines. These salts can sometimes be isolated and converted into stable diazo anhydrides if the imidazole has a free NH group. Reviews of diazoazole chemistry have appeared (82H(19)559, 86AHC(40)129, 90AHC(48)65).

The primary nitrosamino derivatives (155) of 2-aminobenzimidazoles are quite stable because they can exist in the polarized nitrosoimino form, indicated by strong absorption in the 1360–1350 and 1405–1380 cm^{-1} regions in the infrared, and very strong long-wave absorption in the ultraviolet. (Scheme 92) The nitrosamino group is replaced by phenyl (86%) on prolonged heating in benzene, and by halogen when treated with hydrogen halide in acetonitrile in the presence of copper (yields: X = Cl, 71%; X = Br, 63%) (87CHE1090).



Scheme 92

Diazonium salts form readily when aminoimidazoles are treated with nitrous acid or suitable alkyl nitrites (83JCS(P1)809, 88CPB2730). Imidazole diazonium fluoroborates are highly stable salts which give fluoroimidazoles on photolysis (84JOC1951, 93AHC(57)291). The usual range of nucleophilic substitution reactions of diazonium salts is known (83JCS(P1)809, 88CPB2730, 90AHC(48)65), and coupling reactions are common. In concentrated acid benzimidazole-2-diazonium salts couple (mainly) at the 4-position of 1-naphthol (92CHE58). Indeed, benzimidazole diazonium salts are so reactive that they are capable of coupling with normally quite unreactive arenes (83CHE534, 90CHE538).

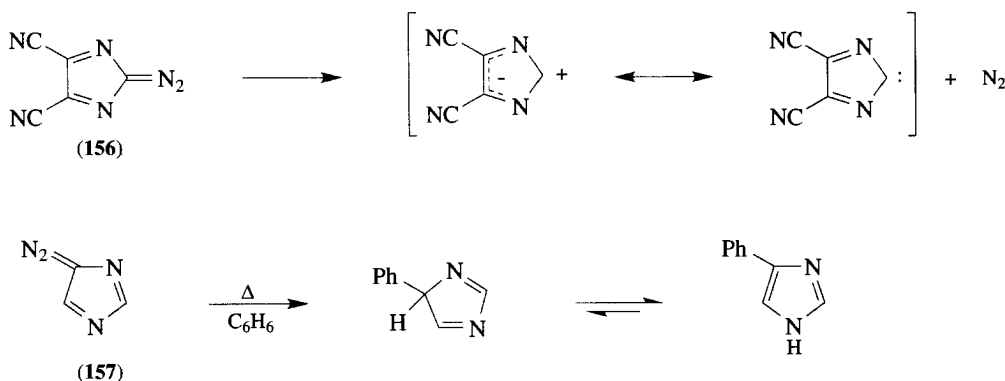
Imidazole diazo anhydrides can usually only be made by conversion of an amino group, using nitrite in strong acids at -10 to -20°C because of the instability of these diazoimidazoles (87JMC2222). Oxidation of a nitroso group has been used in preparation of 4-diazo-5-phenylimidazole (87JMC357). 4-Diazo isomers are more stable than the 2-compounds. In neutral aqueous medium the compounds are present as neutral zwitterions (Scheme 93). In the ^{13}C NMR spectrum there is a large upfield shift in the diazo carbon, while “ortho” carbons are also deshielded. 2-

Diazoimidazoles absorb in the region 312–367 nm in the ultraviolet; the 4-isomers absorb at 308–314 nm. The former do not change their λ_{max} on protonation, in contrast to the 4-diazo compounds <87JMC2222>.



Scheme 93

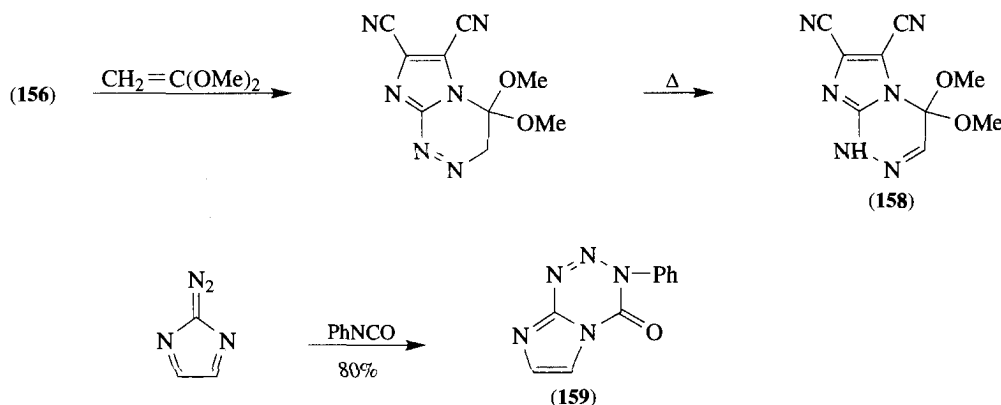
Thermolysis or photolysis of diazoimidazoles causes elimination of nitrogen with formation of a carbene. 4,5-Dicyano-2-diazoimidazole (**156**) forms 4,5-dicyanoimidazole when the carbene reacts with acid <79JOC1717>, while the products from 4-diazo-4*H*-imidazole (**157**), heated or irradiated in benzene or cyclohexane, are 4-phenyl- or 4-cyclohexyl-imidazole (Scheme 94). In cyclohexane the product presumably forms by insertion of the carbene into a C—H bond of the solvent; with benzene the reaction is more likely to be carbene attack on the π -electrons. In halogenobenzene solvents the carbene inserts into the carbon–halogen bond giving 4-haloaryl- and 4-halo-imidazoles, but when the aryl compound has an unshared electron pair, as in anisole, ether cleavage takes place to give 4-phenoxyimidazole. Benzonitrile and nitrobenzene are subject to a high proportion of *ortho*-substitution <86TL901, 90AHC(48)65>.



Scheme 94

When nucleophiles react with diazoimidazoles coupling occurs (e.g., with phenols) <90CHE538>. Compounds with an active methylene form azo derivatives, and cycloaddition reactions are common. Thus, (**156**) reacts with 1,1-dimethoxyethene to give (**158**) <84CC295, 86CC1127, 87JOC5538>, and (**157**) adds to electron-rich dipolarophiles by overall 1,7-cycloaddition followed by elimination <87JOC5538>. Both 2- and 4-diazoimidazoles add to isocyanates to give imidazotetrazinones (**159**) in high yields. Such products are effective anticancer agents, perhaps because they are capable of retrocycloaddition (Scheme 95) <87JMC357, 87JOC5538, 90AHC(48)65>.

Strong bases can deprotonate aminoimidazoles to form stable imines which are readily alkylated and acylated <83S861>.



Scheme 95

3.02.7.1.7 Other N-linked substituents

(i) Arylazo groups

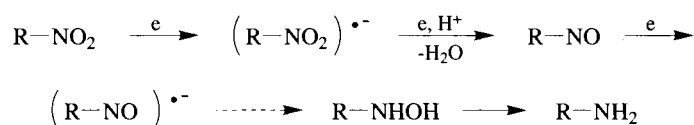
These functions can be reduced to hydrazino or cleaved by oxidation or catalytic hydrogenolysis to amino. The latter process is not valid for the preparation of 2-amino-4-fluoroimidazoles because the fluorine is reduced simultaneously. Formamidinesulfinic acid, however, achieves the desired conversion in good yield [84JOC1951].

(ii) Nitro groups

Nitroimidazoles are of increasing importance as chemotherapeutic agents (see Section 3.02.9). Their mode of action seems to be associated with some reductive process, whether to radical anion, nitroso- or hydroxylaminoimidazole, and considerable efforts have been applied to studies of these processes. Nitro groups may also be displaced by nucleophiles under certain circumstances. Metronidazole (**89**) reacts with excess 2-aminoethanethiol (analogous to glutathione) under nitrogen to form 4-[(2-aminoethyl)thio]-2-methylimidazole-1-ethanol (98%). The final stage of this reaction is elimination of nitrous acid from a Meisenheimer complex, that is a “*cine*”-substitution analogous to the reaction of 1,2-dimethyl-5-nitroimidazole with nitroalkanes (see Section 3.02.5.6.2) [89H(28)849].

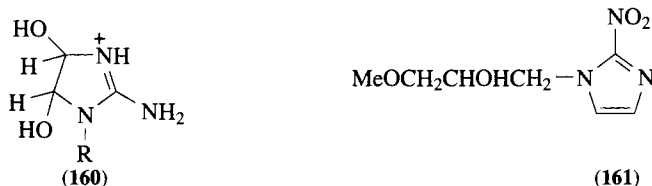
Ab initio studies of molecular structure and relative proton and electron affinities of isomeric nitroimidazoles suggest stabilities of the parent compounds in the gas phase lie in the order $5\text{-NO}_2 \approx 4\text{-NO}_2 > 2\text{-NO}_2$. In solution the much greater stability of the 4- over the 5-tautomer is attributed to greater solvation of the more polar 4-nitroimidazole. The electron affinity order ($2\text{-NO}_2 > 5\text{-NO}_2 \gg 4\text{-NO}_2$) closely matches the radiosensitizer activities of the isomers, and this is consistent with suggestions that the nitro–nitro radical anion redox cycle is an important determinant of biological reactivity [89CJC1666]. In all three isomers the nitro groups are essentially coplanar with the ring making resonance interaction probable [92JCS(P1)2779].

Nitroimidazoles are useful sources of the less well-known amino derivatives, and can be converted into them by catalytic reduction with palladium and carbon [89CC551, 90ACS67, 92JCS(P1)2779] or with zinc in hydrochloric acid [93CJC427]. During the catalytic reduction process some diimidazole products are formed perhaps through reaction between nitro- and aminoimidazoles. Since nitroimidazoles have very low energy LUMOs they are soft enough electrophiles to be very reactive with ring carbons adjacent to an amino group [92JCS(P1)2789]. The biological properties of nitroimidazoles are believed to be very bound up with their one-electron reduction potentials which in turn are closely related to the LUMO energies [92JCS(P1)2779]. The reduction of a nitroimidazole probably follows the sequence of Scheme 96 [85CHE688, 85JA1762, 87JA4308, 89JA8172, 90TL3221].

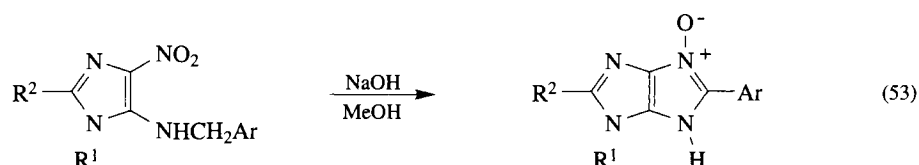


Scheme 96

Radical anions can be detected by ESR techniques. The nature of the species involved in biological reactions is, however, still not entirely clear. Nitro radical anions do not appear to interact with DNA (they are surprisingly stable and do not decompose into nitrite ions and aromatic σ -radicals). Nor are the hydroxyamino and amino species active. Nitroimidazoles are much poorer oxidizing agents for thiols than nitrosoimidazoles [88JMC323, 90JCS(P1)919, 90TL3221]. 2-Nitroimidazoles can be further reduced to glyoxal and a guanidinium fragment which could be formed from the *cis*- and *trans*-isomers of (**160**), a known reduction product [87JA4308]. Misonidazole (**161**) and similar radiosensitizers certainly seem to be involved in reductive metabolism. They have preferential toxicity towards hypoxic rather than aerobic cells (solid tumors develop regions where cells are hypoxic and become resistant to radiation therapy). Such compounds are mutagenic, chemosensitizers, and they affect DNA binding and depletion of cellular thiols [87JA4308].



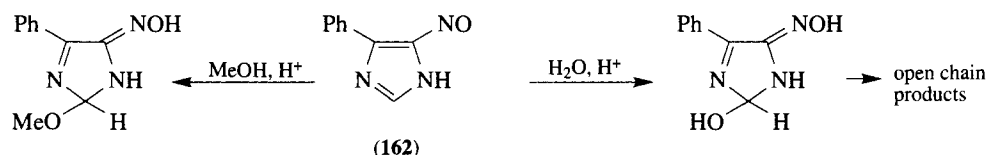
Intramolecular cyclizations of suitably substituted nitroimidazoles can give bicyclic *N*-oxides (Equation (53)) <85CHE1303>.



(iii) Nitroso groups

As mentioned above nitrosoimidazole radical anions (Scheme 96) may be implicated in the mode of action of nitroimidazole antibiotics <88JMC323, 90TL3221>. Reverse phase liquid chromatography has been a valuable tool for separating nitroso- and nitroimidazoles in studies of their activity <88JMC323>. The nitrosoimidazoles can be converted into diazoimidazoles <87JMC357>.

Methylation of 4-nitroso-5-phenylimidazole in basic medium gives a 5:1 mixture of 1-methyl-5-nitroso-4-phenyl- and 1-methyl-4-nitroso-5-phenylimidazole <88JMC323>. 4-Nitroso-5-phenylimidazole (**162**) is quite an acidic compound which is rather unstable in acidic media (Scheme 97) <87JOC1357>.



Scheme 97

3.02.7.1.8 Oxygen-linked substituents

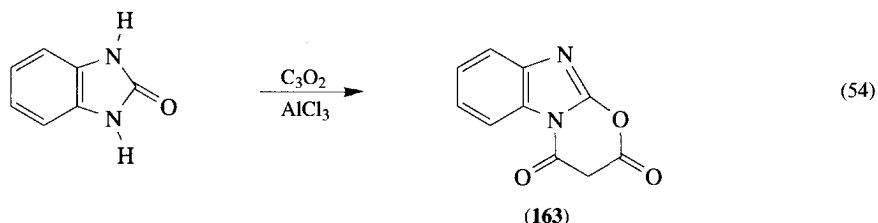
The tautomeric forms have been discussed earlier (see Section 3.02.4.3.2). Discussion in this Section is confined to reactions which do not cleave the ring.

(i) Hydroxy

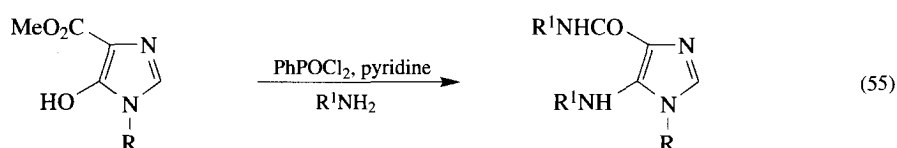
Theoretical study of the 2-hydroxyimidazole $\rightleftharpoons$ 2-imidazolone tautomerism predicts that in solution the oxo form should exist (as observed experimentally). The dipole moment of the oxo tautomer is substantially altered in solution compared with that of the hydroxy form <90JCS(P2)195>.

Some reagents are able to alkylate or acylate an “hydroxy” function, and the group is also subject to nucleophilic substitution. Thus, whereas ethyne with cadmium acetate catalyst at 230°C is able

to convert 2-benzimidazolone into a mixture of *N,N*- and *N,O*-divinyl derivatives, 4,5-diphenyl-2-imidazolone is only *N,N*-divinylated <88IZV1882>. Carbon dioxide, with added aluminum chloride, also reacts at both N- and O-sites to give the bicyclic species (**163**) (Equation (54)) <92JHC1033>.



In a one-pot process, 4-carbomethoxy-5-hydroxyimidazole is converted via the 5-chloro species into a 5-aminoalkyl-4-carbamoylimidazole (Equation (55)) <85H(23)2247>.



(ii) Alkoxy

Although methoxy-substituted imidazoles are not common (see CHEC-I) 4-methoxyimidazole has now been prepared <84LA831, 84TL363>.

3.02.7.1.9 Sulfur-linked substituents

(i) Thiones and thioethers

The 2-thiones of imidazoles and benzimidazoles are common, and their structures and tautomerism have been well described (see Section 3.02.4.3.2). Less well-known are 4- and 5-thiol-imidazoles. The corresponding thioethers are, however, well described <87JOC2977>. Charge-transfer complexes form between 2-thiones and halogens and halogen derivatives <88JA2586>.

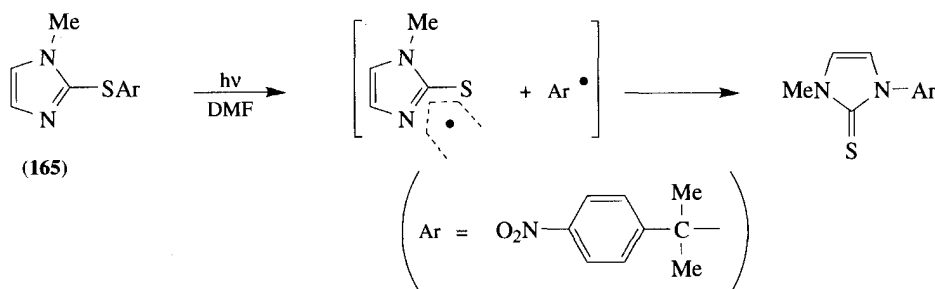
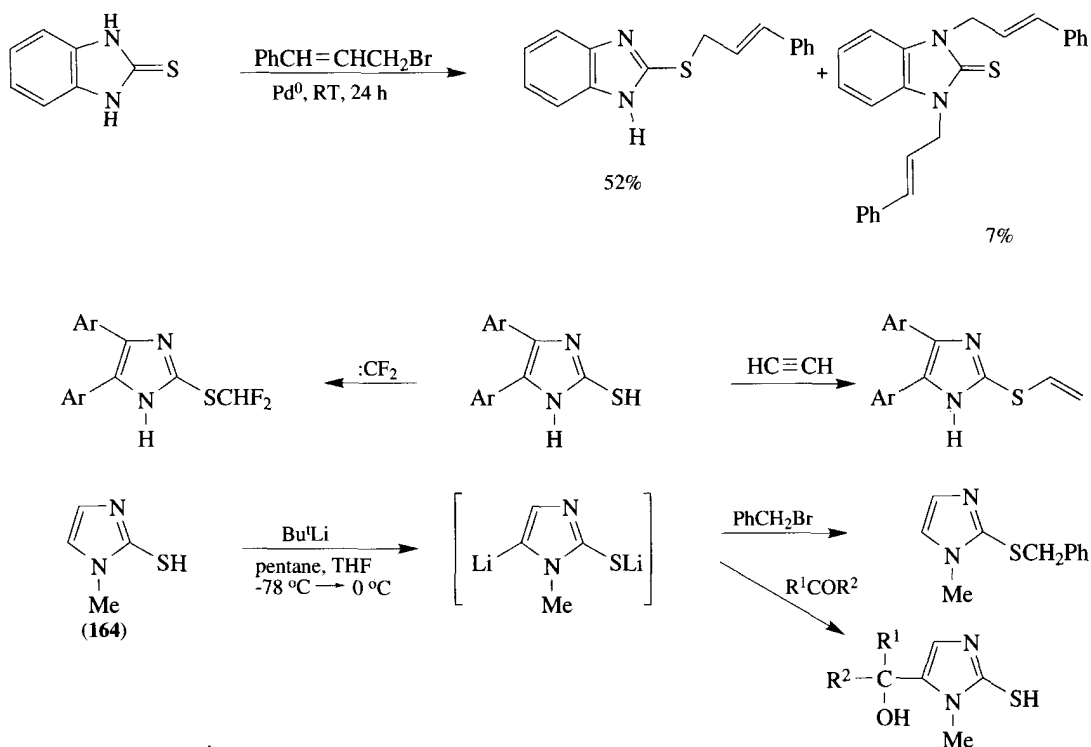
Whenever there is competition between an annular nitrogen and exocyclic sulfur as an alkylation site, whether in neutral or basic medium, the sulfur group invariably reacts more readily. This is true for both imidazoles <83CHE1141, 83JHC419, 85JMC1188, 88S767, 90JCS(P1)955, 90JMC781, 91JPR355> and benzimidazoles <81AJC1729, 84CHE505, 84JOU1854, 88SC805, 91SC1789, 92CHE167, 93T1465>. Unsaturated reagents, too, preferably attack a thione or thiol function (Scheme 98) <85BAU635, 85JMC1188>. The sulfur centre is much softer than the annular nitrogen or a carbanion, and so soft electrophiles such as alkyl bromides naturally react preferentially at sulfur. Thus, when 1-methylimidazole-2-thiol (**164**) is treated with two moles of *t*-butyllithium, the dilithiated species reacts with benzyl bromide to give the benzylthio derivative. Hard electrophiles like ketones, diphenyldisulfide, and epoxides do not affect the sulfur function (Scheme 98) <90S761>.

S-Arylation is common with suitably activated aryl halides <83JHC1287, 84JHC1241>. Ambident anions of imidazole-2-thiol react with α -*p*-dinitrocumene under photostimulation by an $S_{RN}1$ mechanism leading initially to the 5-aryl product (**165**). This is followed by a photochemical rearrangement in which homolytic cleavage of the carbon-sulfur bond is followed by recombination of the aryl anion with the ambident heterocyclic radical (Scheme 99) <86H(24)1013>.

S-Acylation, which usually involves a hard electrophile, will only take place subsequent to *N*-acylation <91SC1789, 92JHC1033>.

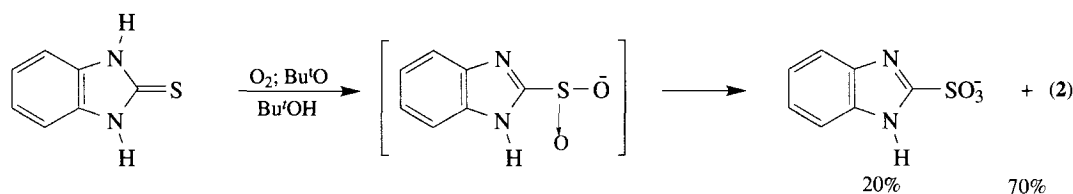
Removal of a thiol, thione, or substituted thiol group is usually accomplished by a reductive technique using such reagents as Raney nickel or aluminum amalgam <84JOC5003, 90JCS(P1)1645, 90JMC781, 91BCJ2255>. In behavior typical of thioethers, dissociative electron capture of 1-methyl-2-methylthioimidazole in the ESR gives methyl radicals and thiolate anions <90JCS(P2)975>.

Oxidation of thiols (or thiones) can give disulfides or sulfonic acids. Imidazole thioethers are



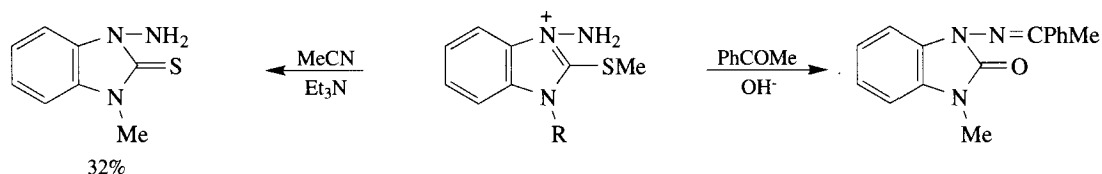
similarly oxidized to sulfoxides or sulfones. With ferric chloride 1-phenyl-2-tosylimidazole-5-thiol is converted into the disulfide; further oxidation by peracetic acid gives the 5-sulfonic acid. Potassium ferricyanide treatment results only in desulfurization ^[82RTC28]. There are many examples of thioethers being oxidized to sulfones ^[82JHC561, 85JHC1269, 87AJC1415, 91JHC577, 91JOC4058], but the process can be retarded by steric hindrance ^[91JHC577]. Milder conditions may give sulfoxide products. Thus, a 67% yield of 5-methylsulfinyl-4-nitroimidazole is formed when the 5-methylthio precursor is oxidized with 0.5 equivalents of magnesium monoperoxyphthalate in acetic acid ^[94UP 302-02]. In a number of 1-alkyl-2-thiolimidazole-5-carboxylic esters peroxide, chlorine water, or chlorine in 15% acetic or 3M hydrochloric acid induce oxidation to the sulfonic acids. Chlorine in 20% acetic acid causes desulfonation, while in 50% acetic acid the 5-sulfonyl chloride is believed to be formed ^[82JHC561]. Other suitable oxidizing agents for imidazole thioethers include KHSO_5 and *m*-chloroperbenzoic acid, both of which give mixtures of sulfoxides and sulfones ^[91JOC4058]. Milder reagents for oxidation to disulfides include aerial oxidation ^[86BSB1129] and photolysis in the presence of oxygen (which ultimately gives the sulfonic acid, cleaving the sulfur-sulfur bond) ^[85H(23)2917]. Alkaline autooxidation of benz- and naphth-imidazole-2-thiones with oxygen and *t*-butoxide in *t*-butanol gives the parent condensed imidazoles and their 2-sulfonic acids (Scheme 100) ^[84CC1064]. In the apparent nucleophilic displacement of the sulfur function by chloride when thionyl chloride reacts with benzimidazole-2-thione, the process is believed to proceed via an S-

SOCl species <85CHE872>. Certainly sulfur functions can be displaced in nucleophilic substitution reactions, particularly sulfone groups <86JOU793, 87AJC1415, 92CHE167>.



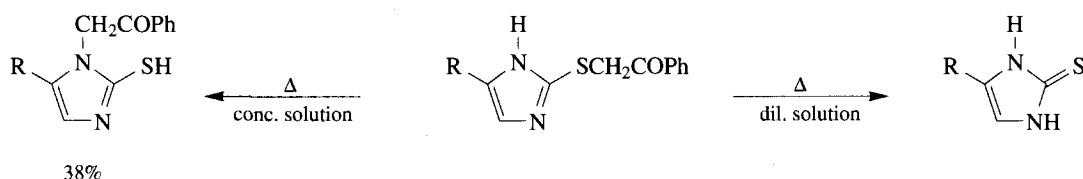
Scheme 100

Dealkylation of thioethers can be achieved by boiling in acetonitrile containing triethylamine; alkaline hydrolysis gives benzimidazolones (Scheme 101) <92CHE167>.



Scheme 101

Treatment of 1-alkyl-2-alkylthiobenzimidazoles with sodium naphthalenide gives 1-alkylthiobenzimidazoline-2-thiones (88–94%) perhaps via a cleavage involving a radical anion <89JHC747>. When 4-substituted 2-phenylacetylthioimidazoles are heated in concentrated solution they thermally rearrange to form 4-substituted 1-phenacylimidazole-2-thiols. In dilute solution cleavage of the sulfur–carbon bond takes place with no *N*-substitution. These reactions do not appear to be homolytic (Scheme 102) <91JCS(P1)488>.



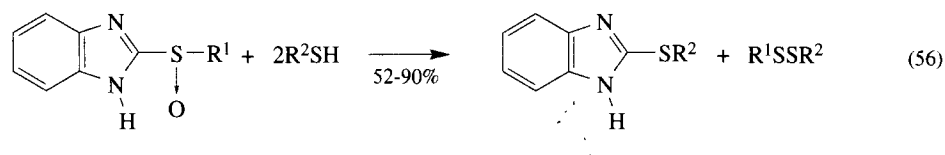
Scheme 102

(ii) Sulfonic acids, sulfoxides, and sulfones

The chemistry of heteroaromatic sulfones and sulfoxides has been reviewed <90AHC(48)1>. Usually, the sulfonyl chlorides are made by direct chlorosulfonation <86JCED257, 88JCED537> because of the difficulty of chlorinating sulfonic acids <82JHC561>. Sulfonyl chloride groups and sulfones can be displaced by a variety of nucleophiles provided that theazole ring is suitably activated <82IJC(B)989, 86JCED257, 87AJC1415, 88CHE880, 88JCED537>.

Unlike other sulfonic acids, benzimidazole-2-sulfonic acids are fairly easily converted into the 2-thiones merely by heating with ammonium formate at 150–160°C. The reaction is accompanied by some desulfurization. When the ammonium salt of the sulfonic acid is heated with formamide the products are the 2-thione and 2-aminobenzimidazole <84CHE224>.

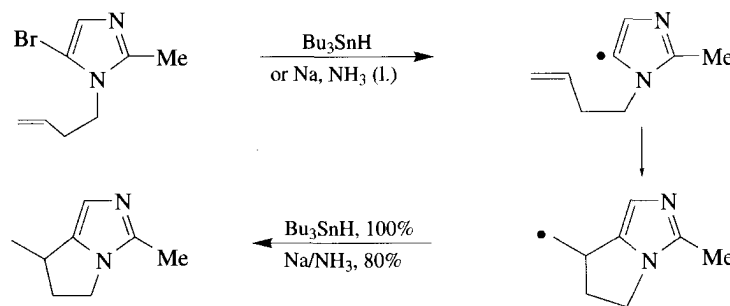
When 2-alkylsulfinyl-, 2-arylsulfinyl-, and 1,2-arylsulfinyl-benzimidazoles react with thiols, the unsymmetrical disulfides are obtained (instead of the symmetrical ones), together with *ipso*-substitution products. The reaction is believed to be initiated by protonation of the benzimidazole nitrogen. The sulfenic acid is then eliminated after the *ipso*-substitution by thiolate. The sulfonic acid, once formed, is so unstable that it reacts immediately with thiol or dimerizes to form thio-sulfonates from which the unsymmetrical disulfides are derived (Equation (56)) <87JOC4620>.



In acidic solution 2-(2-pyridylmethylsulfinyl)benzimidazoles rearrange to thiophilic benzimidazo[1,2-*b*]pyrido[1,2-*d*][1,2,4]thiadiazinium salts which react with 2-thioethanol to form 2-pyridiniobenzimidazolides <86CC125, 87JOC4573>.

3.02.7.1.10 Halogen atoms

Nucleophilic displacements have been covered earlier (see Section 3.02.5.4) as has metal-halogen exchange (see Section 3.02.5.5.1). The latter reaction is useful in dehalogenation <86TL1635, 87JCS(P1)1445, 91JOC4296>. Indeed, stepwise replacement of bromine atoms in 2,4,5-tribromoimidazoles by hydrogen occurs in the order 2 > 5 > 4 <86TL1635>. The use of sulfite for partial debromination of polyhalogenoimidazoles has been known for many years (see CHEC-I) <92SC2971>, but other reagents such as triphenylphosphine <91CB1639> and derivatives <92S552>, Grignard reagents <88S767, 91CB1639>, and thiophenate <87JCS(P1)1437> have been used, along with catalytic hydrogenation methods <87CPB4056>. A 2-halogen is replaced by hydrogen with the greatest facility. Reductions with sodium in liquid ammonia or with tributyltin hydride (and doubtless others) form a radical at the site from which the halogen has been removed. This radical can be trapped by a carbon species rather than a hydrogen (Scheme 103) <90JCS(P1)919>. There are a number of metal-catalyzed cross-coupling reactions which are similar <93JOC997, 93PHC143>. Electron addition to 5-bromo- and 5-iodo-imidazoles is known to give σ^* radical anions which lose halide to form the radicals <89TL1409, 90JCS(P2)975>.



Scheme 103

Photolysis of 1,3-dimethyl-4,5-dibromoimidazolin-2-one in the presence of oxygen converts it into the trione <81AG(E)612>. Aspects of the chemistry of fluorinated benzimidazole have been reviewed <92JFC(56)1, 94AHC(59)1>.

3.02.7.1.11 Metals and metalloid-linked substituents

Some discussion of the properties of the lithium derivatives has appeared earlier (see Section 3.02.5.5.1) and in review articles <85H(23)417, 88CHE117, 94H(33)2487>. Lithiated imidazoles are not always particularly reactive towards electrophiles and yields may be low <83JA2382, 86TL4095, 88JOC1107, 92JHC1091>. The nature of the quenching electrophile is the critical factor. Hard reagents like benzophenone tend to give better yields than the softer methyl iodide; heteroaryl lithiums have hard carbanion centres.

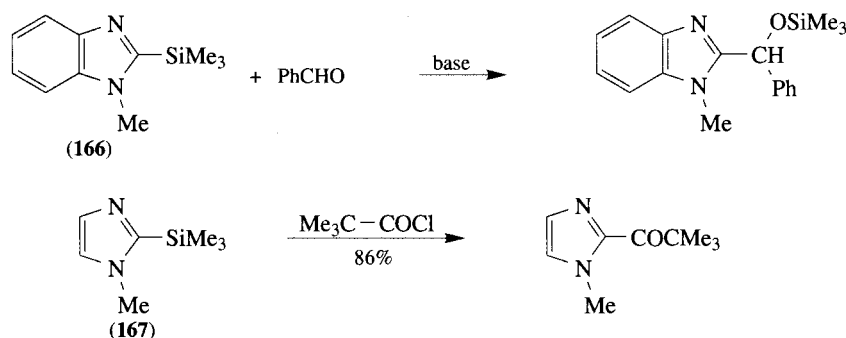
2-Lithioimidazoles are thermodynamically (and possibly kinetically) more stable than the 5- or 4-isomers <90JHC673>. The adjacent lone pair effect makes 4-lithioimidazoles difficult to prepare, though they are accessible through metal-halogen exchange under certain conditions <81CC1095, 83JCS(P1)279, 83JCS(P1)735, 85JHC57> (see Section 3.02.5.5.2). Before 5-lithioimidazoles can be prepared the 2-position needs to be blocked <81CC1095>, but when a 2,5-dilithioimidazole is made it is possible to quench the more reactive 5-anion before the 2-anion <84JCS(P1)481>. If the 2-position is unsubstituted a 4- or 5-lithioimidazole (made by metal-halogen exchange) rapidly isomerizes to the 2-isomer. Only very reactive electrophiles are able to functionalize a 5-lithioimidazole when the 2-position is unsubstituted because the reaction must take place at a sufficiently low temperature to prevent transmetalation <91JOC4296>. Attention is drawn to the similar "carbon-silicon dance"

reaction below. Grignard functions at C-4 seem to be much less prone to rearrangement, and they can be converted into tertiary alcohols by treatment with ketones at room temperature <91JOC5739>.

When 1,2-dimethylimidazole is lithiated both 2- and 5-isomers are formed, the former under kinetic control. Transmetalation at temperatures above -100°C gives the 5-lithio derivative. Because the 5-anion is harder than the 2-methylene anion, harder Lewis acids (e.g., D_2O , R_3SnCl , Me_3SiCl) react better at the 5-position <83JCS(P1)271>. Sometimes a particular regioisomer of a lithioimidazole can be stabilized by coordination. Thus, some 1-alkoxymethyl groups are able to stabilize an anion at C-5 <90JCR(S)58>.

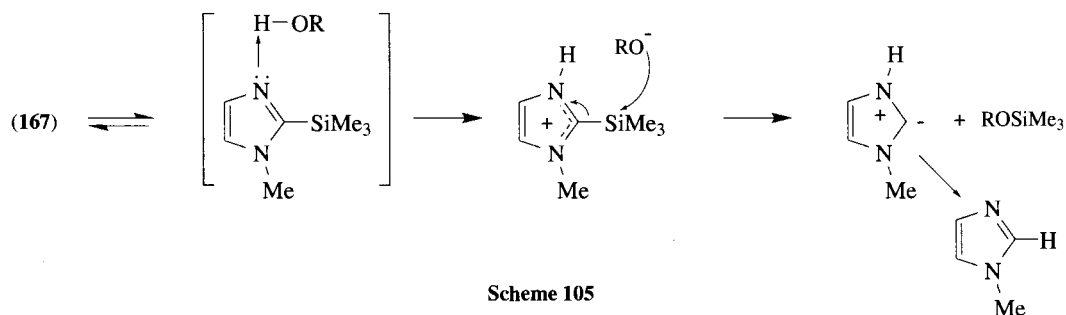
Trialkylsilyl groups have often been used as blocking agents during metallation procedures even though their use is limited by rather ready desilylation. A *t*-butyldimethyl- or *t*-butyldiphenyl-silyl group at C-2, however, allows quantitative lithiation at the 5-position in both *N*-substituted and *N*-unsubstituted imidazoles (*N*-lithiation is hindered by the bulky silyl substituent at C-2). The blocking group can be removed later by treatment with tetrabutylammonium fluoride, NBS, caesium fluoride, or acetic or hydrochloric acids <88JHC1845, 90JCS(P1)1645, 93TL3401>. Trimethyl- and triethyl-silyl groups are also cleaved under mild hydrolytic regimes, with the 2-trimethylsilyl isomers more readily hydrolyzed than the 5-isomers <83JCR(S)196, 92JOC2963>.

The mechanism of base-catalyzed desilylation of heteroaryltrimethylsilanes may be attack of base on the silicon atom as the first step, with subsequent dissociation of the pentacovalent intermediate in the rate determining step to give the carbanion at C-2. The relative rates correlate with Hammett σ values rather than the corresponding arylanion stabilities. The anion reacts readily with a proton, or with aldehydes (Scheme 104) <85CB3872>. Similarly the replacement of a stannyl or silyl group by ketone occurs very readily, even with bulky groups. The carbon-tin bonds are even more reactive than carbon-silicon bonds (Scheme 104) <83JHC1011, 84SC947>.



Scheme 104

In neutral methanol, ethanol, or water 1-methyl-2-trimethylsilylbenzimidazole (**166**) is also cleaved rapidly, possibly by a cyclic mechanism involving the solvent molecule, or one in which RO^- ions ($\text{R} = \text{Me}$, Et, H) attack the protonated substrate. In acidic medium cleavage is retarded; presumably a solvent molecule attacks the silicon in the protonated species to generate a zwitterion <81JCS(P2)1051>. A subsequent study of 1-methyl-2-trimethylsilylimidazole (**167**) confirms a dominant mechanism over a range of pH values in which hydroxide or alkoxide ion attack the silicon in the *N*-protonated base, forming a zwitterion. Below pH 5 the nucleophile is a neutral solvent molecule (Scheme 105) <84JA5979>.



Scheme 105

When 5-bromo-1-methyl-2-trimethylsilylimidazole is treated in turn with one equivalent of butyllithium and DMF, a 40 : 60 mixture of 1-methylimidazole-2-carbaldehyde and 1-methyl-5-trimethyl-

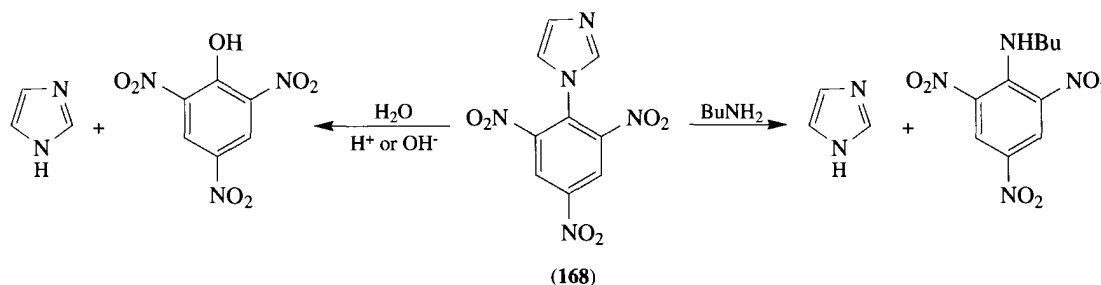
silylimidazole-2-carbaldehyde is formed. Presumably the 5-lithio-1-methyl-2-trimethylsilyl intermediate disproportionates to (167) and 1-methyl-2,5-dilithioimidazole. Subsequent disproportionation of the latter organometallic compound with (167) gives 2-lithio-1-methyl-5-trimethylsilylimidazole which reacts with DMF to form the 2-carbaldehyde. This is an example of a "silicon dance" reaction. Even the more hindered *t*-butyldimethylsilyl group is capable of similar migration [93TL3401]. In THF at -100°C butyllithium converts 1,2-dimethyl-5-trimethylstannylimidazole into the 5-lithio derivative; the analogous trimethylsilyl compound is exclusively lithiated at the 2-methyl group under the same conditions [83JCS(P1)271].

3.02.7.2 Substituents Attached to Ring Nitrogen Atoms

3.02.7.2.1 Aryl groups

These groups are usually weakly electron withdrawing with the electrical effect being largely inductive. Frequently the aryl and imidazole rings are forced out of coplanarity by adjacent substituents on either ring. Electrophilic substitution reactions normally occur on the *N*-aryl substituent, especially when acidic reagents have protonated N-3 of the heterocycle. *Para*-substitution is frequently observed (see CHEC-I).

It is usually very difficult to remove an *N*-aryl substituent unless it can sustain ready nucleophilic attack. Reaction of 1-(2',4',6'-trinitrophenyl)imidazole (168) with butylamine is an addition-elimination process in which departure of the imidazole leaving group is acid-catalyzed (Scheme 106) [82TL4423]. The same substrate (168) is also hydrolyzed easily to picric acid and imidazole at a range of pH values, with both acid and base catalysis being observed [81JA1533]. Even 1-(2',4'-dinitrophenyl)imidazole is sufficiently activated to nucleophilic substitution by water or amines [84JOC3978]. Such derivatives as (168), which are formed when anionic imidazole is treated with trinitrobenzene in DMSO, may be subsequently converted into the 2-, 4-, or 5-isomers which are thermodynamically more stable [85CJC866].



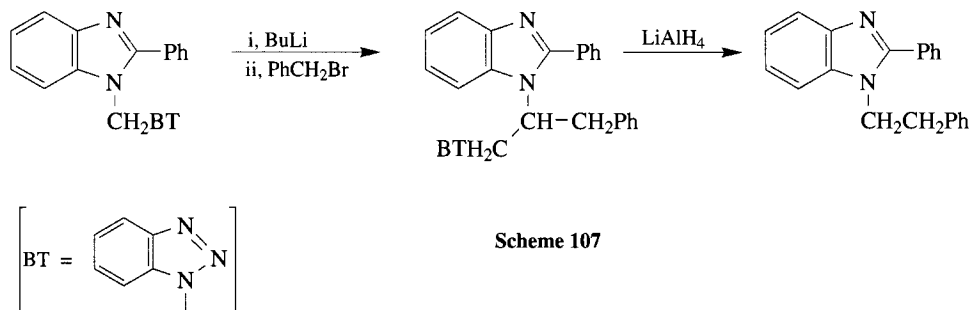
Scheme 106

3.02.7.2.2 Alkyl groups

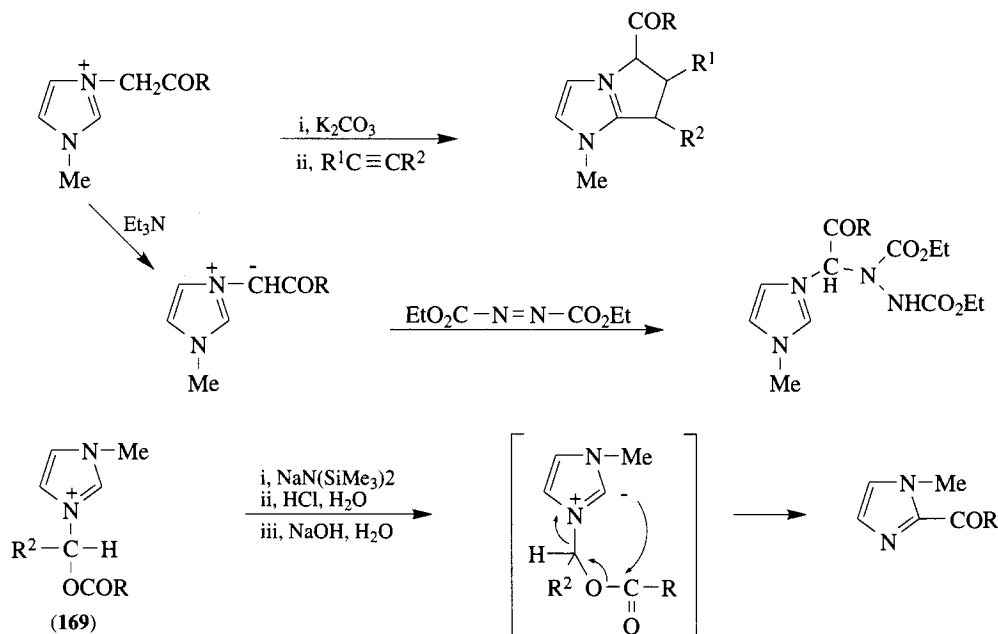
Alkylation of annular nitrogen in imidazole or benzimidazole has a profound effect on the properties. Decreased intermolecular hydrogen bonding makes the *N*-alkyl derivatives more soluble in aprotic solvents, and lowers their melting and boiling points. While most alkyl groups resist removal from unquaternized imidazoles, benzyl groups are subject to reductive or oxidative cleavage. Thermal dequaternization of imidazolium salts, and thermal *N*- to *C*-rearrangements in *N*-alkylimidazoles are well known (CHEC-I).

Methyl and methylene groups attached to imidazole nitrogen are not particularly 'active', but the groups can be metallated [85H(23)417, 85S302, 94H(38)2487]. In 1-benzylimidazole the extent of benzylic metallation increases with temperature and with the amount of butyllithium used [84JCS(P1)481]. Although 1-phenylthiomethylbenzimidazole is initially lithiated at C-2 at low temperatures, when the temperature is raised rearrangement to the rather unstable methylene-lithiated species occurs. This anion can be trapped by weak electrophiles. Exclusive α -lithiation can be achieved either by using the corresponding sulfoxide or sulfone, or by blocking the 2-position [87JCS(P1)775]. Even stronger electron attraction is present in the benzotriazol-1-ylmethyl group which has a highly acidic

methylene group (^{13}C NMR 58.0–48.7 p.p.m.) which lithiates with great facility when C-2 is blocked by suitable groups (Scheme 107) <89JHC829>. The *N*-benzotriazolyl group can be cleaved by nucleophiles <93T2829>.



Base treatment of 1-methyl-3-acylmethylimidazolium salts deprotonates the methylene group to give an ylide which reacts with electrophiles (Scheme 108) <86CC1745>. When sodium bis(trimethylsilyl)amide reacts with (169) the 2-acylimidazole is formed (Scheme 108) <84TL1715>.



Halogenation of *N*-methyl groups is possible under radical conditions <93ZOB1879>. Nitromethyl substituents are subject to $\text{S}_{\text{RN}}1$ substitution under photolytic stimulation, and the exocyclic nitro group can also be replaced by malonate ion, or reduced to hydrogen by tributyltin hydride <94BSF200>.

3.02.7.2.3 Alkenyl groups

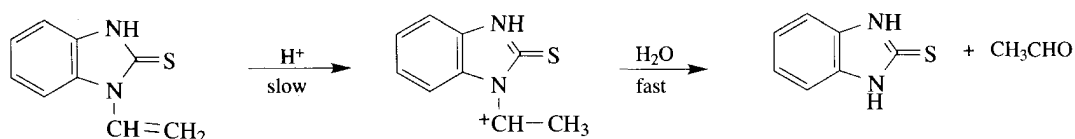
The basic $\text{p}K_{\text{a}}$ of 1-vinylimidazole (5.14) is nearly 2 pK units lower than that of imidazole <84JHC171>. Examination of ^{15}N NMR spectra of 1-vinylimidazoles and -benzimidazoles shows that the nitrogen attached to the vinyl group resonates in a stronger field than N-3 <91CHE845>. In accord with these results 1-vinylimidazoles form less stable complexes with transition metals than 1-alkylimidazoles <89JCR(S)240>. The photoelectron spectra of 1-vinylimidazoles have been discussed <87JGU2471>.

The rotational barrier in the vinyl compounds is so small that about equal quantities of *cis*- and *trans*-isomers exist <90CHE1121>, but a 5-substituent stabilizes the *cis*-isomer for steric reasons

<89CHE157>. Photolysis of 1-imidazolyl-1,2-dibenzoylalkenes can lead in some instances to intramolecular phenyl migration giving rise to ketene mediated 3-butenic acids and esters <86JOC3420>. Additions to *N*-alkenylimidazoles do not occur typically probably because of a degree of conjugation with the heteroring (Equation (57)); similarly a vinyl group is not cleaved when 1-vinyl-3-alkyl quaternary salts are thermolyzed and 1-vinylimidazole is not subject to thermal rearrangement <80AHC(27)241, 82CHE1190, 84JHC133>.



The kinetics of hydrolysis of 1-vinylbenzimidazole-2-thione point to the reaction sequence depicted in Scheme 109 <82CHE1190>.



Scheme 109

3.02.7.2.4 Acyl and aroyl groups

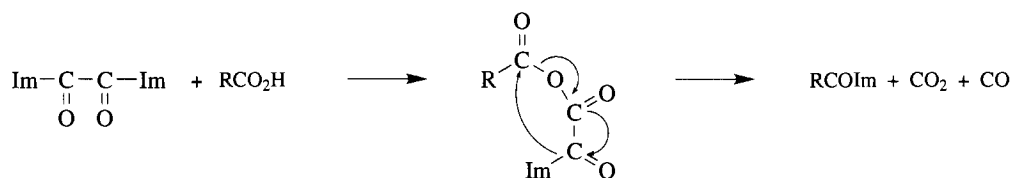
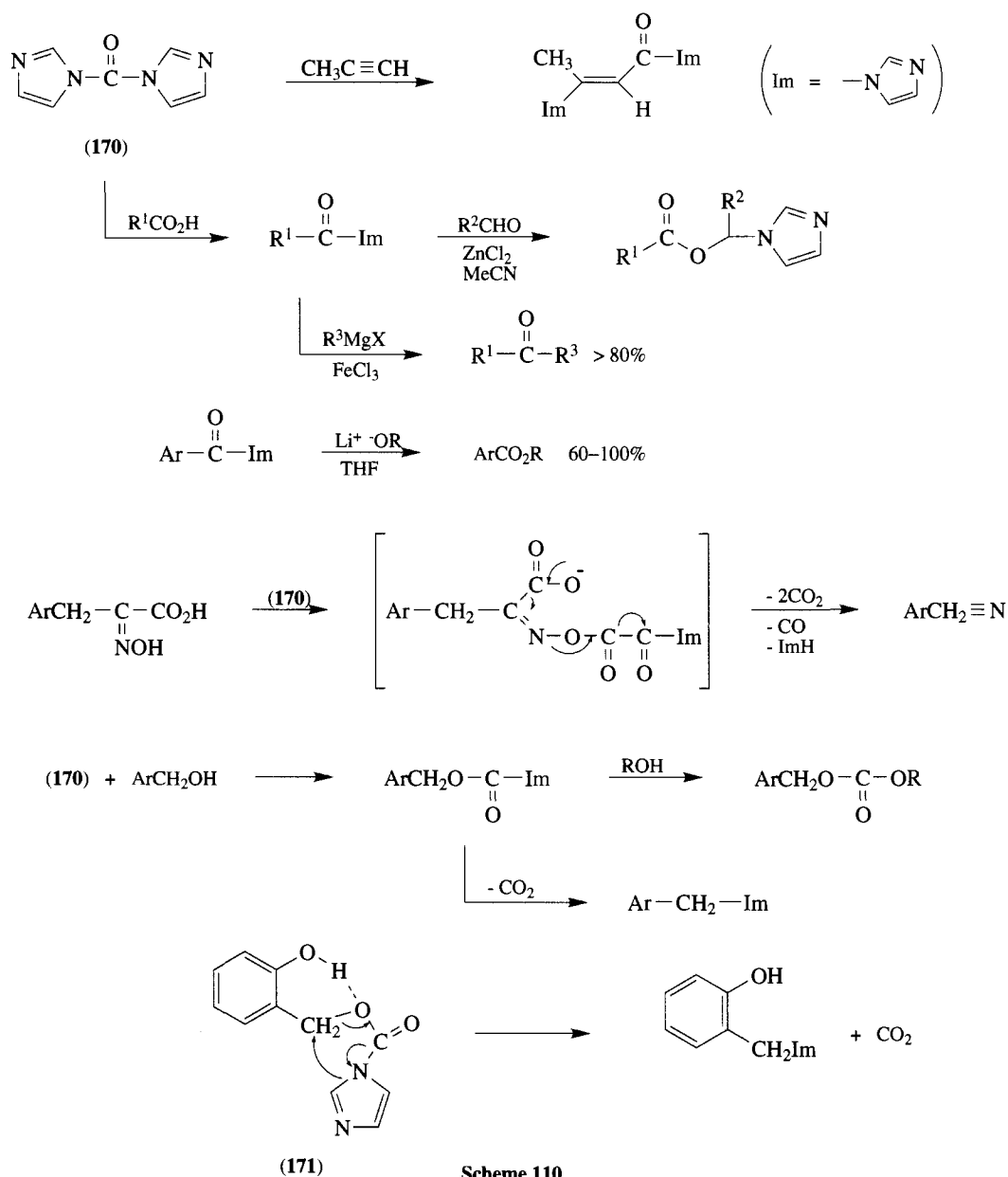
The synthetic utility of azolides has been reviewed in detail (see CHEC-I) <B-86MI 302-02>, and there are many examples of their use in the synthesis of carboxylic acids, esters, and thioesters <82CPB4242, 83CL1819, 84CPB5044, 85HCA1644, 89H(28)593, 90JHC813, 90SC773, 92JCR(S)196>, amides and thioamides <82CPB4242, 85CJC951, 85UKZ860, 89JHC901, 90SC2683, 92JCR(S)196>, nitriles <91CPB187>, aldehydes and ketones <81JOC211, 93H(36)1381, 90MI 302-01, 90SC2683, 93TL5159>, and phosphorylated imidazoles and benzimidazoles <90CHE599>. Acyl groups are naturally easily removable *N*-protecting groups because of their high reactivity with nucleophiles <83CPB1213>, and 1-alkyl-3-acyl salts are even more powerful acylating agents <87CC317>.

Hydrolysis rates have been measured for a number of azolides in order to compare the effects of extra annular nitrogens and benzannulation. Rate constants for *N*-acyl compounds are larger than for the corresponding thioacyl analogues, and benzimidazolides are less reactive than imidazolides <83BAU1525, 83BAU1934>. Hydroxylated surfactant micelles are powerful catalysts for the deacylation of 1-acylimidazoles under neutral conditions <89JCS(P1)1697>.

N-Acylimidazoles have been used to acylate specific hydroxy groups of ribose in nucleosides and nucleotides <89H(28)593>. 1,1'-Carbonyldiimidazole (**170**) reacts stereoselectively with acetylenic acids to give 1-[(*E*)-3-(1-imidazolyl)-2-alkenoyl]imidazoles <93H(36)1381>. The diazolid (**170**) is a readily available and very reactive reagent, able to react with such weak nucleophiles as carboxylic acids by transacylation to give 1-acylimidazoles which will react with a variety of nucleophiles. With alcohols (**170**) gives 1-carbalkoxyimidazoles which undergo carbonyl transfer (or less commonly imidazole transfer) reactions <80CI(L)85, 90SC2683>. The imidazole-transfer process needs a six-membered hydrogen bonded ring (**171**) in the intermediate. Scheme 110 gives some typical examples of azolide reactions <85HCA1644, 90JHC813, 90SC2683, 91CPB187>.

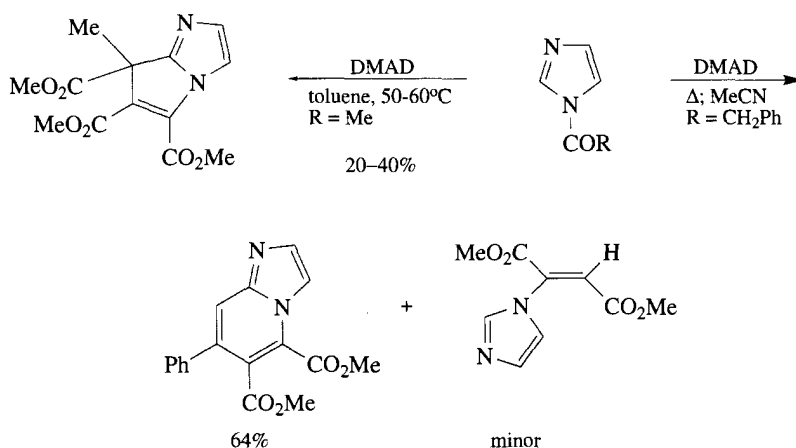
Carbonyldiimidazole (**170**) can be used to convert alcohols into alkyl halides by a one-step reaction using an excess of such reactive halides as allyl bromide or methyl iodide <83CPB4189>, and (**170**) can be made even more reactive by quaternization <84CPB5044>. The disadvantages of (**170**) are its cost and the fact that phosgene must be used in its preparation. An alternative is 1,1'-oxalyldiimidazole (made from 1-trimethylsilylimidazole and oxalyl chloride). Transacylation reactions occur very readily with this reagent (Scheme 111) <83CL1819, 87CPB4294>.

With dimethylacetylene dicarboxylate (DMAD) 1-acylimidazoles form novel functionalized derivatives as a consequence of electrophilic attack on the "pyridine" nitrogen followed by intramolecular transacylation (Scheme 112) <88CC1151, 90JCS(P1)1821, 92CB1939>. Ketoximes undergo Beckmann rearrangement and primary carboxamides are dehydrated to nitriles on treatment with (**170**)



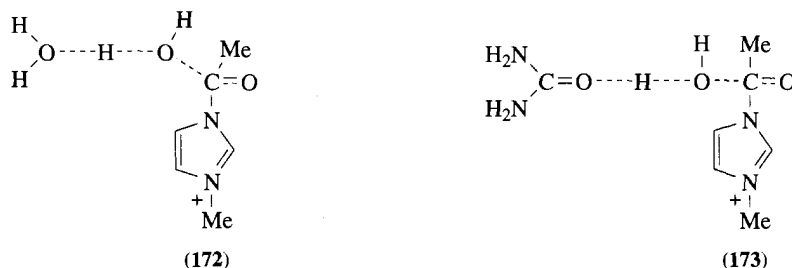
and excess reactive alkyl halide. Quaternization of the imidazole ring by the alkyl halide promotes these reactions ^[84CPB2560].

During the aqueous hydrolysis of 1-acetyl-3-methylimidazolium (**172**) a water molecule acts as a general base to abstract a proton from another water molecule acting as a nucleophile ^[83JOC2038]. 1-Acetylimidazole and 1-acetylbenzimidazolium salts hydrolyze similarly provided that the non-quaternized substrates are in their protonated forms. The driving force for these reactions is



Scheme 112

presumably increased resonance stabilization $\langle 83\text{CJC}2059 \rangle$. In the presence of urea, the magnitude of the solvent deuterium isotope effect is diminished indicating a transition state (**173**) containing a urea–water complex $\langle 81\text{JOC}4350 \rangle$. The exceptional ease of these C–N bond cleavages leads to hydrolytic reactions with early transition states, and these may proceed without stable tetrahedral intermediates. Qualitatively similar effects should occur in enzymatic reactions of peptides because of restriction of amide group resonance and a strained C—N bond $\langle 93\text{ACR}325 \rangle$.



1-Carboxylimidazole is an unstable compound which readily decarboxylates. The ethyl ester, though, is stable enough to be distilled and to form stable salts with acids $\langle 87\text{H}(26)1333 \rangle$. Thermal decarboxylation to the 1-alkylimidazole will occur, analogous to the thermal decarbonylation of a 1-acetylimidazole $\langle 80\text{AHC}(27)241 \rangle$. In the mass spectrum imidazole-1-carboxylate esters lose CO_2 (cf. loss of CO from 1-acetylimidazoles) $\langle 84\text{BSB}1057 \rangle$. The potassium salt of imidazole-1-dithiocarboxylic acid is reported to be relatively stable in air, as is the benzimidazole analogue. Such species form esters with alkyl halides and they also form metal complexes of the type $(\text{ImCS}_2^-)_2\text{M}^{2+}$ $\langle 87\text{H}(26)1657 \rangle$.

The photo-Fries and thermal rearrangements of 1-acetylimidazole have merited more study (see CHEC-I). Under flash vacuum pyrolysis conditions 1-acetylimidazole rearranges to a mixture of 2- and 4-isomers. This has been demonstrated by a real time analysis of the products using mass and ion kinetic energy (MIKE) spectroscopy. Electron-induced fragmentation of 1-acetylimidazole gives rise to a non-classical ionic structure which is a consequence of interaction between ionized methylene and 2*H*- or 4*H*-imidazole. At temperatures above 730 K 1-acetylimidazole rearranges to the 4-acetyl compound with some contribution of the 2-isomer. This was ascertained by looking at the (MIKE) spectrum of the molecular ion of 1-acetylimidazole as the temperature increases, and comparing loss of CO with loss of CH_3 (see also Section 3.02.3.8). 1-Propanoylimidazole rearranges similarly $\langle 84\text{BSB}1067 \rangle$.

Photolysis similarly gives a mixture of 2- (20%) and 4-acetylimidazoles (30%) from the photo-Fries rearrangement of 1-acetylimidazole. When the 2-position is already substituted rearrangement to the 4-position only is observed, although in all cases yields are reduced by cleavage of the *N*-acetyl bond. The reaction failed with 1-acetylimidazole-2-carbaldehyde, suggesting it may only apply to *C*-alkylimidazoles $\langle 76\text{HCA}2738, 83\text{JOC}897 \rangle$.

When 5-amino-1-carboxymethylimidazole-4-carboxamide is heated at 180°C the ester function

apparently migrates to the exocyclic amino group $\langle 84\text{CHE}204 \rangle$. Similarly, in 1-acetyl-2-amino-benzimidazole, heating at 100°C induces rearrangement of acetyl to the exocyclic site $\langle 84\text{ZC}57 \rangle$. In refluxing nitrobenzene 1-carbamoyl-4-methylimidazole gives 2-carbamoyl-4-methylimidazole, but the 4-cyano derivative fails to rearrange under the same conditions $\langle 83\text{JHC}1103 \rangle$.

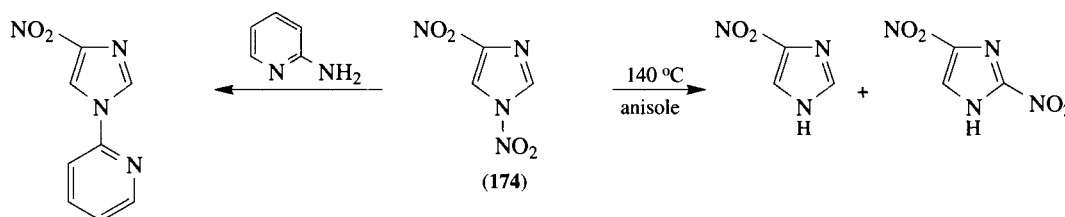
1-Cyanoimidazoles (ν_{max} 2150 cm^{-1}) are very readily hydrolyzed by 20% KOH $\langle 90\text{JHC}711 \rangle$.

3.02.7.2.5 Nitrogen functions

(i) Nitro

When heated at $130\text{--}140^\circ\text{C}$ in anisole or benzonitrile 1,4-dinitroimidazole (**174**) forms a mixture containing 4-nitroimidazole (61%) and 2,4-dinitroimidazole (22%). The 2-methyl analogue of (**174**) gives 2-methyl-4-nitroimidazole (18%) and 2-methyl-4,5-dinitroimidazole (67%). 5-Methyl-1,4-dinitroimidazole failed to rearrange, seeming only to form tars containing a little of the denitration product $\langle 89\text{AJC}1281 \rangle$. An earlier report stated that all of the above 1-nitroimidazoles give C,C-dinitro products when heated in chlorobenzene $\langle 87\text{PJC}913 \rangle$. As this rearrangement offers an alternative route to the important 2-nitroimidazoles further study would seem to be merited.

The *N*-nitroimidazoles are quite stable, even in the presence of water for a time, but treatment with concentrated sulfuric acid cleaves the *N*-nitro group, and strong base opens the ring $\langle 87\text{PJC}913 \rangle$. Much of the interest in such compounds has related to their *cine*-substitution in which sequential nucleophilic addition of amines, ring opening, ring closure, and nitroamide elimination–rearomatization gives 1-aryl-4-nitroimidazoles (Scheme 113) $\langle 84\text{PJC}311, 90\text{PCJ}813, 91\text{MI} 302\text{-}01, 91\text{PJC}515, 92\text{AP}317, 92\text{PJC}943, 93\text{PHC}143, 93\text{T}3899 \rangle$. This method can also be used to prepare isotopically labeled imidazoles when labeled amino acids are used as the amine $\langle 93\text{PHC}143 \rangle$.



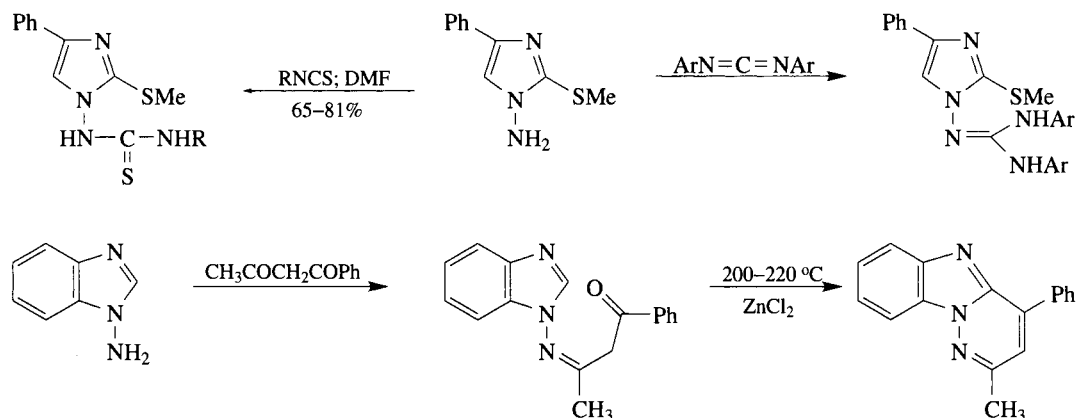
Scheme 113

(ii) Amino

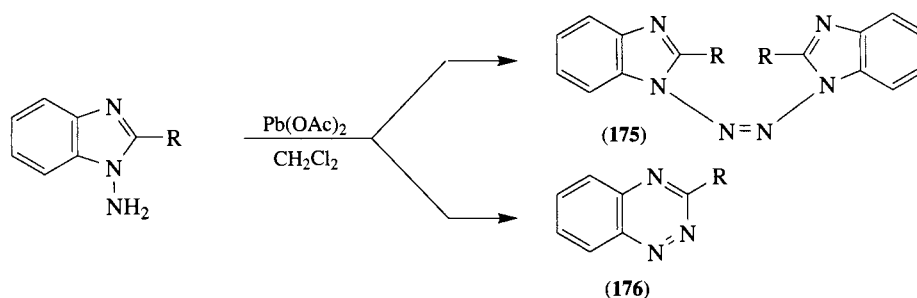
The chemistry of *N*-amino-imidazoles and -benzimidazoles has been reviewed $\langle 90\text{AHC}(49)117, 92\text{AHC}(53)86 \rangle$. *N*-Amino groups have virtually no π -interaction with the imidazole ring, and only small inductive effects are apparent when the $\text{p}K_{\text{a}}$ values are examined. In contrast, the heteroring has a strong electron-acceptor effect on an exocyclic amino group. Protonation of 1-amino-benzimidazole, for example, occurs at N-3, the basicity of which is reduced by the amino substituent ($\text{p}K_{\text{a}}$ 4.95). As an acid 1-aminobenzimidazole has a $\text{p}K_{\text{a}}$ of 12.83 $\langle 93\text{JCS}(P2)1687 \rangle$.

N-amino groups can be alkylated and acylated by way of their anions $\langle 89\text{CHE}180, 92\text{JCS}(P1)913 \rangle$, and they can take part in the usual reactions with carbonyl compounds $\langle 84\text{CHE}1152, 89\text{S}843, 93\text{JCR}(S)260 \rangle$, with carbodiimides $\langle 88\text{H}(27)161 \rangle$, and in aza-Wittig reactions (Scheme 114) $\langle 88\text{H}(27)1935, 94\text{H}(37)997 \rangle$. 1-Aminobenzimidazoles and their quaternary salts react similarly, and the Schiff bases formed may lead to cyclized products $\langle 83\text{CHE}209, 83\text{CHE}314, 86\text{CHE}282, 88\text{T}7185, 92\text{CHE}167 \rangle$. 1-Amino-imidazolium salts are exocyclically alkylated in basic medium by polarized alkenes to give imidazolium *N*-vinylimino ylides $\langle 94\text{CPB}454 \rangle$.

When silver or copper acetylides are heated with 1-aminobenzimidazolium salts, pyrazoles form $\langle 84\text{JGU}1493 \rangle$. Oxidation of 1-aminobenzimidazoles with manganese dioxide or lead tetraacetate can give either 1,1'-azobenzimidazoles (**175**) or 3-substituted benzo-1,2,4-triazines (**176**). Electrochemical measurements have shown that the first step in this reaction is removal of an electron from a π -orbital of benzimidazole rather than from the amino group. Because the cation radical which is formed must be stabilized by loss of a proton, for (**176**) to form the 2-substituent must contain an



NH or OH group. This is unnecessary for the formation of the azo product (**175**) which may form via a nitrene intermediate. Such nitrenes can be trapped with methyl acrylate to yield 1-aziridinobenzimidazoles (Scheme 115) <86CC832, 87JCS(P1)2787, 89CHE1241>.

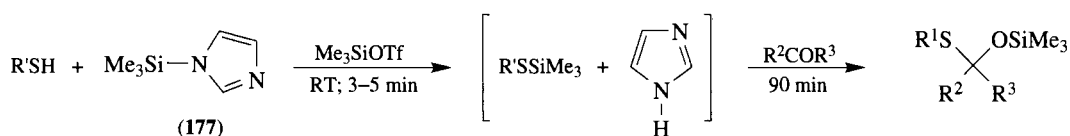


3.02.7.2.6 Silicon, phosphorus, and related groups

N-Trialkylsilyl- and -stannylimidazoles and -benzimidazoles are useful *N*-protected derivatives for a number of transformations, and suitably volatile for GLC analysis. The groups are thermally stable, but susceptible to hydrolytic processes and analogous displacements, with the stannyl compounds less readily hydrolyzed than the silyl species.

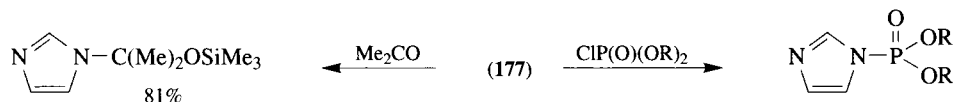
The silyl-Hilbert-Johnson method of nucleoside synthesis, using trimethylsilyltriflate as catalyst, is useful for the preparation of *N*-3 nucleosides (e.g., from 4-carbamoylimidazolium-5-olate) <84JHC529>, and a similar silyl displacement method has been used to make 1-alkylthio- and 1-phenylthio-1-trimethylsilyloxyalkanes and -cycloalkanes. This latter process uses 1-trimethylsilylimidazole (**177**) and trimethylsilyltriflate as catalyst <84CHE662, 90S104>. The use of two equivalents of the thiol prevents the formation of imidazole adducts (Scheme 116) <90S104>.

Analogues of (**177**) react with derivatives of phosphorus-containing acids to form 1-phos-



phorylimidazoles <90CHE599>. The same compound also silylates ketones to give enol silyl ethers and/or siloxyalkylimidazoles (Scheme 117) <87JC271>.

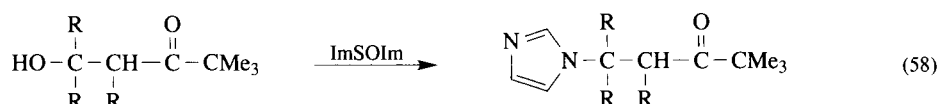
N-Phosphorylimidazoles are useful phosphorylating agents <81JA5784, 90CHE599, 94JCS(P1)817>.



Scheme 117

3.02.7.2.7 Sulfur groups

1,1'-Sulfonyldiimidazoles and 1-chlorosulfonylimidazole have similar applications to the carbonyl analogues in transfer reactions (Equation (58)) <80SC733, 84JHC1489, 85CJC3613, B-86MI 302-02>. Treatment of arylsulfonylimidazoles with hydrogen peroxide in alkaline medium gives arylsulfonyl peracids which are useful epoxidizing agents <93SL915>. The dimethylaminosulfonyl group is useful for *N*-protection in lithiation procedures; it can be removed by refluxing with dilute hydrochloric acid <91SI021>.



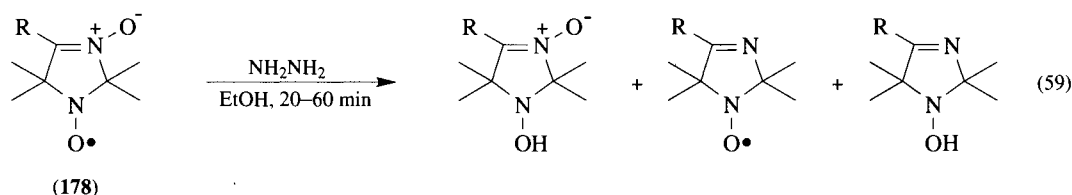
The charge transfer compounds formed when imidazole and benzimidazole are sulfonated by sulfur trioxide have been discussed earlier (see Section 3.02.5.3.3).

3.02.7.2.8 Oxygen functions

The chemistry of imidazole and benzimidazole *N*-oxides has been reviewed <93CHE127>, and methods of preparation have been summarized <88JCS(P1)681, 93CHE127>. The oxides, which can be in tautomeric equilibrium with *N*-hydroxy species, are so thermally unstable that at times they may be explosive <84CB30, 89S773>. Although the aromatic oxides can only be made by ring synthetic methods, direct *N*-oxidation of 2*H*-imidazoles has been reported <83JCS(P1)2065>.

Deoxygenation of the compounds can be accomplished by catalytic hydrogenation <83JCR(S)76, 89S773>, with Raney nickel <89S773>, with titanium(III) chloride in methanol <84TL1319>, by metal-acid reduction <85CHE1303, 91CHE802>, or with phosphorus halides <93CHE127>.

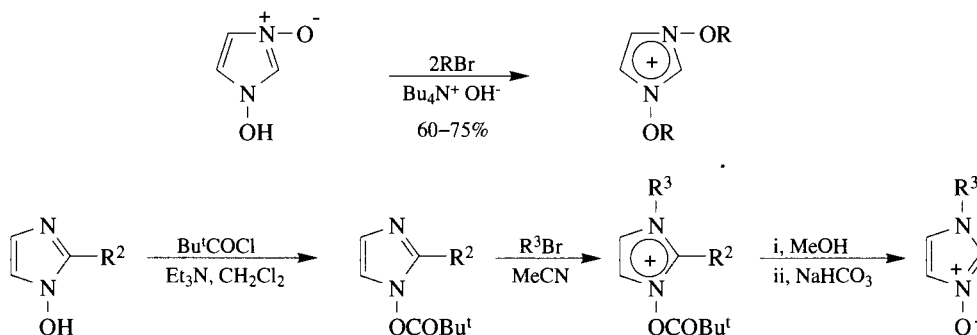
As with most *N*-oxides the compounds are weakly basic, but they can form salts with strong acids. Often both the oxygen and annular nitrogen are protonated in these derivatives, and liberation from the salts requires only treatment with aqueous ammonia <88JCS(P1)681>. Further oxidation of the compounds with such reagents as lead tetraacetate or lead dioxide gives stable nitroxide radicals <82BAU1287, 82JOU1881, 85BAU2165, 91IZV2113, 91IZV2122, 93CHE127>. Attempts to reduce the *N*=C bond in the nitroxide derived from 1-hydroxy-3-imidazoline was only successful when the substrate was complexed with boron trifluoride etherate <85BAU2165>. Many reactions in acid solution do not affect the nitroxide groups <82BAU1287>. In the 3-imidazoline 3-oxide radicals (178) the radical centres increase the oxidative properties of the nitroxide group, allowing its reduction by hydrazine (Equation (59)) <83BAU1030>.



When the *N*-oxide does not have a 2-substituent the compounds readily rearrange to the cor-

responding 2-imidazolones or 2-benzimidazolones, but 1-hydroxyimidazole 3-oxides will not undergo this rearrangement <93CHE127>.

Alkylation of *N*-oxides usually takes place firstly at the oxygen <89S773, 90S795, 91CHE802> as does acylation <89TL4353, 90S795>. In order to obtain 3-alkylimidazole 1-oxides an acylation–alkylation–deacylation sequence can be followed (Scheme 118) <90S795>.



Scheme 118

Electrophilic processes which cause *C*-substitution are not well known. Nitration with nitric and sulfuric acids 2-nitrated 1,4,5-trimethylimidazole 3-oxide <93CHE127>, but ring cleavage is common with this reagent <92ZOR2582>. Whereas some examples of nucleophilic attack in the 2-position are known, simultaneous deoxygenation is also likely to occur <93CHE127>.

Treatment of 1-alkyl-3-*t*-butoxycarbonylimidazolium salts with methanol hydrolyzes the ester group <90S795>. Catalytic hydrogenation of 1-benzyloxy-2-imidazolone converts it into the 1-hydroxy derivative, while treatment with methanolic alkali causes elimination of benzaldehyde to form 2-imidazolone <87S1058>.

The *N*-oxide function in imidazole *N*-oxides, in conjunction with the adjacent carbon atom, gives the molecule properties of a 1,3-dipole, and there are a number of examples of dipolar additions involving these compounds (see Section 3.02.5.7.1) <93CHE127>.

3.02.7.2.9 Halogen groups

Although *N*-halogenoimidazoles and -benzimidazoles may be intermediates in *C*-halogenation, they are presumably not very stable (see Section 3.02.5.3.5). The reduced imidazoles, though, often have quite stable *N*-halogeno derivatives. Thus, 1,3-dichlorohydantoins are a source of electrophiles which substitute at *C*-2 and *C*-5 of 1-methylpyrrole <93H(36)1059>.

3.02.8 SYNTHESIS

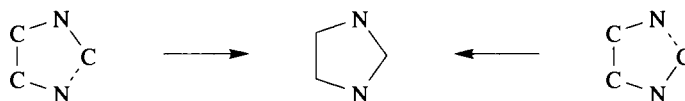
As mentioned in CHEC-I there is no single, widely applicable method for the synthesis of imidazoles. Only the reactions based on 1,2-diaminobenzene and related compounds which can be converted into a wide range of benzimidazoles have broad application. Many current approaches to the synthesis of imidazoles with particular functionality focus on modification of the preformed ring. In this, the metallation techniques are proving valuable.

3.02.8.1 Ring Synthesis from Non-heterocyclic Compounds

3.02.8.1.1 Formation of one bond

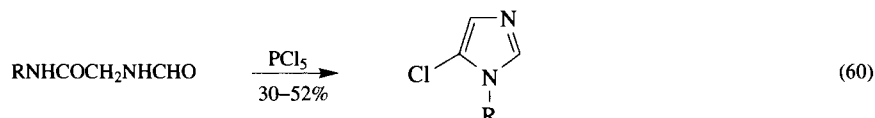
(i) Formation of the 1,2- (or 2,3-) bond (Scheme 119)

The old Wallach synthesis, which ring closed an *N,N'*-disubstituted oxamide, has been adapted to the synthesis of imidazopyridines. Kinetic and labeling experiments support a mechanism involving a nitrile ylide species in this transformation <93JCS(P1)675>. Chlorination and cyclization of

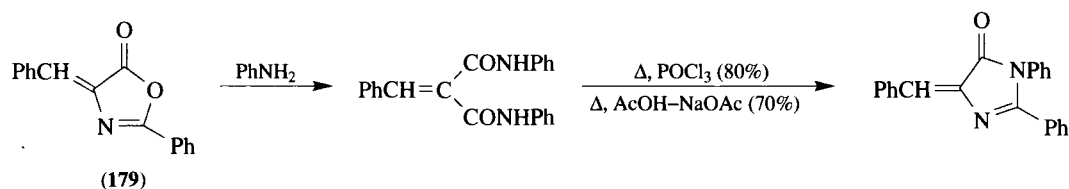


Scheme 119

N-formylethanamides with phosphorus pentachloride has provided the first reported general method for making 1-alkyl- and 1-aryl-5-chloroimidazoles (Equation (60)) <90KFZ56>.



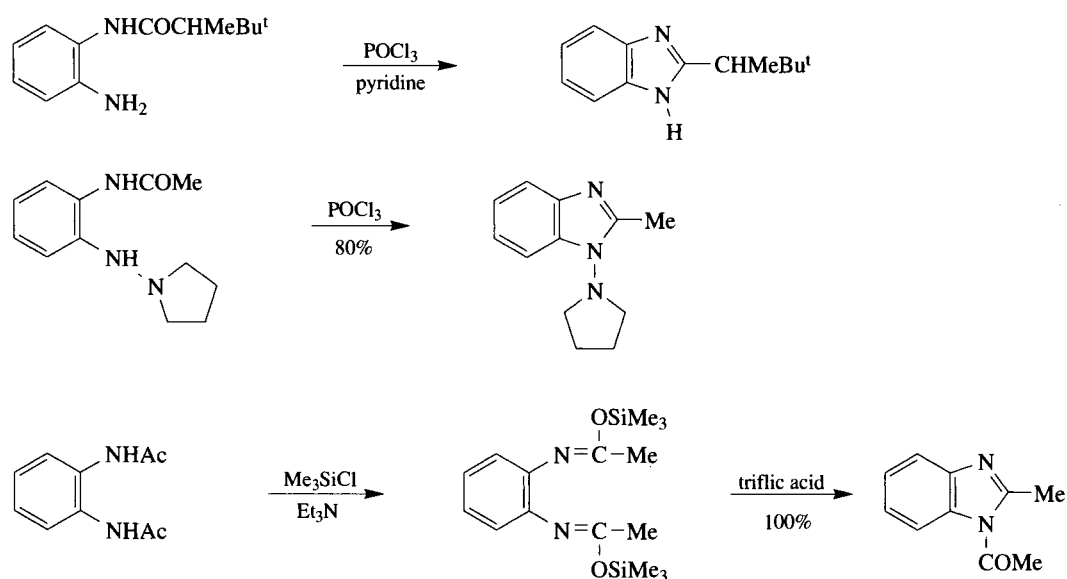
Arylamines ring-open 2-aryl-4-arylmethylene-5(4*H*)-oxazolones (**179**) to give arylamides of α -arylcaboxamido- β -arylacrylic acids which sometimes recycle to form imidazolones (Scheme 120) <84H(22)2775>.



Scheme 120

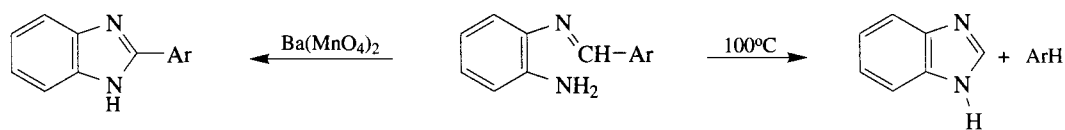
A common benzimidazole synthesis (>40% of all references to 1,2-bond formations since 1983) cyclizes arylen-1,2-diamines in which at least one of the amino groups has been acylated or thioacylated <83S757, 83S861, 84JOC4800, 86CC832, 88SC167, 89CCC206, 91JHC359, 91JHC1121>. Some examples are shown in Scheme 121. Adaptations of the method to the synthesis of 2-aminobenzimidazoles have been covered in a review article <83S861>.

Schiff bases of *ortho*-phenylenediamines can be oxidatively cyclized to 2-substituted benz-



Scheme 121

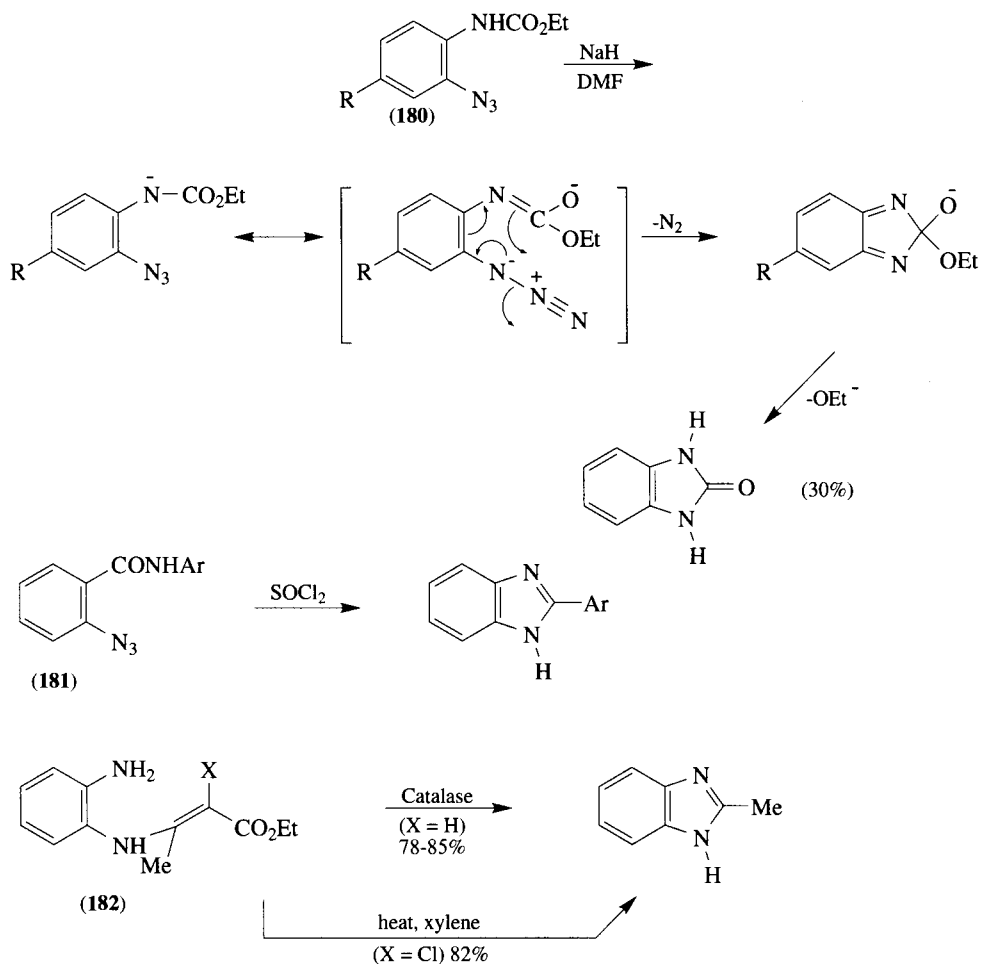
imidazoles by active manganese dioxide, lead tetraacetate, nickel peroxide, or barium permanganate <88SC1537>. Heating in anaerobic conditions may also be successful (Scheme 122) <83JOC727>.



Scheme 122

When the Schiff base has been formed by reaction with trichloroacetonitrile the products are 2-aminobenzimidazoles <83CI(L)439>. In basic conditions, the adducts which form in reactions between secondary enaminones (or enaminosulfones) and diethoxycarbonyl- and benzylethoxycarbonyl-1-diazene cyclize to give 2-imidazolones <91G401>.

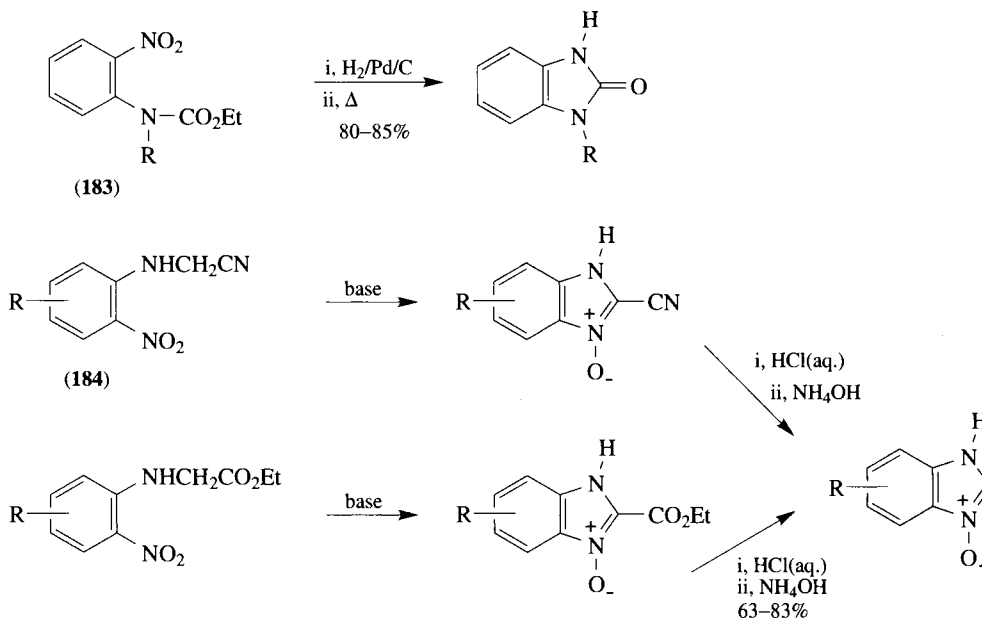
Related reactions include cyclizations of *ortho*-azidoarylcarbamates (**180**) <84TL1389> or *ortho*-azidoarylcarboxamides (**181**) <84CI(L)222>, and reaction of ethyl 3-(2-aminoanilino)crotonates (**182**) with catalase <90H(31)969>. The corresponding chlorocrotonate, when heated in xylene, gives the same 2-methylbenzimidazole by an intramolecular process which eliminates ethyl chlorocrotonate (Scheme 123) <81CHE941>.



Scheme 123

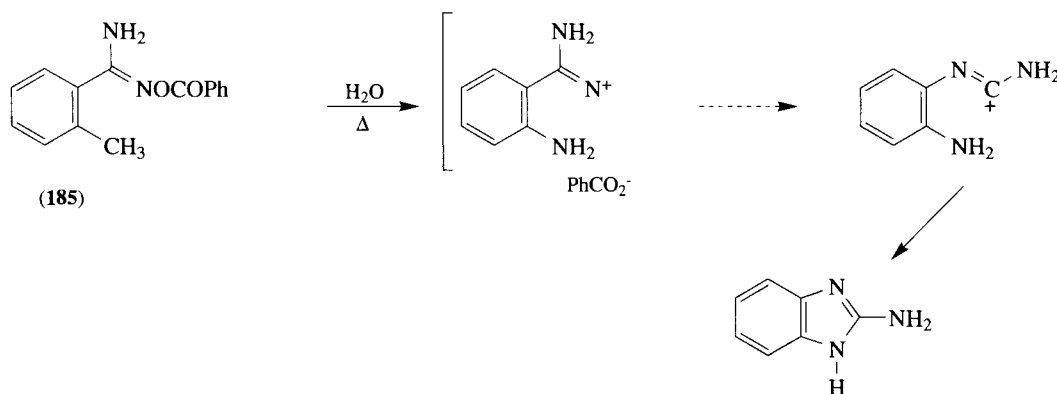
Reductive cyclizations of *o*-nitroanilides (**183**) are also frequently used as an alternative <85M639, 88JHC9>. Base treatment of *N*-cyanomethyl *o*-nitroanilines (**184**) gives 2-cyanobenzimidazole 1-oxides in good yield. In some cases *o*-nitrophenylglycine esters can be used in place of (**184**). These methods circumvent the problems which arise with attempts to partially reduce *o*-nitroformanilides for preparation of the oxides <88JCS(P1)681, 88JCS(P1)1939>. 2-Vinylbenzimidazole 1-oxide (45%) has

been made from the action of sodium ethoxide on *o*-allylaminonitrobenzene <91CHE802>. Treatment of *o*-cyanoaminonitrobenzene with nickel and hydrogen, or iron in acetic acid, gives 2-amino-benzimidazole (Scheme 124) <83S861>.



Scheme 124

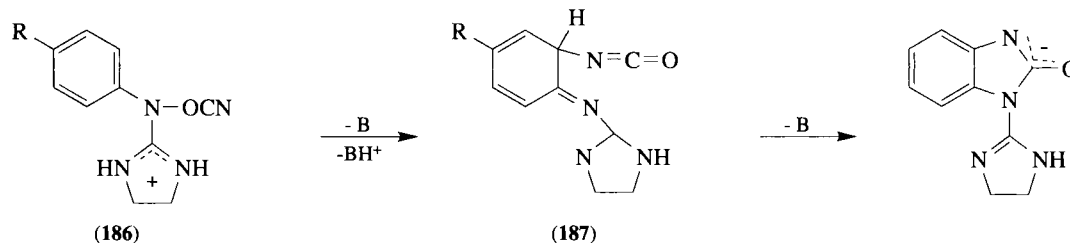
In *O*-benzoyl 2-aminobenzamide oxime (185) the two nitrogens of the amidoxime, the amino nitrogen, and C-1 of the aminophenyl group are all competing for the role of nucleophilic centre. There can, in consequence, be a number of cyclization products, but when (185) is heated in pure water the electron-rich C-1 attacks the oxime nitrogen. In this way, Beckmann rearrangement followed by ring closure gives a quantitative yield of 2-aminobenzimidazole (Scheme 125) <88JCR(S)209>.



Scheme 125

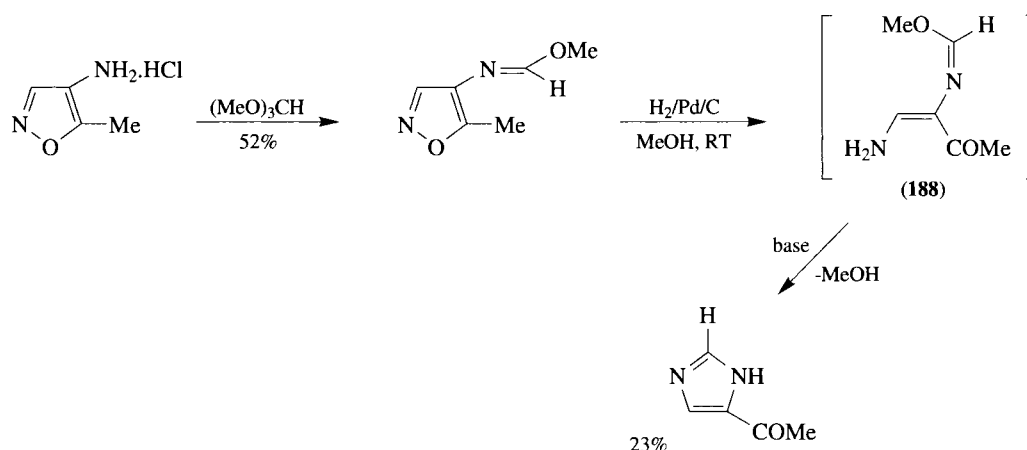
A novel tandem 1,4-diazo-3-oxo-Cope rearrangement–nucleophilic addition reaction which forms benzimidazolones has been rationalized as an initial [3,3]sigmatropic rearrangement of the *N*-cyanatoaniline (186) followed by intramolecular nucleophilic addition in the isocyanate (187) (Scheme 126) <93TL2843>. Reactions of hydroxamic acids with cyanogen bromide give *N*-substituted benzimidazolones also via a hetero-oxy-Cope rearrangement <89H(28)693>.

Analogous reactions in the aliphatic series cyclize alkylenediamines in which one amino group has been acylated (i.e., α -(acylamino)enaminones). These substrates can be made by catalytic reduction of 4-aminoisoxazoles <85TL3423, 87JOC2714> or 4-amino-5(4*H*)-isoxazolones <91S127>. These α -(acylamino)enaminones (188) cyclize in the presence of bases to form a wide range of 2-substituted 4-acylimidazoles. If the isoxazole has no *N*-substituent, treatment of the enaminone with



Scheme 126

a primary amine serves to incorporate a substituted amino function in the β -position with concomitant expulsion of ammonia, allowing access to 1-substituted and 1,2-disubstituted 4-acylimidazoles. Yields usually lie in the range 75–92%. The method will not, however, give satisfactory yields of 5-substituted 4-acylimidazoles because of steric hindrance to amine exchange (Scheme 127) $\langle 87\text{JOC}2714 \rangle$. Other methods of making 4-acylimidazoles are less general, for example from organolithium derivatives $\langle 83\text{JOC}897 \rangle$, and reaction of 3-bromo-4-ethoxy-3-buten-2-one with amidines, a process which is limited by the availability of the butenones $\langle 84\text{JOC}566 \rangle$. Substitution of an alternative starting material, 3-chloro-4,4-dimethoxy-2-butanone does allow the synthesis of 4-acetyl-2-methylimidazole on a large scale, but the generality of this reaction, too, is restricted by the availability and reactivity of amidines $\langle 84\text{JOC}3494 \rangle$.



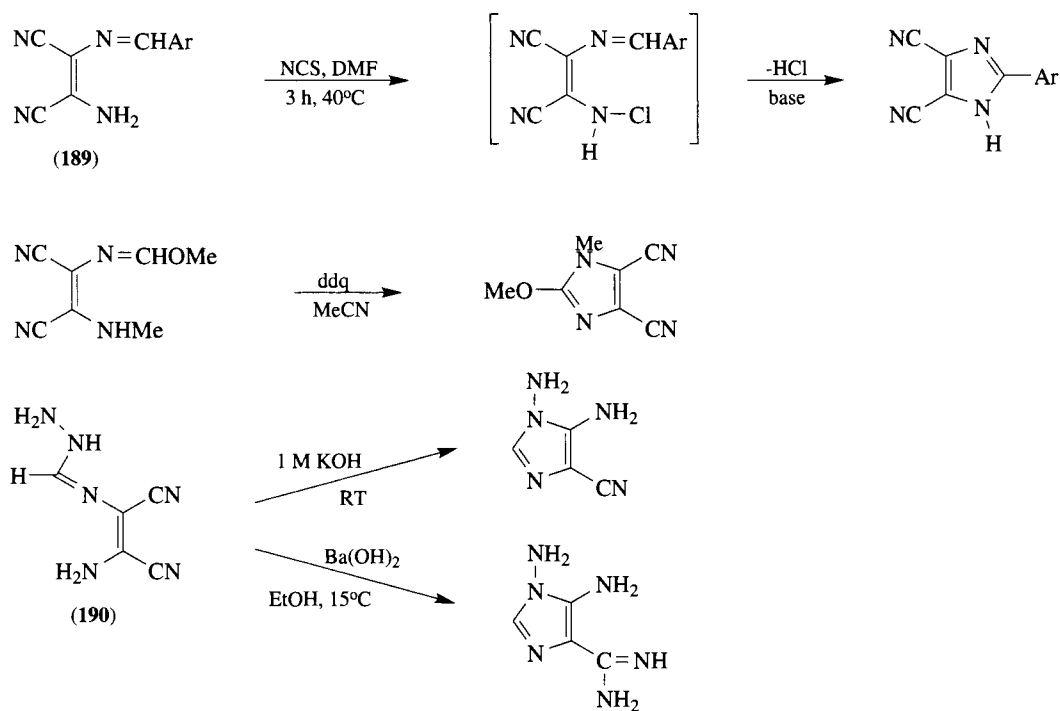
Scheme 127

Methods in which imidazoles are prepared by reactions between isothiocyanates and tosylmethylisocyanide (TOSMIC) are discussed later (see Section 3.02.8.1.2(ii)).

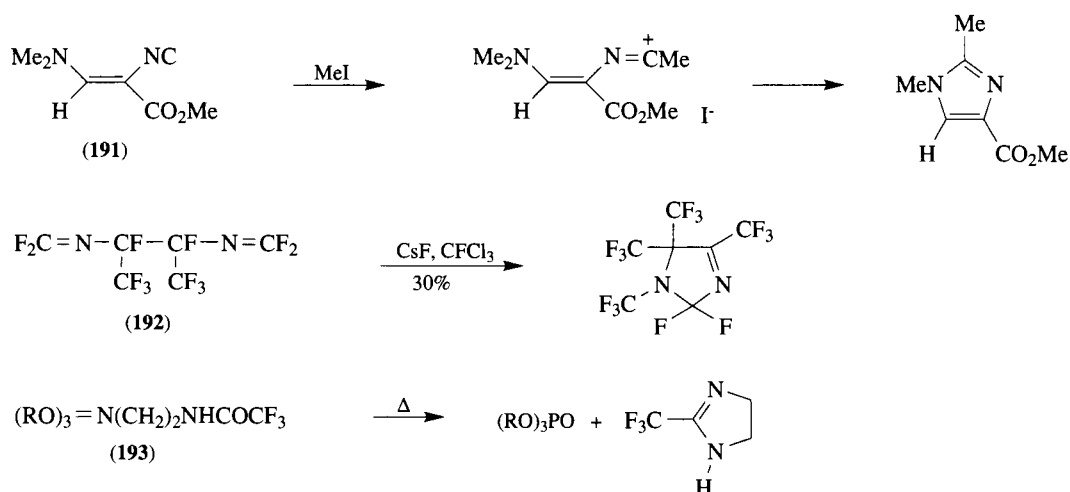
There are a number of synthetic procedures which involve cyclizations based on oxidation of 1,2-diaminomaleonitrile derivatives (see CHEC-I) $\langle 81\text{CC}110, 84\text{S}1057, 85\text{JOC}747, 89\text{JMC}119, 92\text{JCS(P}1\text{)913} \rangle$. Such oxidative cyclizations of Schiff's bases (189) of the reagent are more rapidly and conveniently accomplished using NCS in basic conditions than with DDQ or diaminosuccinonitrile. Formation of the Schiff's bases with aromatic aldehydes is essential to facilitate elimination of the hydrogen from the α -position $\langle 84\text{S}1057 \rangle$. Cyclization of analogous amidrazones (190) gives 1,5-diaminoimidazoles (Scheme 128) $\langle 92\text{JCS(P}1\text{)913} \rangle$.

Other similar methods which involve cyclization of *N*-substituted diaminoalkenes or -alkanes include the preparation of 2-alkyl- and 2-acyl-1-methylimidazole-4-carboxylates from methyl (*Z*)- β -dimethylamino- α -isocyanoacrylate (191) in reaction with an alkyl or acyl halide $\langle 82\text{LA}2093 \rangle$, the preparation of perfluorinated 3-imidazolines (192) $\langle 83\text{S}169 \rangle$, the high yield synthesis of 2-imidazolines by decay of phosphaza compounds (193) in a version of the intramolecular Staudinger reaction $\langle 85\text{T}793 \rangle$, and the formation of 1,3-diaroylimidazolidines (34–71%) when bis-alkylidene- or -arylidene-ethylenediamines react with acid chlorides in polar solvents (Scheme 129) $\langle 83\text{BAU}1231 \rangle$.

A new synthesis of 2-imidazolin-5-ones (194) utilizes an intramolecular aza-Wittig reaction. Readily available azidoimides are treated with triphenylphosphine to give (194) by sequential Staudinger and intramolecular aza-Wittig processes (Scheme 130) $\langle 89\text{T}6375 \rangle$.



Scheme 128

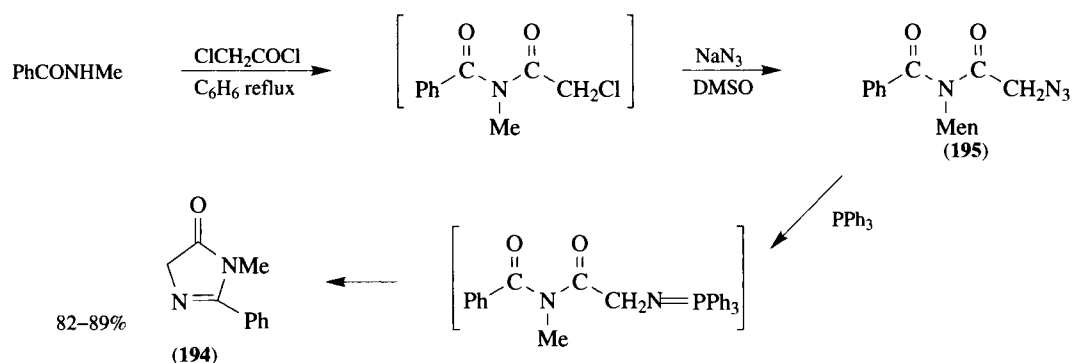


Scheme 129

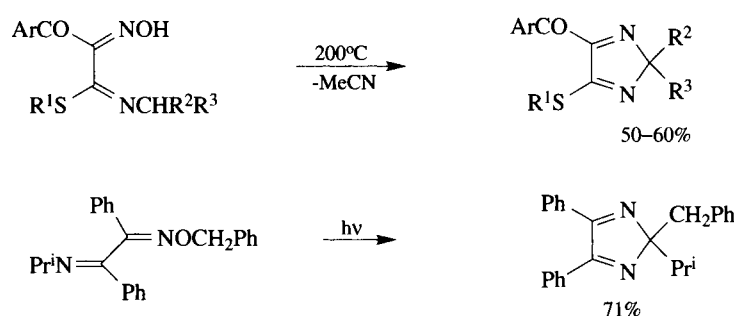
Suitable substituted 1,2-diamines and derivatives can be cyclized to 2*H*-imidazoles, either photochemically or by thermolysis in the presence of a base [87S547, 87TL4605, 89JCS(P1)2035]. The 2*H*-imidazole products cannot be isomerized to the 1*H*-isomers either thermally, or by boiling with acetic acid (Scheme 131) [87S547].

The rather uncommon 4- and 5-imidazoethiols can be made by a dehydration-cyclization of (195), a reaction promoted by formic acid, trimethylsilyl triflate, or triethylamine [87JOC2977]. Similarly, when the 1,2-diamine has a carbonyl function replacing one of the methylene groups the products are 4-imidazolidinones, as in the 2-iminohydantoin (196) synthesis illustrated (Scheme 132) [87HCA1930, 87SC1677, 89S530].

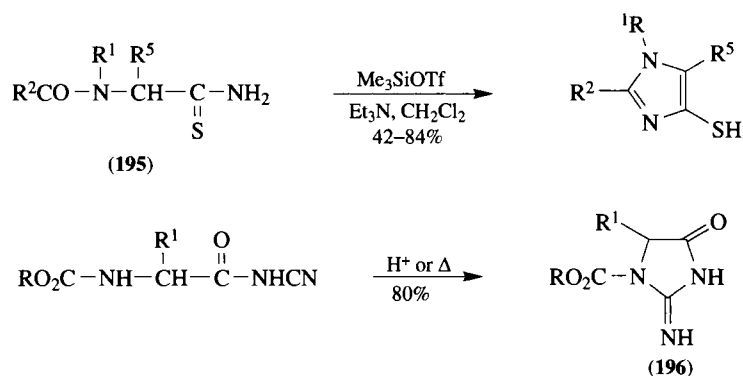
It has been found convenient to prepare 5-aryl-2-methoxycarbonyl-1-phenacyl-2-imidazolines by acid-catalyzed cyclization of 1,2-bis(methoxycarbonyl)-3-(2-anilinoalkyl)guanidines (198) made from *N*-alkylideneanilines (197) [92S664]. Cyclization of 3-[*N*-methyl-*N*-(ethoxycarbonyl)amino]-3-



Scheme 130



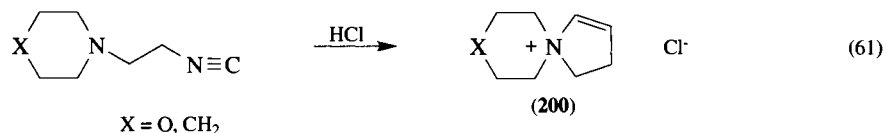
Scheme 131

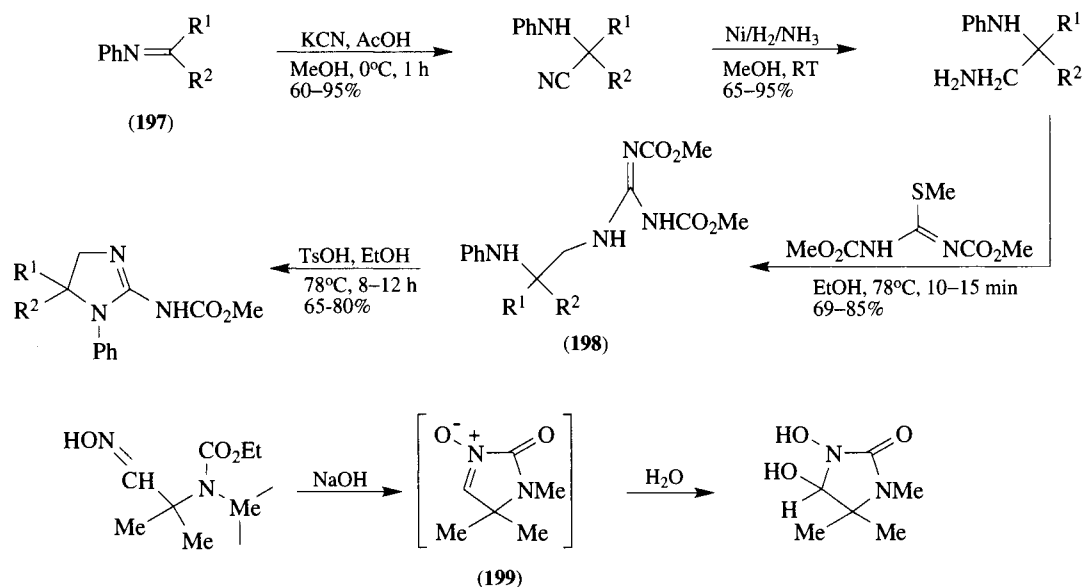


Scheme 132

methyl-2-butanone oxime in alkaline medium gives the 3-imidazolin-2-one 3-oxide (**199**) (Scheme 133) <83CHE540>.

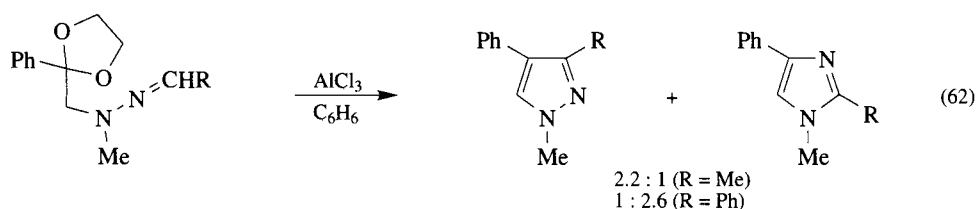
Amino-nitriles or -isonitriles react with acids to give imidazolium salts (**200**) (Equation (61)) <83CHE684>, and hydrogenation of 2-acylaminoethanenitriles yields 2-imidazolines in 61–83% yields <86MI 302-04>. Imidazolidinones and hydantoin can be made by oxidative cyclization of α -acylaminonitriles <94JOC1072>. The photochemical conversion of 3-aminopropenenitrile into imidazole has been the subject of an *ab initio* study which suggests that the most favorable isomerization pathway proceeds via an azirine <81JOC2872>.



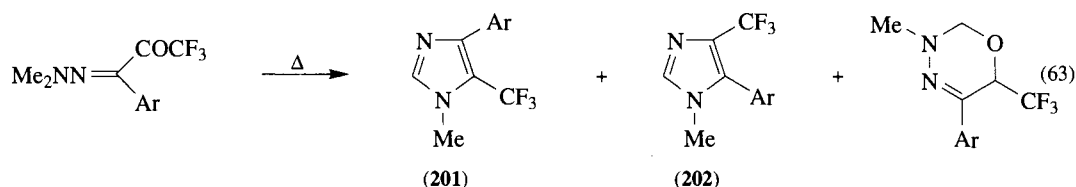


Scheme 133

In an unusual cyclization process, benzil monohydrazones heated in toluene form 4,5-diphenyl-imidazoles (> 80%) rather than the expected pyrazoles. The way in which the N—N bond breaks and reorganizes is uncertain, but either a diaziridine or a diazetidine ylide intermediate may be involved. If it is the latter the 1,2-bond of imidazole is formed; if the former it will be 1,5-bond formation (85TL1595, 86BSB655). Similarly, cyclization of phenacyleneketal hydrazones of benzaldehyde and ethanal yields both pyrazoles and imidazoles (Equation (62)) (86BSB1073).

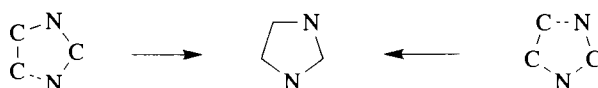


A related synthesis leads to 4-trifluoromethylimidazoles. Trifluoroacetylated aldehyde dimethyl-hydrazones thermally rearrange to give mixtures of oxadiazines and imidazoles. Higher temperatures and more polar solvents suppress formation of the six-membered rings, while solvent variation also alters the proportions of the imidazole regioisomers. In carbon tetrachloride the major product is (201), in toluene a 4:1 ratio of (201) to (202) is isolated, while heating in the presence of silica gel (no solvent) the comparable ratio is 1:3. Such cyclizations occur equally well with other dialkylaminohydrazones bearing other acyl groups (Equation (63)) (90H(31)2103, 90JHC487, 90S467).



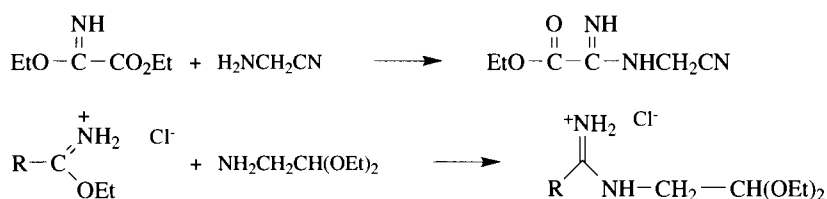
(ii) Formation of the 1,5-(or 3,4-) bond (Scheme 134)

Most syntheses which come under this classification are cyclizations of *N*-substituted amidines or ureas. The amidines can be presynthesized or involved as unisolated intermediates formed



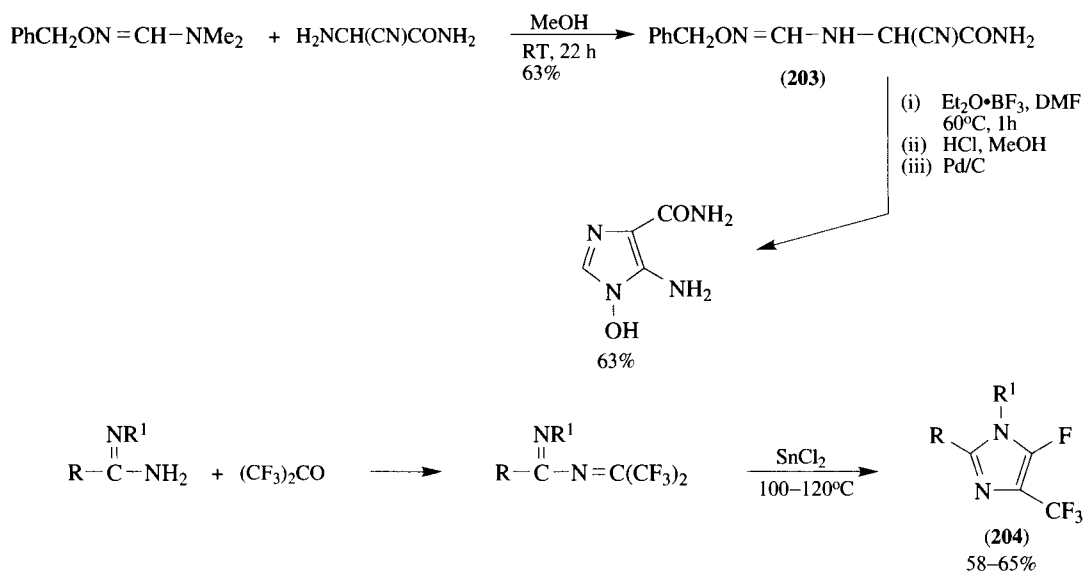
Scheme 134

from smaller fragments, for example, from formimidates and 2-aminonitriles $\langle 83\text{TL}3357 \rangle$, or from reactions of iminoesters with aminoacetals (Scheme 135) $\langle 82\text{JHC}1403, 87\text{H}(25)601 \rangle$. The ureas are less useful synthons because they do not allow variation of the imidazole 2-substituent. Some aspects of these types of synthetic approach have been reviewed $\langle 87\text{H}(25)601 \rangle$.



Scheme 135

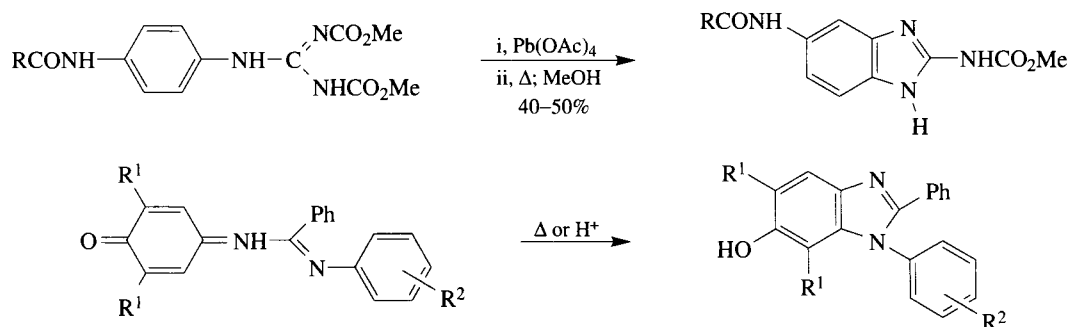
An improved synthesis of 5-amino-1-hydroxyimidazole-4-carboxamide from reaction between *N'*-benzyloxy-*N,N*-dimethylformamidine and 2-amino-2-cyanoacetamide proceeds through an intermediate amidine (**203**) which is cyclized by boron trifluoride etherate $\langle 90\text{S}893 \rangle$. Similar acid-induced cyclizations of amidines have been used to prepare 2-dimethylaminoimidazole (83%) $\langle 91\text{TL}5325 \rangle$, and 5-fluoro-4-trifluoromethylimidazoles (**204**) $\langle 82\text{CB}2494, 88\text{S}189, 88\text{S}194 \rangle$, and there are numerous other examples (Scheme 136) $\langle 88\text{TL}3001, 89\text{TL}2379, 92\text{JCS}(\text{P}1)1643, 92\text{JHC}825 \rangle$.



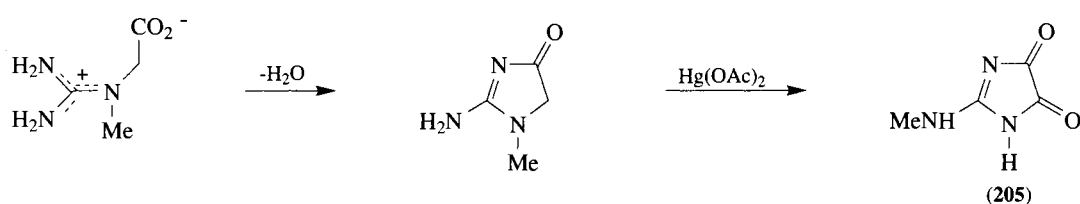
Scheme 136

Similarly, appropriately functionalized aryl-amidines and -guanidines can be cyclized to form 1-alkyl- or 1-aryl-benzimidazoles $\langle 82\text{CJC}1122, 88\text{JHC}1029 \rangle$ or 2-aminobenzimidazoles $\langle 82\text{CPB}2996, 83\text{TL}3155, 86\text{JCR}(\text{S})158, 87\text{BCJ}4115 \rangle$ under oxidative or acidic conditions, or merely by heating the reagents (Scheme 137). The key step in the second reaction of Scheme 137 is the intramolecular addition of the amidine nitrogen to the quinoneimine system $\langle 88\text{JHC}1029 \rangle$. Not all attempts to cyclize arylamidines have proved synthetically viable $\langle 92\text{T}7619 \rangle$.

When 4*H*-1,3-benzothiazine-4-thiones react with propargylamine imidazoles form in 53–72% yields by way of an amidine intermediate $\langle 87\text{LA}103 \rangle$. Oxidation of the dehydration product of creatine gives creatone (**205**) with concurrent Dimroth rearrangement (Scheme 138) $\langle 82\text{BCJ}1912, 87\text{BCJ}4115 \rangle$.



Scheme 137



Scheme 138

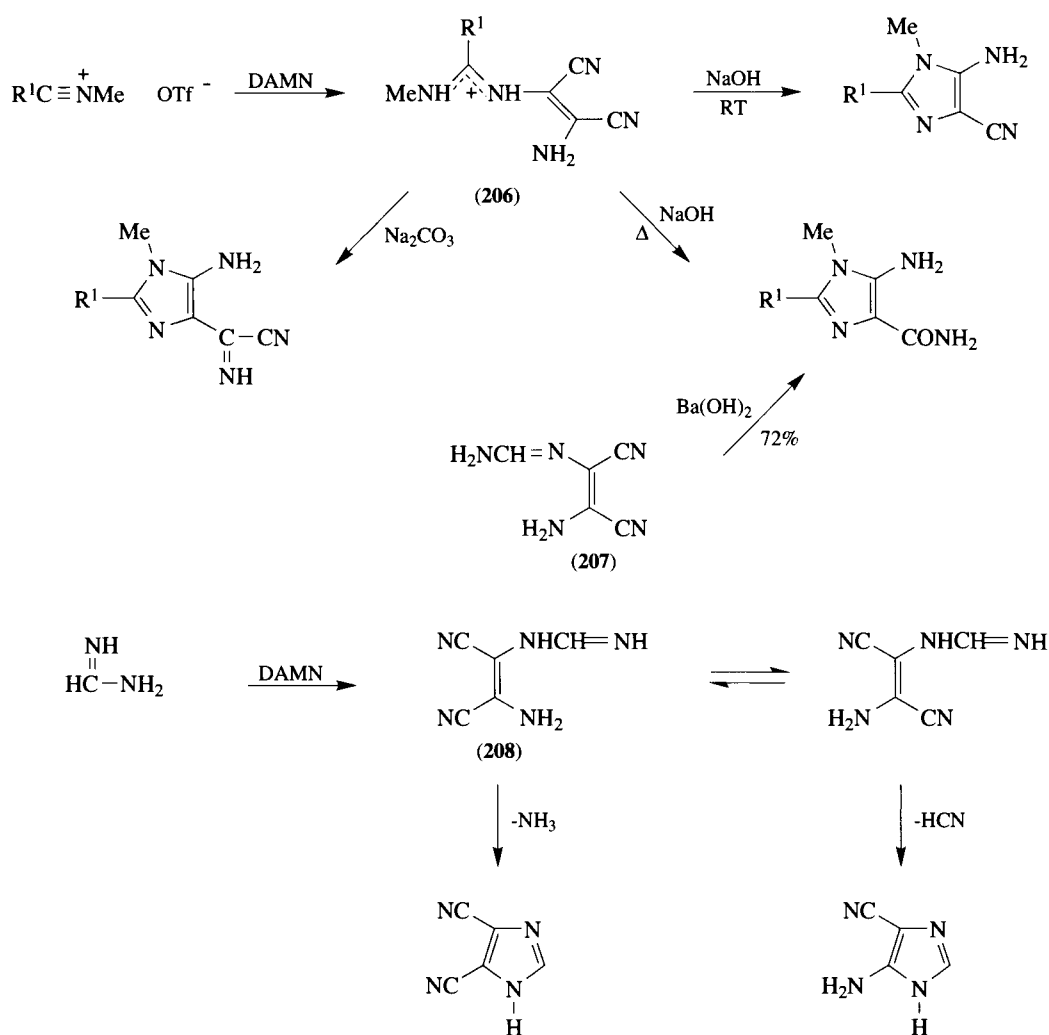
Amidinium salts (**206**) are formed when diaminomaleonitrile (DAMN) reacts with nitrilium triflate salts. Base treatment converts these salts, or the analogous dicyanovinylamidine (**207**), into 5-amino-4-carbamoyl-, 5-amino-4-cyano-, or 5-amino-4-(cyanoformimidoyl)-imidazoles <87JCS(P1)1521, 90JCS(P1)1705>. Similar syntheses lead to 1,5-diamino- <92JCS(P1)913> and 4-amino-5-cyano-imidazoles <93JCR(S)402>. Reaction of DAMN with formamidine gives (**208**) which can eliminate ammonia to form 4,5-dicyanoimidazole or, after isomerization, lose HCN to give 4-amino-5-cyanoimidazole <87H(26)497, 93CRV1991>. The manifold uses of DAMN in imidazole synthesis have been reviewed (Scheme 139) <93CRV1991>.

Acid-catalyzed cyclization of suitably substituted ureas gives imidazoline- or imidazolidine-2-ones <84CHE323, 85BAU1534, 87H(26)3153, 89CC452, 91T2263>, or hydantoins <85CHE359, 90JHC739, 91MI 302-01, 92SC823>. 2-Imidazolinone synthesis has been reviewed <85BAU1534>. The ureas required for these syntheses can be made from isocyanates and primary amines <84CHE323, 87H(26)3153> or hydrazines <83CHE74>, or from thiocyanates with hydrazines <86S559>, α -aminonitriles with carbon dioxide <92SC823>, and 1,3,4-oxadiazolones with α -amino acids (Scheme 140) <90JHC739>.

High yields of 2-imidazolines are obtained on iodocyclization of *N*-allylthiureas <89TL4435>. Reaction of *N*-methoxy-*N'*-arylureas with *t*-butyl hypochlorite gives unstable *N*-chloro-*N*-methoxy-*N'*-arylureas which cyclize in basic conditions to give 1-methoxy-2-benzimidazolones (56–83%) in a one-pot reaction <82G507>. β,γ -Acetylenic carbanilides cyclize and subsequently isomerize to 2(3*H*)-imidazolethiones and 2(3*H*)-imidazolones when treated with hydrogen sulfide and potassium hydroxide respectively in *t*-butanol. Yields are almost quantitative <94TL1585>.

(iii) Formation of the 4,5-bond (Scheme 141)

Such syntheses are quite uncommon, being largely limited to bond formation between an 'active' methylene centre and the carbon of a nitrile or imine. This, of course, will give rise to a 4(5)-aminoimidazole. The cyclizations are usually base-catalyzed because base is needed to form the anion at the "active" methylene group <86JHC913>. In a similar process, carbanions generated from the products of reaction of 1-azirines and formamidine give imidazoles in moderate yield <91JOC7>. Treatment of the perhydrothiazine-2-thione (**209**) with trifluoroacetic anhydride was reported to give an imidazothiazine (Scheme 142) <87MI 302-03>.



Scheme 139

3.02.8.1.2 Formation of two bonds

(i) From [4 + 1] carbon fragments

(a) Formation of the 1,2- and 1,5-bonds (Scheme 143):

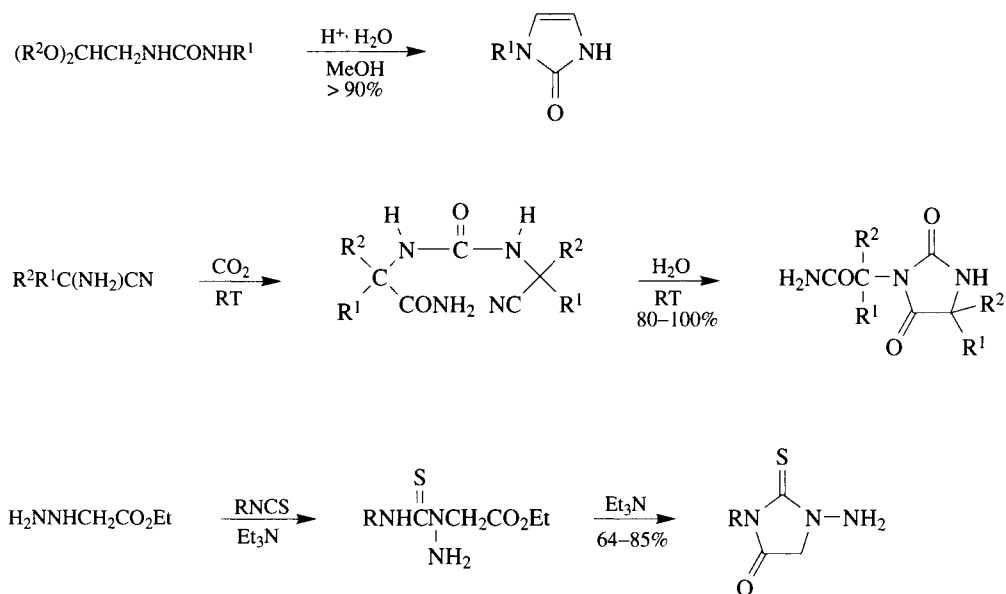
There have been no particularly novel examples of these syntheses since those described in CHEC-I.

Reactions of *N*-acyl- or *N*-cyano-imidates with primary amines, hydrazines, or hydrazides have been used on occasion. The latter two reagents adapt the process to the synthesis of 1-amino-imidazoles (210) <87HCA187, 93AHC(57)1>. Nucleophilic attack by the amino group displaces the morpholine function in the first step. A related synthesis has provided the best method yet for making 2-imidazolin-5-ones (211) (Scheme 144) <85TL1915>. In the sequential addition of β -aminoesters and amines to diphenylcyanocarbonimide the preferred intramolecular cyclization to give five-membered rings has been applied to the synthesis of imidazolidinones <90T7803>.

The cyclization of acylamides with amines or ammonia has been useful on occasion, for example, in the synthesis of 1-aryl-imidazolinones (212) from benzoxazolones (Scheme 145) <80CL659, 86CPB3111, 88CHE1129>.

Tosylmethylisocyanide (TOSMIC) has been used only rarely in syntheses of this type. One example though is the preparation of 2-carbamoyl-4-(2'-deoxy- β -D-ribofuranosyl)imidazole from the deoxyribosealdehyde <91TL6915>.

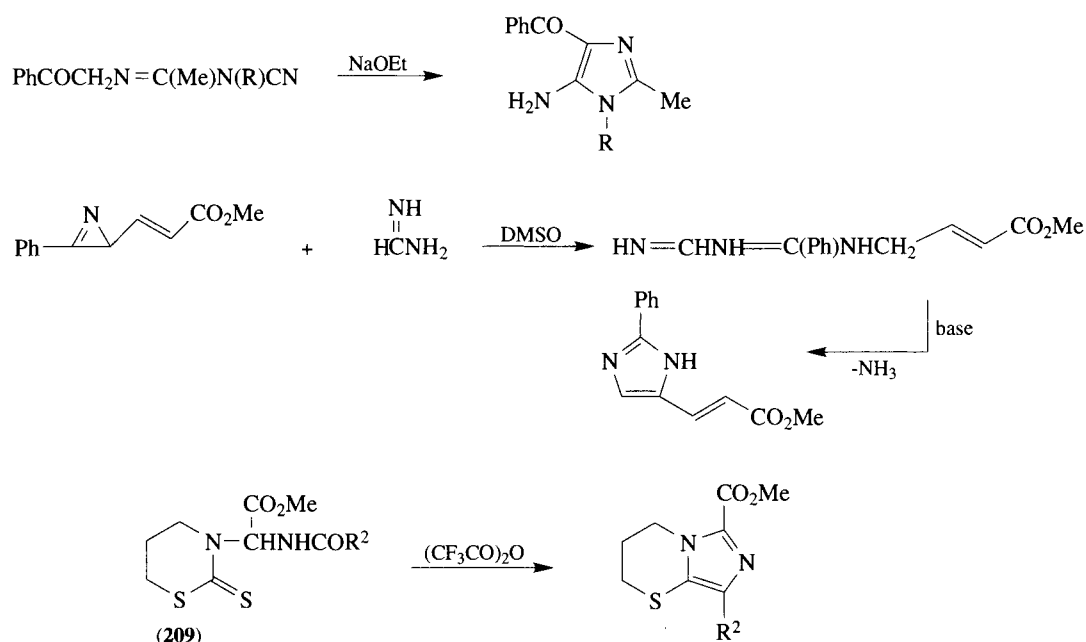
A number of methyl 1,5-disubstituted imidazole-4-carboxylates have been made in moderate to



Scheme 140



Scheme 141

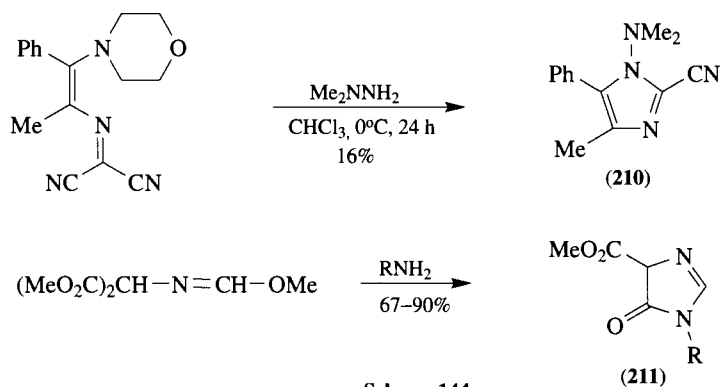


Scheme 142

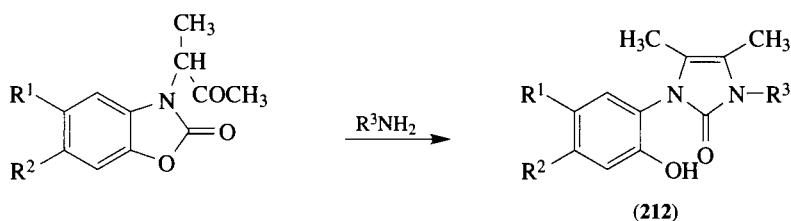
good yields from methyl 3-bromo-2-isocyanoacrylates with a variety of primary amines in the presence of triethylamine. The parent compound ((213), $R^1 = R^5 = H$) was not, however, made by this method (Scheme 146) <90S781>.



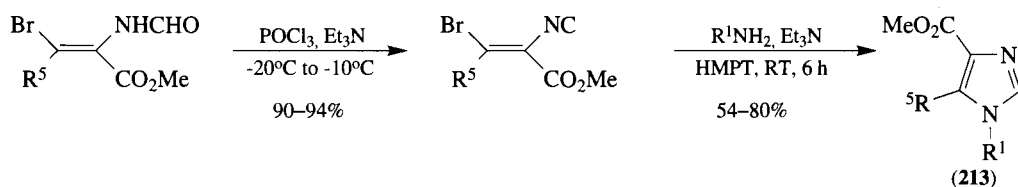
Scheme 143



Scheme 144

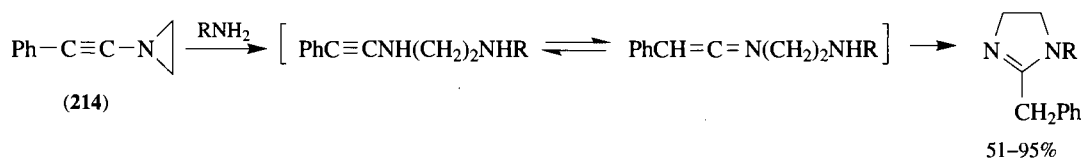


Scheme 145



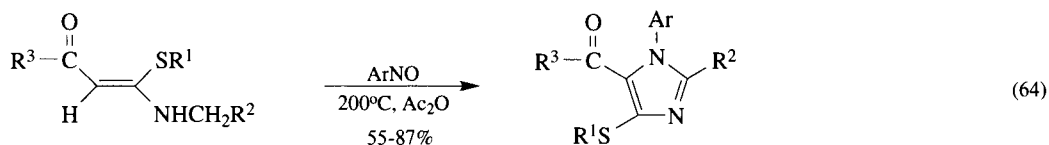
Scheme 146

When 4-amino-2-azabutadienes are heated with primary amine hydrochlorides the products cyclize to form imidazoles (CHEC-I). Related to this is the reaction of 1-phenylethynylaziridine (**214**) with a primary amine (Scheme 147) <87CHE1143>.

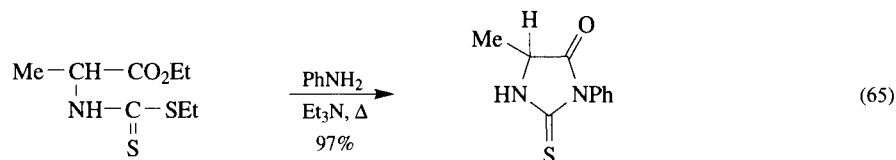


Scheme 147

Heating oxoketene acetals with nitrosoaromatic compounds in acetic anhydride at 200°C gives imidazoles. With nitrosyl chloride in pyridine or acetonitrile the *N*-unsubstituted imidazole can be made (Equation (64)) <84CC430, 85IJC(B)463>.



3,5-Disubstituted 2-thiohydantoin can be prepared by heating *N*-(alkylthiocarbonyl)amino acids with primary amines (Equation (65)) <83S391>.



Formation of the 1,2- and 2,3-bonds (Scheme 148):



Scheme 148

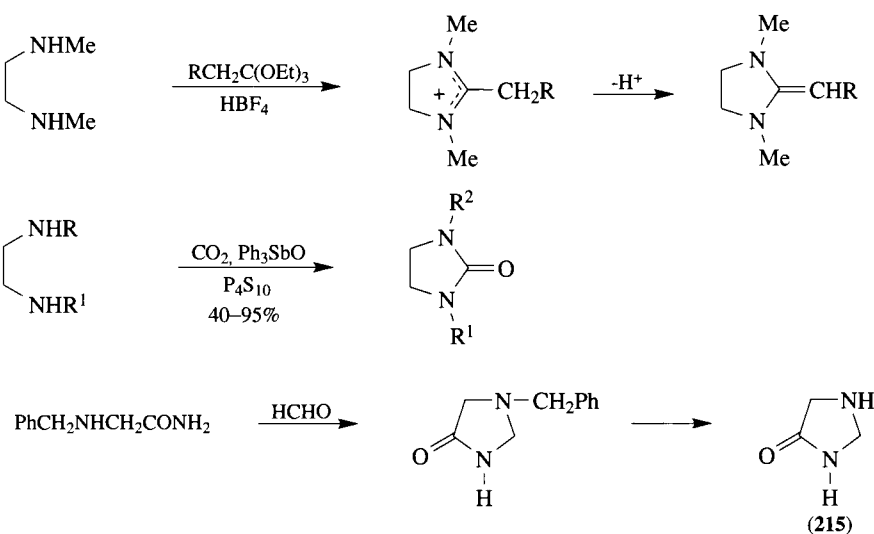
This is the most common annelation approach with cyclization of 1,2-diaminoalkanes, -alkenes, or -arenes the methods of choice. The variant which cyclizes an acylated diamine has already been covered (see Section 3.02.8.1.1(ii)).

Reactions of 1,2-diaminoalkenes with alcohols, aldehydes, or carboxylic acids and derivatives at high temperatures in the presence of a dehydrogenating agent are common approaches to the synthesis of 2-substituted imidazoles <89KFZ1246>. In the absence of the dehydrogenating agent the products are imidazolines. The method is particularly applicable to the synthesis of purines from 5,6-diaminopyrimidines <92JOC559>. When 1,2-diaminoalkanes are used the products may be imidazolidines or imidazolines <85JHC177, 85S657, 87CHE592, 87CJC282, 87CB205, 87S64, 87S357, 88LA993, 89IZV140, 90CHE599, 90JOC1772, 91CHE1140, 91T9901, 92JOC7339, 92MI 302-01, 93JOC3387, 93S1013, 93ZOR881, 94H(37)1233>. A substituted diamine can lead to the formation of a quaternary salt which, if capable of deprotonation, can give 2-alkylideneimidazolidines <87CB2053>. Use of carbon disulfide leads to 2-thiones <91TL4791>, while carbon dioxide gives 2-imidazolidinones <92JOC7339>. With *N*-(1-chloroalkyl)pyridinium chlorides (prepared from pyridine, thionyl chloride, and the appropriate aldehyde) as the source of C-2 a variety of 2-substituted imidazolidines is possible <92BSB233>. Efforts to prepare 4-imidazolidinone (**215**) have focussed on the reaction of appropriate glycnamides with formaldehyde. The product is rather unstable <88LA993>, but the 2-*t*-butyl derivative has been successfully made in this way <93AG(E)1765>. Some examples are shown in Scheme 149.

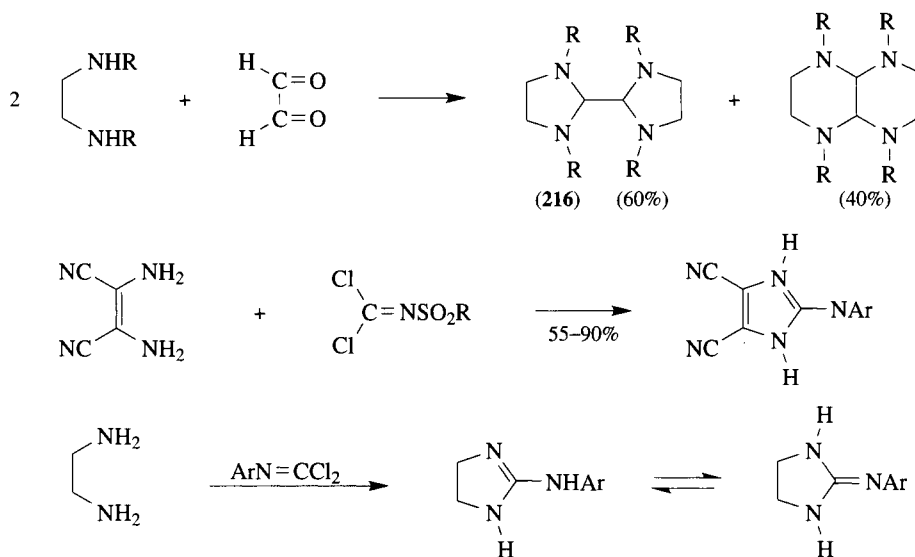
The one-step conversion of diaminoethane into 2-imidazolines (89–96%) uses reaction with esters in the presence of trimethylaluminum <81JOC2824>. When 1,2-diamines are treated with glyoxal biimidazolidine (**216**) and azadecalin products are both formed <85JOC2365>. Other carbon sources which have proved useful include diphenyl *N*-sulfamoylcarbonimidate <91S753>, *N*-dichloromethylenesulfonamides and arylcarbonimidates (Scheme 150) <82S984, 87S64>.

Reactions of *ortho*-phenylenediamines (or *N*-acyl derivatives) with carbon fragments is the major route for preparing 2-substituted benzimidazoles <82S984, 84SC947, 85H(23)2705, 86AG(E)650, 87JHC31, 87JHC885, 87JOC4137, 88JHC403, 88SC167, 89BSF443, 89H(29)57, 89JHC409, 89JHC1163, 89JFC(42)245, 90CHE599, 90JHC1177, 90SC955, 91H(32)1003, 91JHC1245, 91JOC2260, 91S753, 92AJC525, 92JCS(P1)3129, 92JMC539, 92S395, 92S1283, 93BSB357, 93CB1819, 93OPP703>. A simple, one-step process uses ethyl triethoxyacetate to convert *o*-phenylenediamines into benzimidazole-2-carboxylates (**217**), an improvement over the customary multistep processes <84SC947>. Quantitative yields of 2-methylbenzimidazole (**218**) are achievable by silylation of diacetylated *o*-phenylenediamine, and then cyclization in the presence of hexamethyldisilazane and a catalytic amount of triflic acid <88SC167>. The use of dichloro- or dithiocarbonimidates is useful in the synthesis of 2-aminobenzimidazole (**219**) <83S375, 83S861>, as are cyanamino species (Scheme 151) <83M789>.

It has been shown that when *o*-phenylenediamine condenses with aromatic carboxylic acids in a melt at 185–250 °C (or in high boiling point solvents) in the presence of acids such as polyphosphoric



Scheme 149



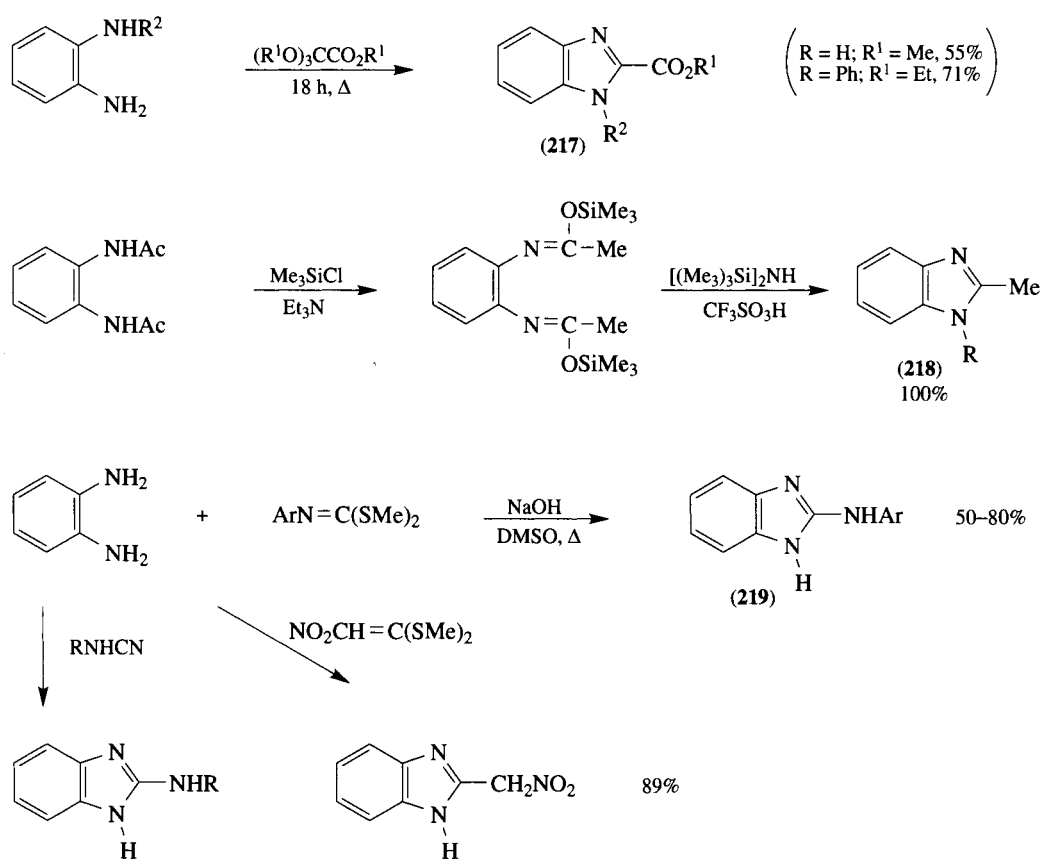
where Ar = 2,6-dichlorophenyl; the product is the drug "clonidine"

Scheme 150

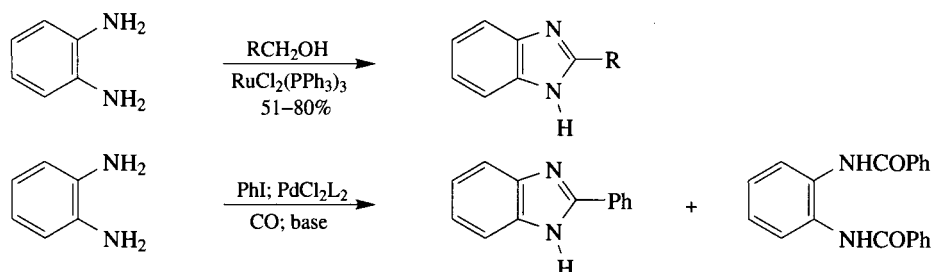
acid (especially with tetrabutoxytitanium as catalyst) the yields of 2-arylbenzimidazoles decrease in the order $2\text{-NO}_2 > 2\text{-Me} > 4\text{-Cl} > 2\text{-Cl} > \text{H} > 4\text{-NO}_2 > 2\text{-NH}_2$ (yields 48–95%) (86JOU2215). There has been a review of the applications of high pressure to reactions of this type (85S1). When hydroxybenzaldehydes react with *o*-phenylenediamine, the initial reaction at low temperature results in the formation of monoanils. When the monoanil of *o*-hydroxybenzaldehyde is boiled in butanol the product is the 2-arylbenzimidazole, but the corresponding anils of *m*- and *p*-hydroxybenzaldehydes give 1-alkyl-2-arylbenzimidazoles. In nitrobenzene, however, the 1-substituents are not introduced. Dianils of *o*-hydroxybenzaldehyde in boiling butanol give both types of benzimidazole (83RTC73).

Ruthenium complexes catalyze the reaction of primary alcohols with *o*-phenylenediamine. The catalyst apparently has dual roles in promotion of cyclization and oxidation of the alcohol to aldehyde (91CL1275). A novel palladium-catalyzed carbonylation of iodobenzene has been linked to base-induced coupling and cyclization with *o*-phenylenediamine to give 2-arylbenzimidazoles without having to use an arylcarboxylic acid (Scheme 152) (93JOC7016).

3-Arylamino-2-nitro-2-enones (220) condense with orthoesters in the presence of reducing agents to form imidazoles (Equation (66)) (87JHC1757). Similarly, reductive cyclization of 2-nitroanilines

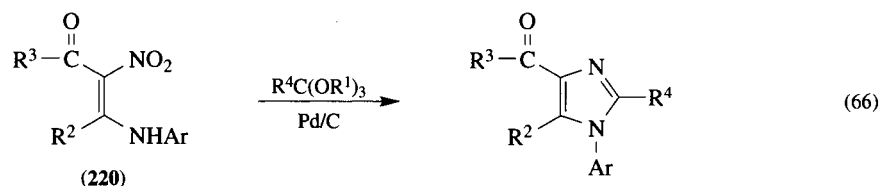


Scheme 151



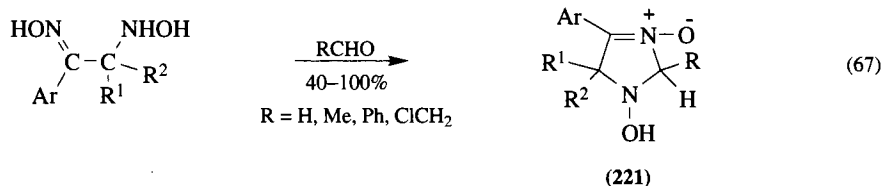
Scheme 152

gives benzimidazoles $\langle 85\text{JOC}2456, 87\text{JOU}576, 92\text{JMC}877, 92\text{JMC}4455 \rangle$. This reaction has been adapted to the synthesis of benzimidazolones by reductive carbonylation of 2-nitroanilines with ammonium formate and elemental sulfur. The formate is an efficient carbonyl source which is preferable to the alternative source, carbon monoxide $\langle 92\text{CE}949 \rangle$.

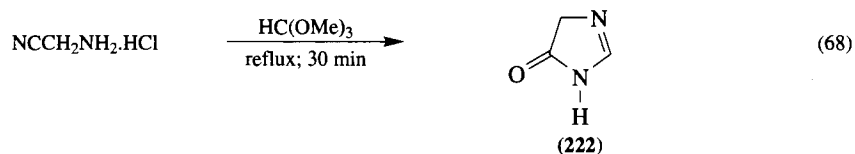


Glyoxal reacts with primary amines to give diazadienes which cyclize in the presence of dry HCl to form imidazolium salts $\langle 86\text{CB}1868 \rangle$. Similar methods have been applied to the synthesis of imidazoline and benzimidazole 1-oxides (or their tautomers). Thus, 1-hydroxylamino oximes react at room temperature with formaldehyde (or on heating with other aldehydes) to give 1-hydroxy-3-

imidazoline 3-oxides (**221**) (Equation (67)) <86S704>. Hydroxylaminocyclohexanone oxime gives mixtures of 1-hydroxyimidazoles and pyrazine 1,4-dioxides under similar conditions <83CHE1104>. Again, *o*-benzoquinone dioxime reacts with aromatic aldehydes in the presence of strong acids to form 2-aryl-1-hydroxybenzimidazole 3-oxides <90JPR345>.



Aminoacetonitrile and derivatives are converted by aldehydes or orthoformates into 2-imidazolin-4-ones (**222**). The major reaction product, however, is *N*-formylaminoacetonitrile, and so the process is not very efficient (Equation (68)) <84LA831, 88LA993>. A rapid method for preparing *N*-substituted α -aminonitriles has application to this procedure (Equation (68)) <85SC157>.



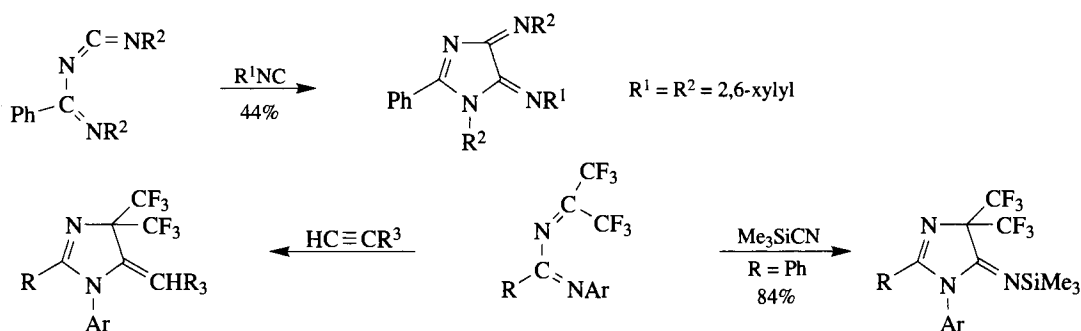
Diiminosuccinonitrile reacts with trifluoroacetic anhydride to give 2*H*-imidazoles <91CB1517>.

(b) Formation of the 1,5- and 4,5-bonds (Scheme 153):



Scheme 153

This is an uncommon scenario in imidazole synthesis, largely confined to reaction of alkynes, nitriles or isocyanides with 1,3-diazadienes <83CZ271, 84CZ209, 88CB271, 88S44, 93AHC(57)1>. Some examples are shown in Scheme 154. The trapping of diazatrienes with isocyanides is a regiospecific [1 + 4]cycloaddition <85JOC771>.



Scheme 154

(ii) From [3 + 2] carbon fragments

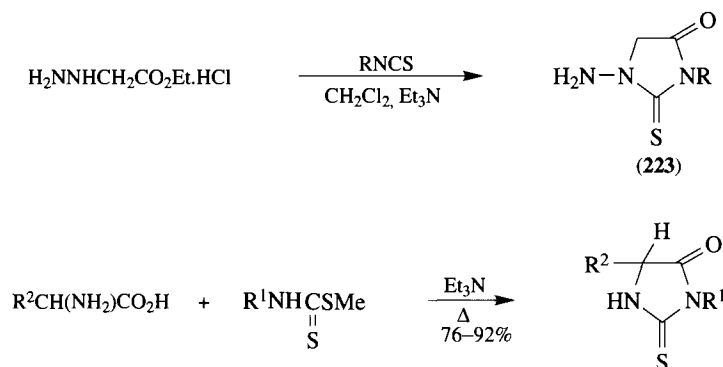
(a) Formation of the 1,5- and 2,3- (or 1,2- and 3,4-) bonds (Scheme 155):



Scheme 155

The most common examples utilize the old Marckwald synthesis in which an α -aminocarbonyl species (or equivalent aminonitrile) reacts with cyanates, thiocyanates, cyanamide, etc. to give 2-imidazolones, 2-imidazolethiones, 2-aminoimidazoles, or reduced versions in cases where aromatization is not favored. Often oxidation or dehydrogenation will accomplish the aromatization.

Thus, 1-aminothiohydantoin (**223**) can be made in good yields by reaction of ethyl 2-hydrazinoacetate with a suitable alkyl thiocyanate $\langle 92\text{MI } 302\text{-}02 \rangle$. Similarly, an α -amino acid, heated with a dithiocarbamic ester, gives a thiohydantoin. An adaptation of this is a one-pot procedure from amino acid, amine, carbon disulfide and base without isolating the dithiocarbamic ester (Scheme 156) $\langle 83\text{S}391 \rangle$.



Scheme 156

A high-yielding synthesis of 2,2'-biimidazole (**224**) follows the normal sequence $\langle 86\text{S}336 \rangle$. Carbodiimides, too, can act as the two-atom fragment in reaction with α -aminocarbonyl compounds $\langle 93\text{CPB}301 \rangle$, as can imidic esters $\langle 82\text{JHC}659, 85\text{JHC}537, 85\text{JOC}1134, 87\text{JMC}150, 90\text{SC}2519, 93\text{JOC}6354 \rangle$. Conversion of α -bromoketones into α -aminoketones, followed by heating with formamide gives 20–82% yields of 1,4-disubstituted imidazoles $\langle 94\text{JOC}1589 \rangle$. There are many similar examples (Scheme 157) $\langle 83\text{CPB}4549, 84\text{CPB}2536, 85\text{JHC}741, 86\text{CPB}3111, 88\text{S}767, 89\text{JHC}1523, 89\text{SC}2947, 89\text{S}38, 90\text{TL}3849, 94\text{HCA}575 \rangle$.

Aziridines undergo palladium-catalyzed cycloadditions with carbodiimides to form imidazolidinimines in regiospecific processes which involve cleavage of the more substituted ring C—N bond $\langle 92\text{JOC}157 \rangle$. With alkyl or aryl isocyanates in the presence of sodium iodide there is also regiospecific formation of 2-imidazolidinones. Thus, with (**225**) ($\text{R}^1 = \text{SO}_2\text{Ph}$; $\text{R}^3, \text{R}^2 = \text{Ph}$) the main product is (**226**) (98%) (Scheme 158) $\langle 92\text{TL}7949 \rangle$.

2-Dimethylaminoazirines (**227**) react similarly with isocyanates or isothiocyanates to form imidazolinones or the corresponding thiones $\langle 88\text{JOC}5298 \rangle$. With carbamate or thiocarbamate esters (**227**) gives imidazolin-2-ones $\langle 82\text{H}(19)2079 \rangle$ or thiohydantoin (Scheme 159) $\langle 90\text{HCA}594 \rangle$.

Dimerization of α -(*N*-trimethylsilyl)imino esters in methanol gives 2-alkoxycarbonylimidazole-4(*2H*)-ones $\langle 89\text{JCS}(P1)279 \rangle$, while imines of diethyl aminomalonate also dimerize slowly in ethanol or dichloromethane at 40 °C (Scheme 160) $\langle 89\text{T}4649 \rangle$.

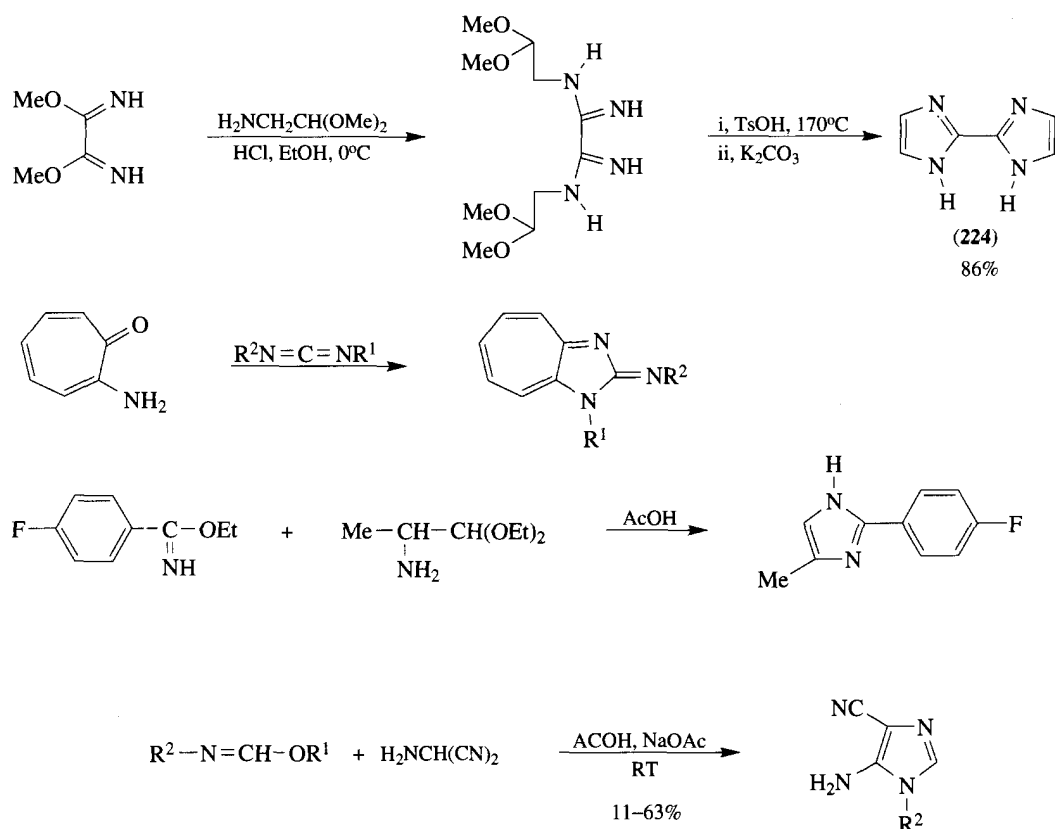
When α -hydroxyimino- β -dicarbonyl compounds are refluxed with allylamine, the products are 2-vinylimidazoles (Equation (69)) $\langle 85\text{S}300 \rangle$.

Reaction of 1,2-diketone monophenylhydrazones with aminomalononitrile gives imidazole-2-carboxamides $\langle 92\text{H}(34)2373 \rangle$. Aromatic Schiffs bases cyclize with *syn*-2-bromoacetophenone oxime to give low yields of 3-imidazoline 3-oxides $\langle 93\text{SC}1699 \rangle$. Reaction of an oxime with *N*-methylbenzenecarboximidoyl chloride initially generates an amidine via a sigmatropic rearrangement. In the presence of acids 2-phenylimidazoles (42–96%) are formed $\langle 93\text{JOC}7093 \rangle$. Aryl cyanides react with α, α -dilithioarylnitromethanes to form 2,4,5-triarylimidazoles in moderate to good yields, possibly via an unusual cyclization–elimination process $\langle 94\text{H}(38)575 \rangle$.

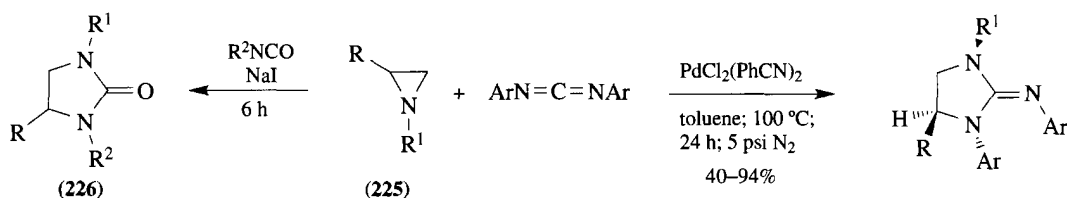
(b) Formation of the 1,2- and 4,5-bonds (Figure 3):



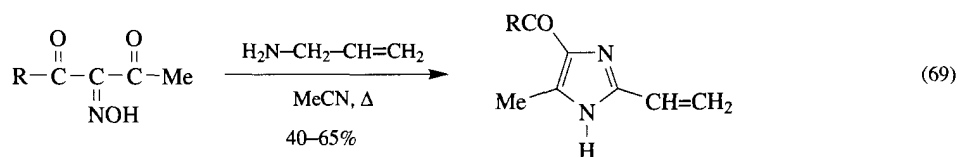
Figure 3



Scheme 157

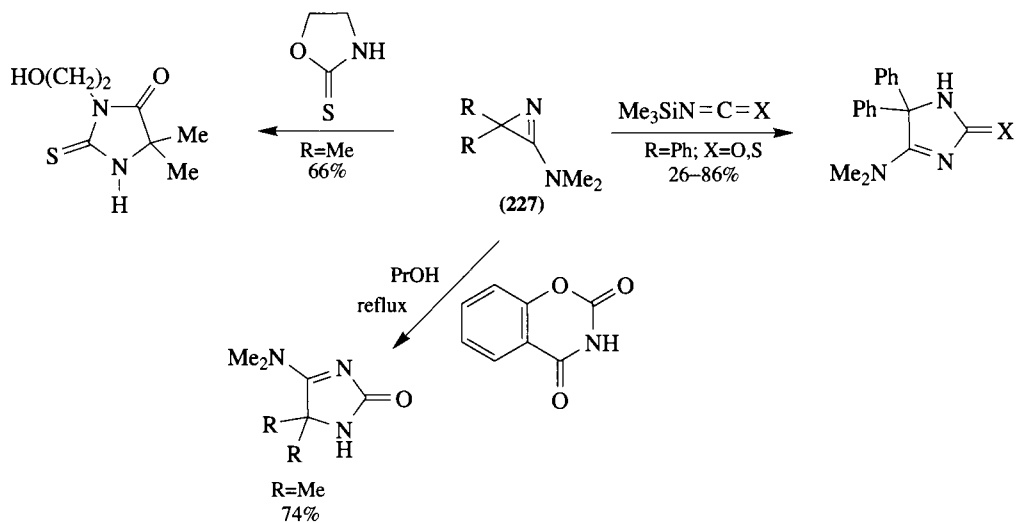


Scheme 158

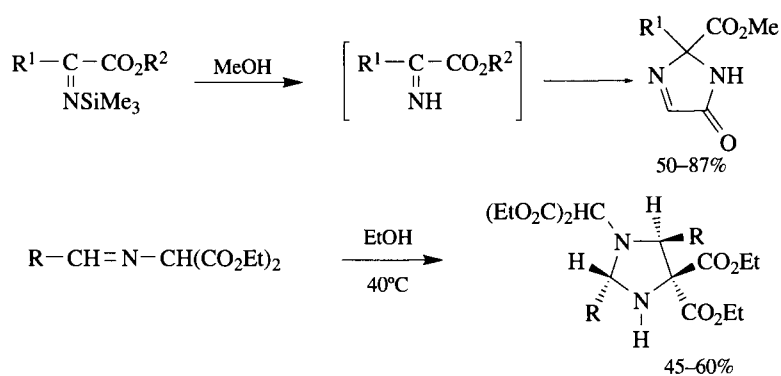


Applications of toluene *p*-sulfonylmethyl isocyanide (TOSMIC), which enters into base-catalyzed cycloaddition reactions with aldimines in protic media to form 1,5-di-, 1,2,5- and 1,4,5-trisubstituted imidazoles, and 2-imidazolines, were summarized in CHEC-I. Later examples include the reactions of the reagent with heterocyclic iminoethers <82JOC2043>, and the modification which involves the cycloaddition of *N*-trimethylsilylamines with lithiotosylmethylisocyanides to form 4- and 4,5-disubstituted imidazoles from readily accessible aldehydes and organolithium reagents in a one-pot reaction. Although yields are only moderate the readily available starting materials offset this problem (Scheme 161) <93TL595>.

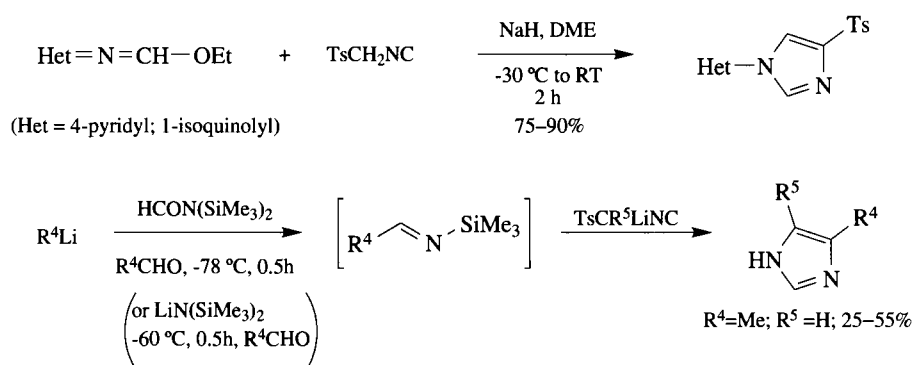
The cycloaddition of the mesoionic isoxazole (228) to an *N*-(phenylmethylene)benzene sulfonamide provides a versatile entry to 1,4,5-tri- and 1,2,4,5-tetrasubstituted imidazoles which form via elimination of carbon dioxide and benzenesulfonic acid. The mesoionic (228) are masked 1,3-dipoles ('munchones') (Equation (70)) <91JCR(S)188, 93JCS(P2)1511>.



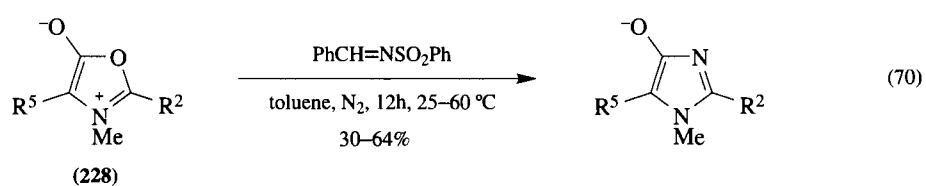
Scheme 159



Scheme 160

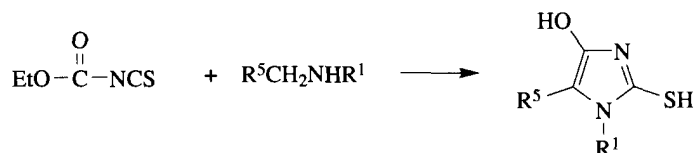


Scheme 161

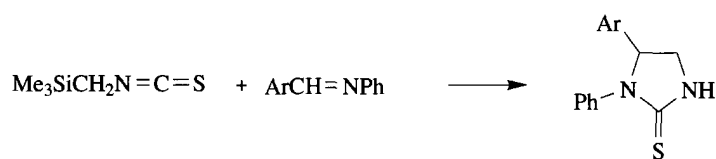


(70)

With *N*-alkylaminoacetates or *N*-alkylaminoacetonitriles, ethoxycarbonyl isothiocyanate forms 1,5-disubstituted 4-hydroxy-2-thiolimidazoles <83JHC1127>. Conversion of trimethylsilyl isothiocyanates into isothiocyanatomethanides, and reaction of these with suitable imines gives moderate yields of imidazolidine-2-thiones (Schemes 162 and 163) <83H(20)139>. Although the reactions of isothiocyanates with metal salts of α -cyanoacetate esters usually give thiazoles as major products and imidazoles only as minor by-products, adjustment of the reaction conditions can raise the imidazole proportion to 24% <87H(26)651>.

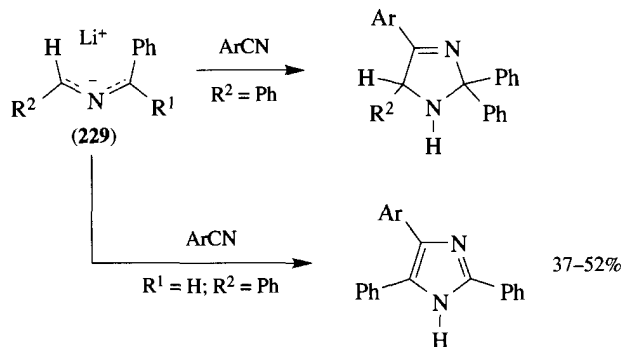


Scheme 162



Scheme 163

Among the cycloaddition reactions which lead to imidazole products is the [3 + 2] cycloaddition of imines to 2-azaallenyl radical cations (derived from azirines by photolysis) which yields 1-substituted imidazoles <91AG(E)1336, 93CB543>. Similar addition of 2-azallyl anions (made by deprotonation of *N*-alkylated Schiff bases) to aromatic nitriles can give rise to either 3-imidazolines or imidazoles depending on the substitution pattern in the azaallyl species (**229**) <83CB492>. These reactions have been reviewed (Scheme 164) <90CHE1>.

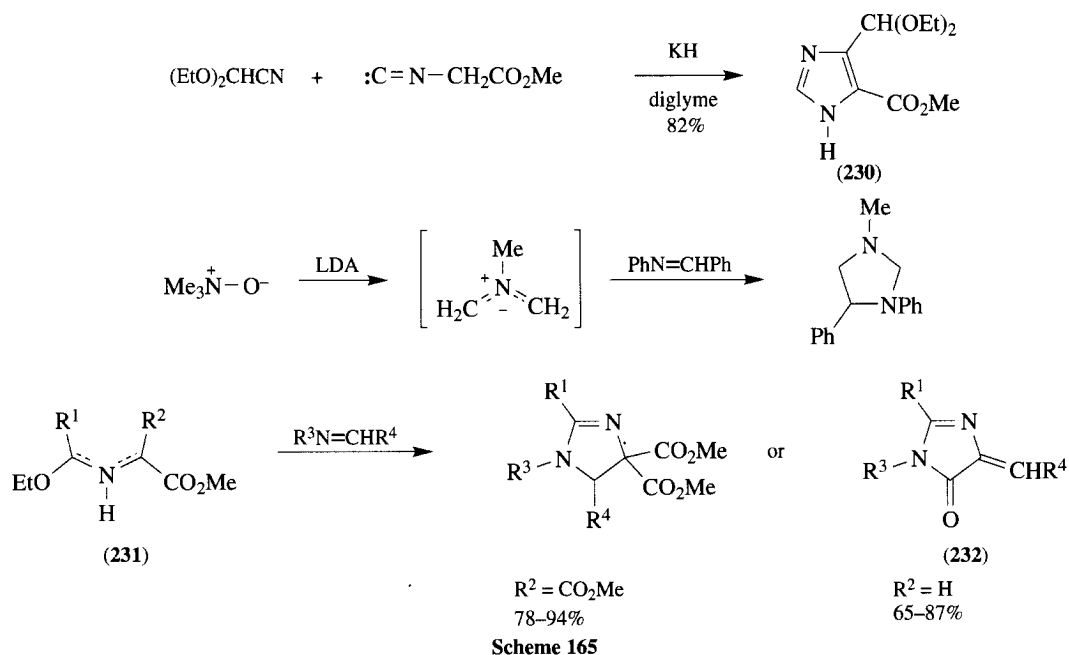


Scheme 164

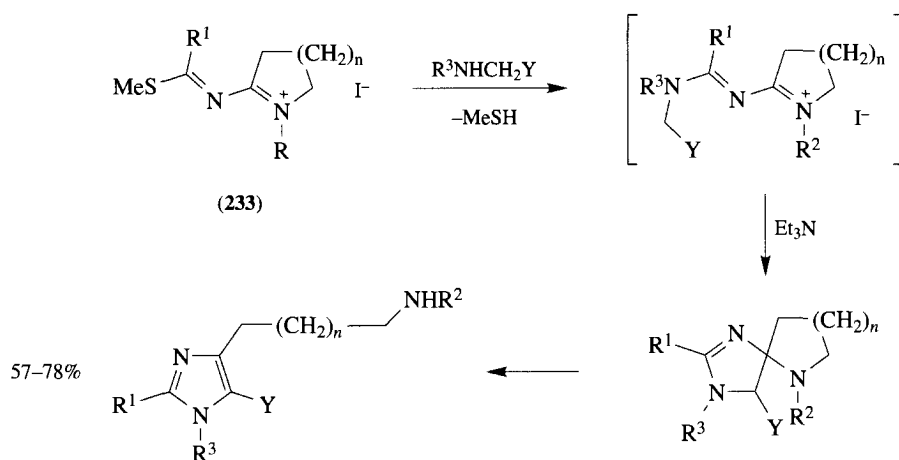
Similarly, the anionic cycloaddition of methyl isocyanoacetate to diethoxyacetonitrile gives methyl 5-diethoxymethylimidazole-4-carboxylate (**230**) <82TL4729>. The nitrile carbon is sufficiently electrophilic to react easily with nucleophiles. Cycloaddition of nitrile ylides with ethyl cyanoformate is a further example <90H(31)1855>. Pyridinium methides give imidazopyridines with perfluoroalkylnitriles <91JFC(51)407>. Cycloaddition between a non-stabilized azomethine ylide (generated from trimethylamine *N*-oxide) and a Schiff base gives imidazolidines <87H(26)3197>. Similarly, imidates derived from α -amino esters undergo 1,3-dipolar addition (as stabilized imidates (**231**)) with imines providing new routes to 2-imidazolines and 4-yliden-5-imidazolinones (**232**) (Scheme 165) <93TL4639>. Tetrasubstituted imidazoles have been made by addition of an aryl nitrile to the anion generated when 1-(4'-pyridino)-1-(1'-pyrrolidin-2-ono)methane is regiospecifically deprotonated <94TL273>.

Formation of imidazoles takes place when thioamides react with methyl 2-benzamido-2-chloroacetate <87MI 302-03>.

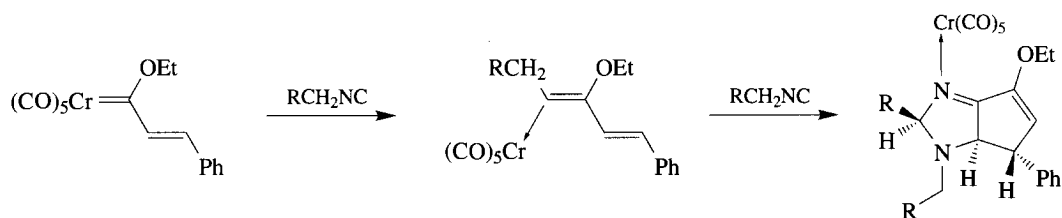
Some novel histamine analogues have been made by applying the ring-chain transfer concept to the reaction of semicyclic 2-aza-3-methylthio-3-propeniminium iodides (**233**) with methylamines



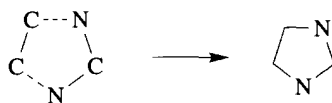
possessing an acidic CH. In this type of ring transformation both the imidazole ring and the desired aminoalkyl substituent can be made within the one procedure (Scheme 166) (92JOC1831).



Bicyclic 3-imidazolines form from primary isocyanides and alkenylcarbene complexes by a metal-induced anomalous insertion of a C=N into the α -C—H bond of the isocyanide (Scheme 167) (87CB1287).

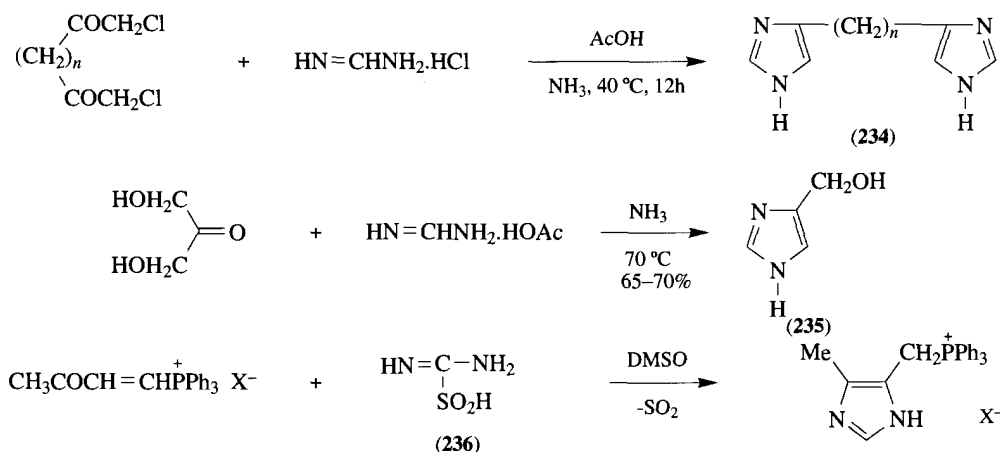


Formation of the 1,5- and 3,4-bonds (Scheme 168):



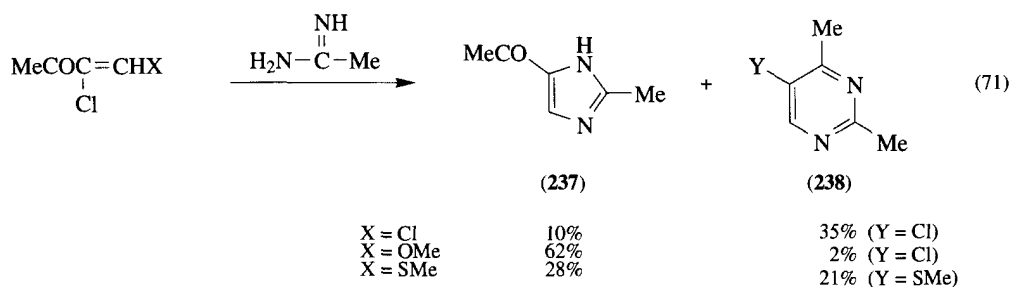
Scheme 168

Most reactions of this type are those of guanidines or ureas reacting with α -substituted carbonyl compounds. Such reactions can form oxazoles and/or imidazoles (see CHEC-I) <80AHC(27)241, 89CHE593>. For example, reaction of formamidine with an α,ω -dichloroalkanedione gives a bis-imidazole (**234**) <93S197>. Similarly a new synthesis of L-homohistidine in 71% yield uses the reaction of formamidine acetate in liquid ammonia with an α -chloroketone <89SC2069>. An improved synthesis of 4-hydroxymethylimidazole (**235**) follows the same general scheme (Scheme 169) <83S576>. With formamidine as the NCN fragment the 2-position of the resulting imidazole can only be unsubstituted; this is also the case with the sulfinic acid derivative (**236**) <81JHC1301>.



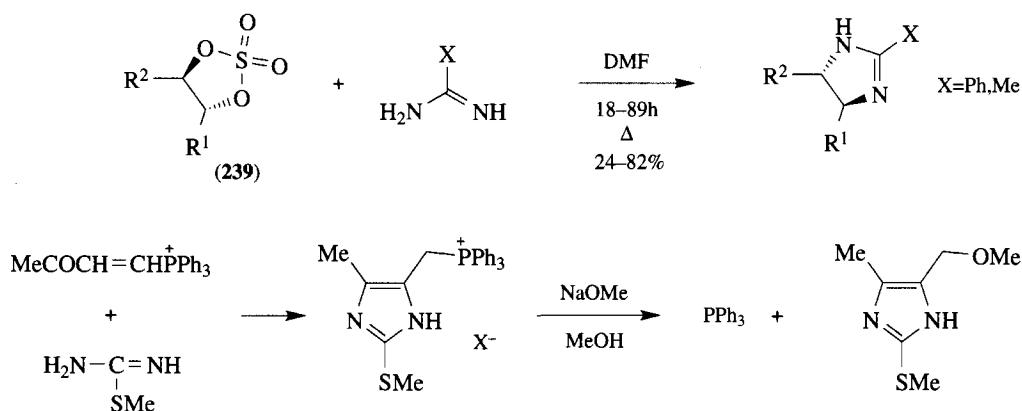
Scheme 169

Other amidines give 2-substituted imidazoles or imidazolines. Thus 2-bromo-2-alkenoic esters (or the analogous aldehydes, ketones, and nitriles) react with monosubstituted amidines to form pyrimidines and 2-substituted 2-imidazolines <85S537>. Reaction of 3,4-disubstituted 3-buten-2-ones with acetamidine gives 4-acetyl-2-methylimidazole (**237**), a 5-substituted pyrimidine (**238**), or a mixture of both. The nature of the product mixture is dependent on the substituents on the enone substrate. A poor leaving group in the 3-position favors exclusive generation of (**238**); a good leaving group at that site combined with a 4-substituent which is not readily eliminated leads to the formation of (**237**). Generation of the aromatic imidazole rather than a 2-imidazoline depends on the ease of elimination of HY <84JOC566, 84JOC3494>. In the general reaction of 2-bromo-2-alkenoic carbonyls with amidines the mechanism of heterocyclization into 2-imidazolines is believed to involve an intermediate pyrimidinone rather than an aziridine (Equation (71)) <93JCS(P2)1123>.



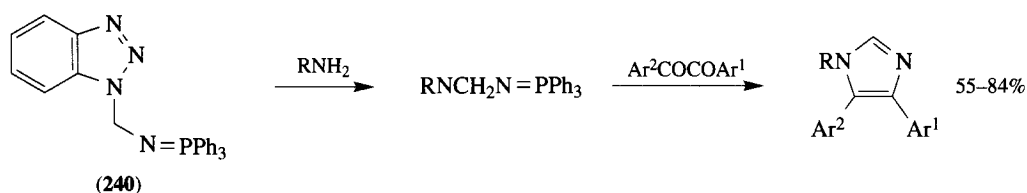
A similar one-pot synthesis of 2-imidazolines uses 1,2-cyclic sulfates (**239**) <91TL999>. Enamines in the presence of one equivalent of bromine react likewise to give 4-amino-2-imidazolines <83S940>.

S-Methylisothiourea reacts with acylvinylphosphonium salts to give multifunctional imidazoles with recovery of triphenylphosphine (Scheme 170) <81JHC1301>.



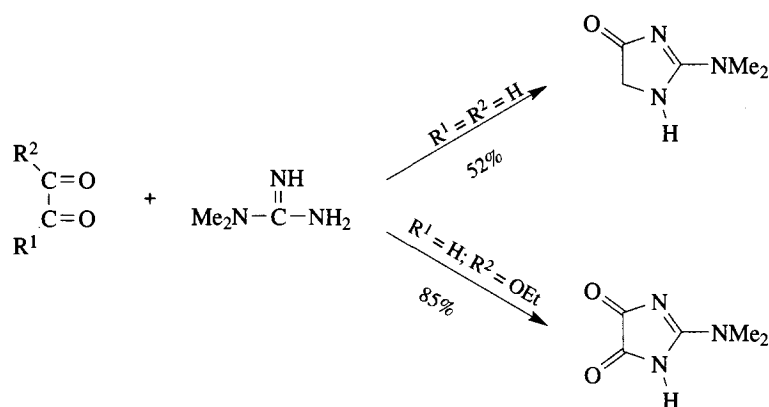
Scheme 170

The reagent 1-(benzotriazol-1-yl)-*N*-triphenylphosphorylidene-methylene (Betnip) (240) is a source of iminophosphoranes which react with α -diarylketones to form 1,4,5-trisubstituted imidazoles in good yields. If the diketone is unsymmetrical the more nucleophilic iminophosphorane nitrogen firstly attacks the more activated carbonyl function. Thus *p*-chlorodibenzoyl specifically forms the 1-substituted-4-(*p*-chlorophenyl)-5-phenylimidazole (Scheme 171) <90H(31)2187>.



Scheme 171

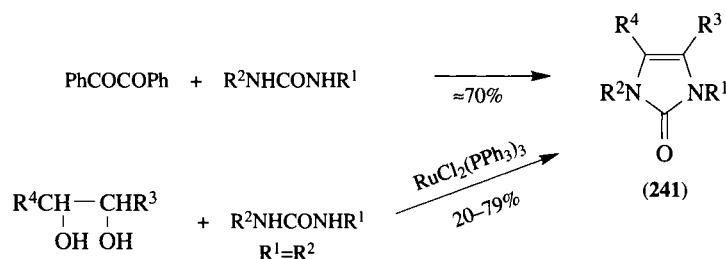
When guanidines are used in place of amidines in the syntheses, the products are 2-amino-imidazoles or -imidazolines <82CHE185, 91M1063, 91TL5325, 92T6385>. A mild and efficient method reported for guanidine synthesis should extend the scope of this approach (Scheme 172) <92TL5933>.



Scheme 172

Ureas and thioureas, too, can act as the NCN fragments in imidazole synthesis. The use of *S*-methylisothiourea (which is more correctly termed a substituted amidine) has already been mentioned above and elsewhere <81JOC1301>. Pyruvaldehyde reacts with ureas to form 4,5-dihydroxyimidazolin-2-ones which dehydrate to hydantoins <86JHC1125>, while benzil gives 4,5-diphenyl-4-imidazolin-2-ones ((241); R², R³=Ph) when heated with thioureas in acidic solution (Scheme 173) <91JCS(P2)1501>. Direct cyclocondensation of an α -bromoketone with urea forms around 50% of 2-imidazolinone when refluxed in ethylene glycol in the presence of an excess of

potassium carbonate, rather better yields than if the corresponding α -dimethylaminoketone is used <85BAU1534>. Other examples have been described <90CHE708, 90T1331, 91MI 302-01, 93S561>. There is a report of a novel ruthenium catalyzed selective synthesis of **(241)** derivatives from vicinal diols and ureas (Scheme 173) <92CC1318>. Carbodiimides similarly react with appropriate dicarbonyls or their sulfur analogues <82SUL37, 86JOC417>.



Scheme 173

3.02.8.1.3 Formation of three or four bonds

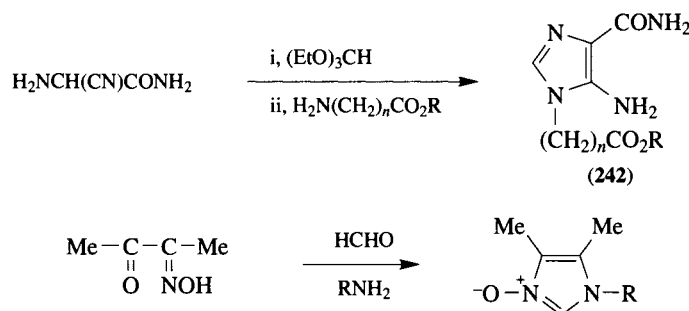
Many of these reactions are variations of the classical methods which reacted α -dicarbonyls or α -hydroxycarbonyls with ammonia. Alkaline cleavage of the α -dicarbonyls provides the C-2 fragment. These reactions naturally tend to form mixtures, and yields are often low. Nevertheless, they still have applications. Modifications have included the use of formamide as the nitrogen source. These reactions were discussed in detail in CHEC-I and so only some late examples are covered in this chapter. A novel synthesis of acyloins (55–95%) may increase the scope of these approaches <94SC367>.

(i) Formation of the 1,2-, 2,3- and 3,4-bonds (Scheme 174)



Scheme 174

Typical of this type of synthesis are the reactions of α -aminocarbonyls with an aldehyde in the presence of ammonia or an amine. An example is the preparation of a series of 1-substituted 5-aminoimidazole-4-carboxamides **(242)** <87JHC1155, 91JMC1187, 91S822>. The major defect of this reaction sequence is the limited range of 2-substituents which can be introduced. Replacement of the α -aminoketone by an α -diketomonoimine leads to 1-hydroxyimidazoles or the *N*-oxides (Scheme 175) <89TL4353, 90PHA830, 91PHA412>.



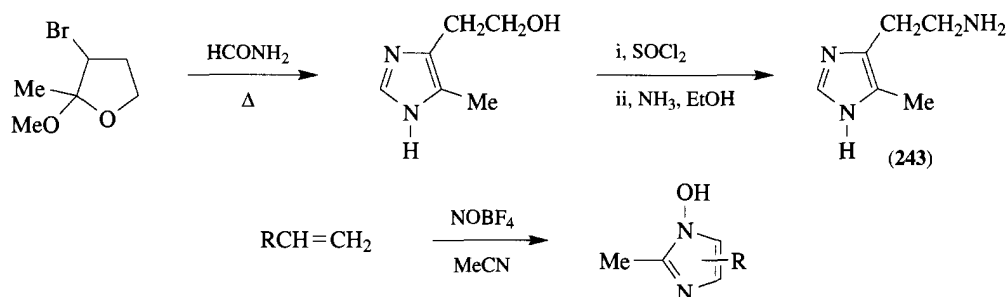
Scheme 175

(ii) Formation of the 1,2-, 1,5- and 3,4-bonds (Scheme 176)



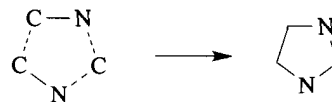
Scheme 176

These reactions are typified by Bredereck's "formamide synthesis". This has been applied to the synthesis of 4,5-dimethylimidazole (as its formic acid complex) from acetoin and formamide <91JHC1819>. A similar reaction leads to 5-methylhistamine (**243**) <81JHC831>. 1-Hydroxyimidazoles are accessible in high yield from reaction of nitrosonium fluoroborate with acetonitrile and appropriate alkenes (Scheme 177) <84TL1319>.



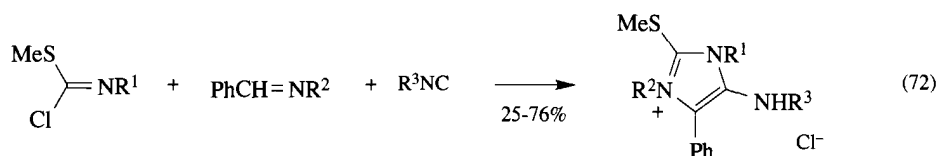
Scheme 177

(iii) Formation of the 1,2-, 2,3- and 4,5-bonds (Scheme 178)



Scheme 178

The reaction between cyanogen, an aldehyde, and hydrogen chloride was an early example of this approach, leading to the formation of 4,5-dichloroimidazoles <80AG(E)130>. A late example is the synthesis of some 4-aminoimidazolium salts by reaction of iminochlorosulfides, benzaldimine, and an isonitrile. This reaction is believed to proceed through a transient *N*-imido-benzylideneiminium chloride intermediate (Equation (72)) <92JOC2121>.



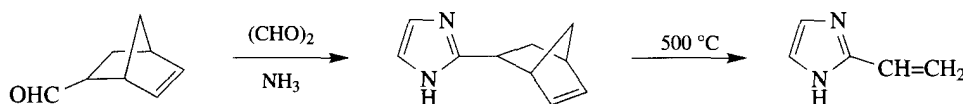
(iv) Formation of four bonds (Scheme 179)

The old method in which an α -dicarbonyl (or precursor) reacts with ammonia or amines, often with added aldehyde still has some application <83AG(E)560, 83JOC3745, 85JMC1188, 85JOC1133, 87CHE854, 91CPB651, 93JMC3595>. The range of unsymmetrical benzils has been increased by the Friedel-Crafts reaction of arenes with α -chloro- α -(methylthio)acetophenones <91CPB1854>, while α -hydroxyketones are now available in 61–87% yields from ion exchange resin mediated hydrolytic cleavage of α -



Scheme 179

nitroepoxides $\langle 92\text{SC}1523 \rangle$, or from saturated ethoxyethyl protected cyanohydrins and α,β -unsaturated aldehydes $\langle 94\text{SC}367 \rangle$. When the amine (or ammonia) is replaced in the reaction mixture by hydroxylamine, 1-hydroxyimidazole 3-oxides can be prepared $\langle 89\text{S}773 \rangle$. A yield of nearly 90% of 2-vinylimidazole has been obtained using this general method of synthesis (Scheme 180) $\langle 83\text{AG}(\text{E})560 \rangle$.



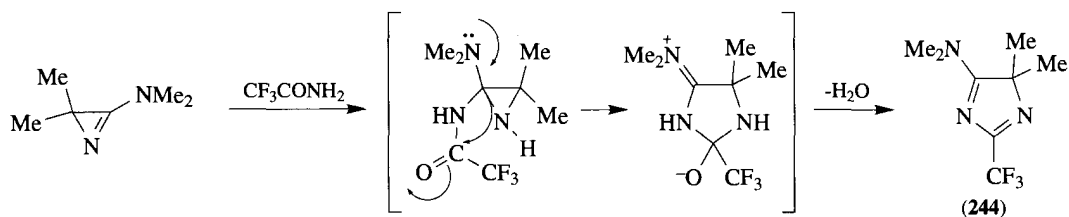
Scheme 180

A one-pot synthesis of imidazolidines (30–67%) reacts aromatic aldehydes with diethyl ketomalonate and a benzylamine with a catalytic quantity of *p*-toluenesulfonic acid $\langle 94\text{H}(38)587 \rangle$. The Ugi four-component condensation of 1,1-diethoxy-2-isocyanoethane, cycloketones, amine hydrochlorides, and potassium thiocyanate gives rise to 2-spiro-2*H*-imidazoles (10–48%) $\langle 93\text{LA}1229 \rangle$.

3.02.8.2 Synthesis by Transformation of Other Heterocycles

3.02.8.2.1 Ring expansions

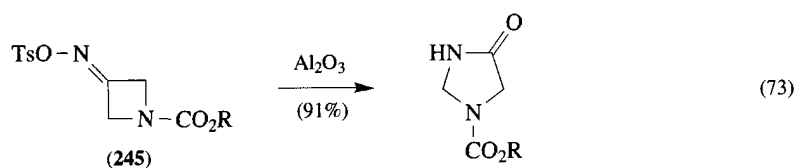
A number of examples of imidazole synthesis from azirines and aziridines have been included under other classifications (see Sections 3.02.8.1.1(iii) and 3.02.8.1.2(i),(ii)). 2*H*-Azirines are intermediates in the rearrangement of oximino *p*-toluenesulfonates to aminoketones in the presence of bases, and with 2-acylphenols these azirines form imidazolones. 4*H*-Imidazoles (**244**) are formed when a 2-amino-3,3-dimethylazirine reacts with an acetamide (Scheme 181) $\langle 90\text{CHE}719 \rangle$.

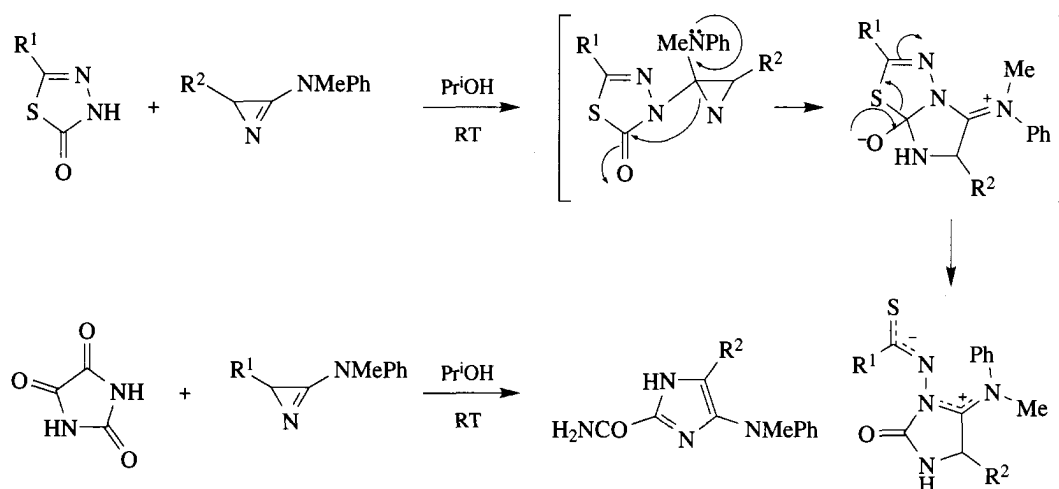


Scheme 181

When treated with heterocycles possessing acidic NH groups, 2-monosubstituted 3-amino-2*H*-azirines ring expand (Scheme 182) $\langle 90\text{HCA}2275, 92\text{HCA}1251, 92\text{HCA}2270 \rangle$.

Beckmann rearrangement of 1-alkoxycarbonylazetid-3-one oxime sulfonates (**245**) under the influence of aluminum oxide, followed by removal of the ester function, has provided the first synthesis of 4-imidazolidinone (Equation (73)) $\langle 86\text{H}(24)25 \rangle$.



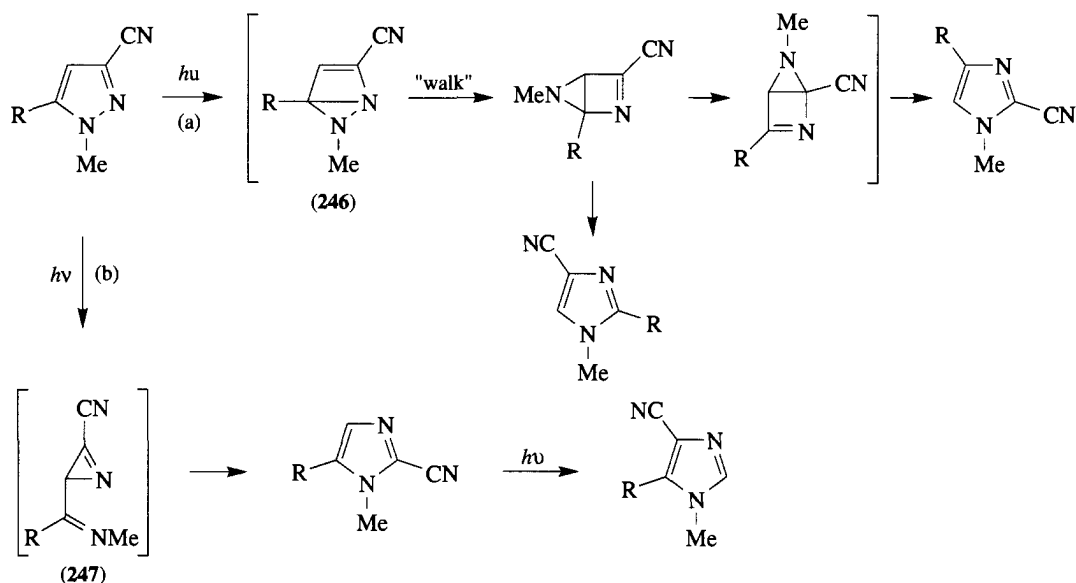


Scheme 182

3.02.8.2.2 Transformations of other five-membered rings

(i) Pyrazoles and indazoles

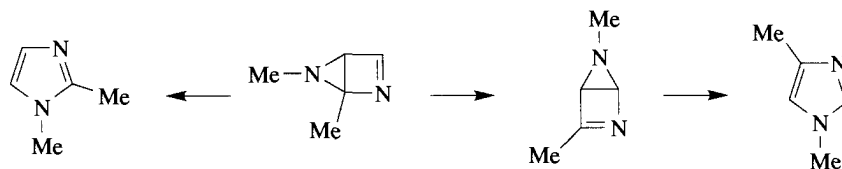
The most studied process is the well-described photochemical rearrangement of pyrazoles to imidazoles and indazoles to benzimidazoles, (see CHEC-I) <84JHC627>. Early work suggested that there are two main pathways which may be concurrent: (a) a 1,5-interchange, probably by 2,5-bonding to a diazabicyclopentane (**246**) which isomerizes by 'nitrogen walk' before rearomatization; and (b) a 2,3-interchange, probably via an intermediate azirine (**247**). The isomerization of 3-cyanopyrazoles to 2- and 4-cyanoimidazoles was believed to follow both pathways concurrently (Scheme 183). In sharp contrast 1,4-dimethyl-3-trifluoromethylpyrazole phototransposes only by pathway (a). Yields of imidazoles can approach 30% <81CC604>. Later, an enaminonitrile intermediate was proposed, and such species have been identified <82CL667, 93JA7645>. The mechanism has been reinvestigated by a semiempirical MO method which supports the products observed <91JOC6321>.



Scheme 183

The phototransposition of 1,5-dimethylpyrazole is known to give all three of the possible products (1,2-, 1,4- and 1,5-dimethylimidazoles) as with the cyanopyrazole above. There is, however, a

dramatic temperature dependence for the formation of the 1,2- and 1,5-isomers, and for the phototransposition of 1,2- and 1,4-dimethylimidazoles. As the temperature decreases the proportion of the 1,4-isomer decreases while 1,2-increases. This is strong evidence for a ground state thermal reaction which supports the MNDO calculations, and also for the proposed "nitrogen walk" steps. That the 1,2-isomer is produced at the expense of the 1,4-isomer points to a common intermediate with a lower barrier to rearomatization than to another [1,3] shift of nitrogen (Scheme 184) <92JOC1937>.



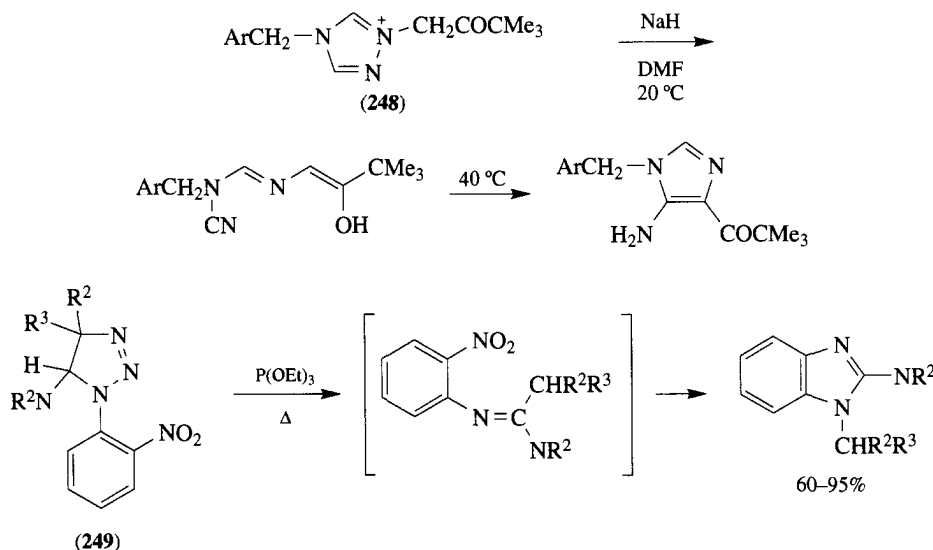
Scheme 184

In the 1-phenyl-2-, -3-, and -4-methylpyrazoles MO calculations imply a process involving N—N cleavage followed by a [1,2] shift and cyclization to the corresponding 1-phenylimidazole product. The [1,2] shift could occur through an undetected azirine intermediate <93JA7645>.

Although photochemical rearrangements of pyrazoles to imidazoles have little synthetic importance for simple imidazoles, especially as mixtures are formed and yields are often low, there may be applications for substrates with more exotic substituents.

(ii) Triazoles and tetrazoles

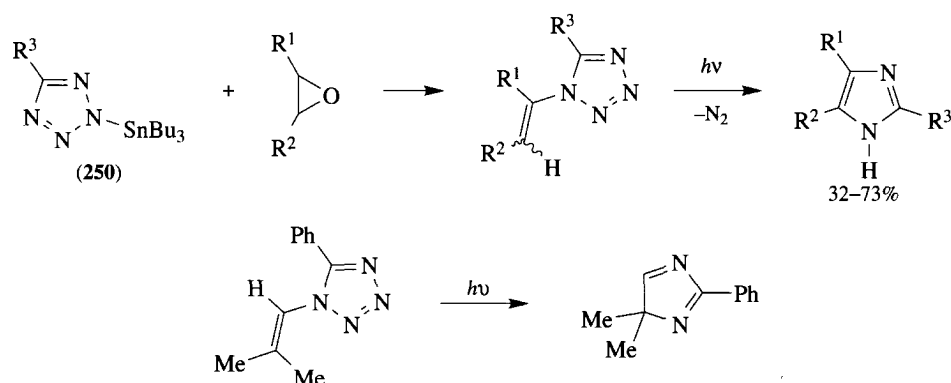
Rearrangement of 4*H*-1,2,4-triazolium salts (**248**) to 4-acyl-5-aminoimidazoles can be accomplished by treating them with sodium hydride <86AG(E)652>. Heating with triethylphosphite opens the ring of 5-amino-1-(2-nitrophenyl)-1,2,3-triazolines (**249**), converting them into benzimidazoles. The reagent reduces the nitro group in addition to its roles in ring opening, cyclization, and rearrangement (Scheme 185) <92JCS(P1)2709>.



Scheme 185

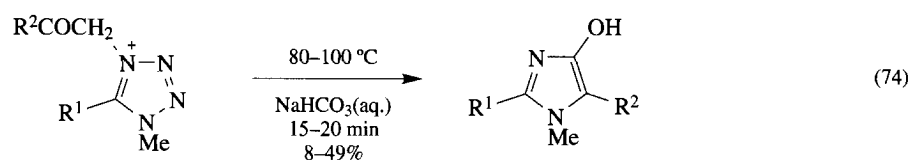
Photolysis of 1-vinyltetrazoles gives moderate yields of imidazoles presumably by cyclization of the imidoyl nitrenes which are generated by nitrogen loss <82CC714>. This method can be adapted to the synthesis of a variety of 4,5-disubstituted imidazoles merely by changing the alkene used for making the 1-vinyltetrazole. The alkene is epoxidized before allowing it to react with a 2-tributylstannyltetrazole (**250**) <84JCS(P1)1933>. The process can be extended by conjugate addition

of (250) to activated alkynes to give isomers of 1-alkenyltetrazoles <85JCS(P1)741>. If the vinyl group is terminally disubstituted the products are non-aromatic 4*H*-imidazoles (Scheme 186) <87JCS(P1)1389>.



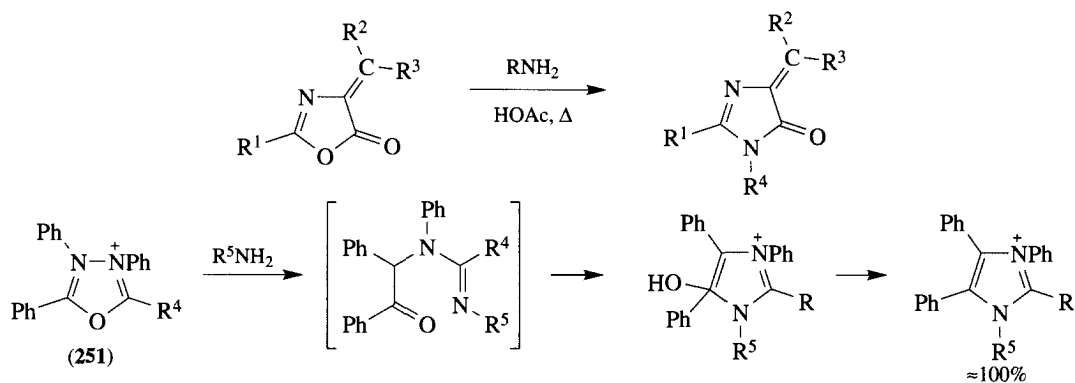
Scheme 186

Heating suitably substituted tetrazolium salts in aqueous base can transform them into imidazolones (Equation (74)) <85CZ432>.



(iii) Oxazoles and isoxazoles

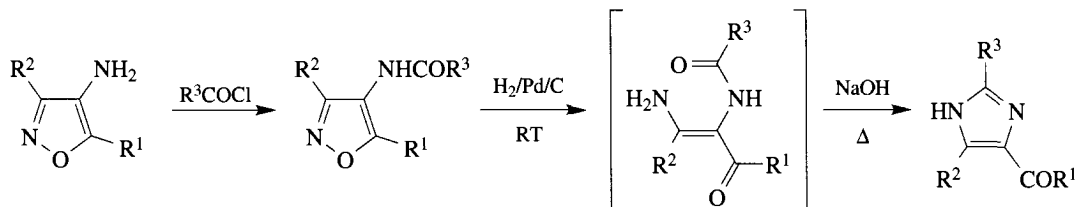
Oxazoles are converted into imidazoles merely by heating them in the presence of ammonia, formamide, or other suitable nitrogen sources. This means that syntheses of oxazoles are potentially also those of imidazoles. The process involves attack by the nitrogen nucleophile at carbon-2, inducing ring-opening followed by recyclization to give 1,3-diazoles with the same substitution pattern as the oxazole. Examples <85S285, 88CPB1593, 92OPP698> also include some which lead to reduced imidazoles, and transformations of oxazolium salts (251) (Scheme 187) <82JCS(P1)131, 86IJC(B)81>.



Scheme 187

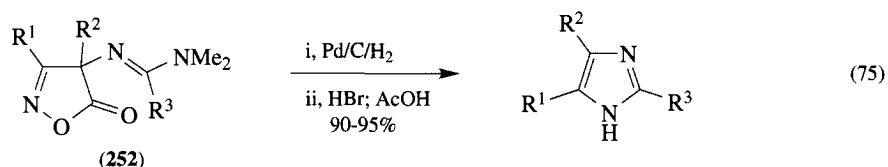
5(4*H*)-Iminoisoxazoles, which cannot aromatize to 5-aminoisoxazoles, undergo uncatalyzed Dimroth rearrangement to give imidazolones <84T2395>. Flash vacuum pyrolysis of heterocyclisoxazol-5(2*H*)-ones gives fused imidazoles <93T8147>. Amides produced by acetylation of 4-aminoisoxazoles can be hydrogenated to give α-(acylamino)enaminones which cyclize to 4-acylimidazoles when subjected to base treatment. Use of *N*-substituted 4-aminoisoxazoles allows

synthesis of 1-substituted 5-acylimidazoles, a substitution pattern not easily achieved by other methods. Yields are usually in the range of 75–92%. Note that the 2-substituent comes from the acylating agent, and alkylation prior to acylation allows synthesis of 1-substituted imidazole products (Scheme 188) <85TL3423, 87JOC2714>.



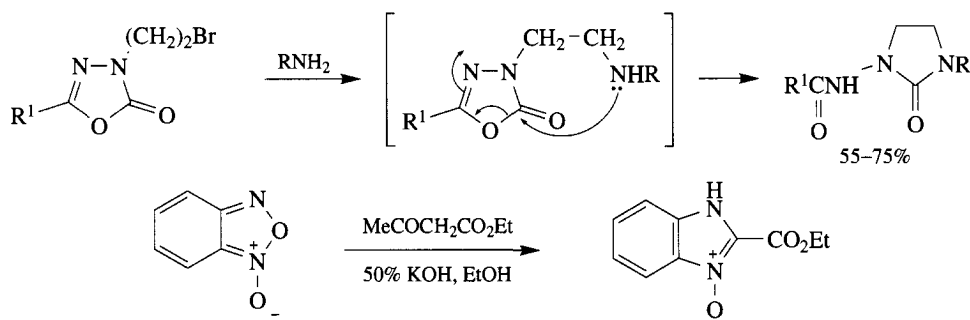
Scheme 188

When isoxazol-5-ones are treated with benzonitrile oxide the products include imidazole 3-oxides <83JCR(S)76, 83JCR(S)172>. Catalytic hydrogenation of the isoxazol-5(4*H*)-ones (**252**) and subsequent recyclization is reported to give high yields of imidazoles (Equation (75)) <91S127>.



(iv) Oxadiazoles

Treatment of 3-bromoethyl-1,3,4-oxadiazol-2(3*H*)-ones with primary amines gives 2-imidazolidinones <92JHC1081>. Benzofuroxan *N*-oxide is transformed into benzimidazole *N*-oxide on treatment in basic medium with acetoacetic ester or barbituric acid (Scheme 189) <87JHC165, 88JCS(P1)681>.

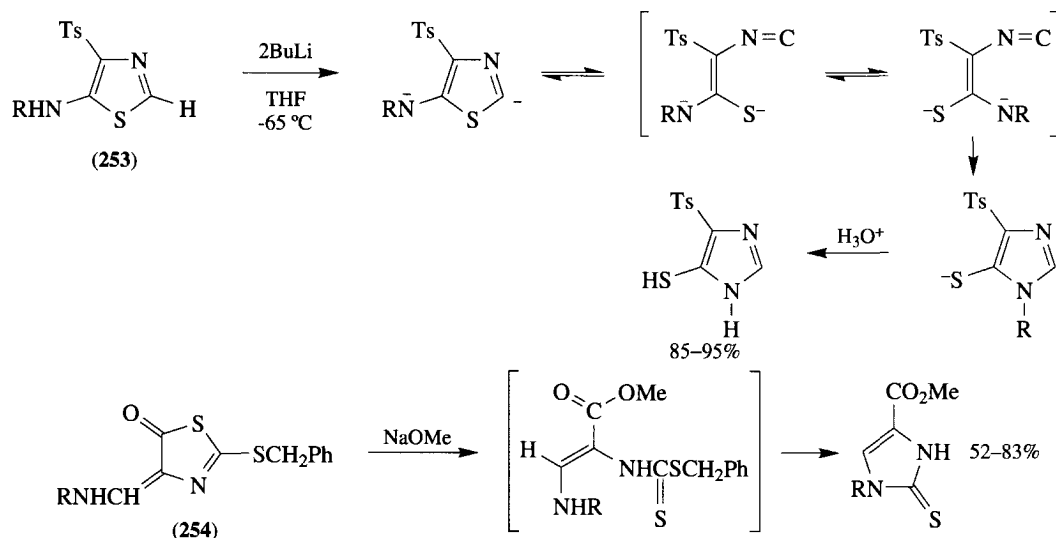


Scheme 189

(v) Thiazoles

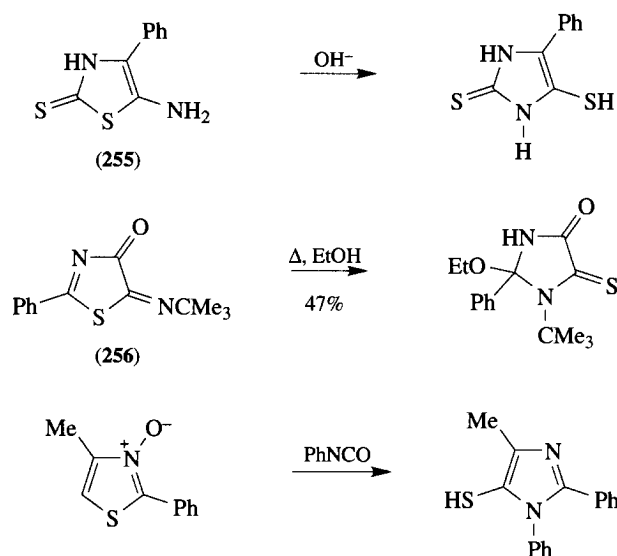
In basic medium 5-aminothiazoles (**253**) are converted into imidazole-5-thiols by a rearrangement which is an electrocyclic ring opening and ring closure of the dianion which is formed <82RTC28>. Similar examples include basic rearrangement of 2-amino-4-imino-4,5-dihydrothiazoles to 4*H*-

imidazoline-5-thiones <90JOC1721>, and 5(4*H*)-thiazolones (**254**) into 4-imidazoline-2-thiones (Scheme 190) <92JHC155>.



Scheme 190

Thiazoles may also be intermediate in some other imidazole syntheses <87CJC282>. Dimroth rearrangement of 5-aminothiazoles ((**255**), (**256**)) gives hydantoin analogues <86BSB1129>. While 2,4-disubstituted thiazole *N*-oxides are converted by aryl isocyanates into imidazoles, the 2,5-isomers are unreactive (Scheme 191) <82CPB1722>.

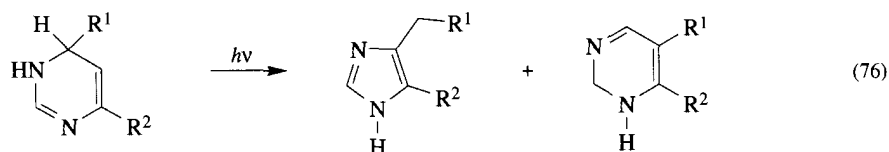


Scheme 191

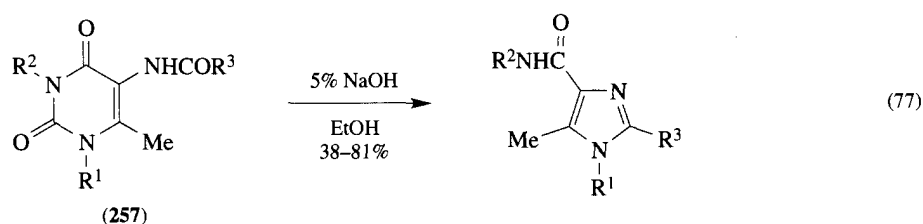
3.02.8.2.3 Ring contractions

(i) Pyrimidines

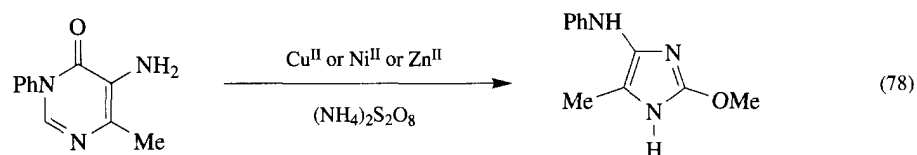
Base-induced ring-opening of pyrimidines, or nitrene formation (as in the pyrolysis of azido-pyrimidines) can give imidazoles (see CHEC-I). There are also a few examples of photochemical ring contraction. For example, 4-heteroaryl substituted 1,4- (or 3,4-)dihydropyrimidines give some imidazole products (Equation (76)) <83RTC364>.



The 5-acylaminouracil (**257**) is transformed into an imidazole by ethanolic sodium hydroxide by a mechanism which is thought to involve hydroxide attack at C-2 inducing ring opening at the 2,3-bond. Recyclization is via NHR^1 attack at the carbonyl group adjacent to R^3 <88TL4607>. This transformation also occurs with 5-acylamino-4-pyrimidinones (Equation (77)) <88TL4607, 91JCS(P1)2821>.

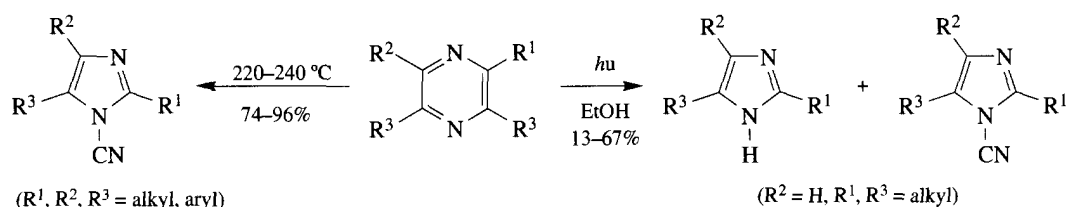


Reaction with nitrous acid transforms 5-aminopyrimidin-4(3*H*)-ones into imidazoles <84CPB2863>, and imidazoles are also found among the ozonolysis products of cytosines and guanine <91JOC4987>. Rhodium acetate converts 6-alkoxy-5-diazodihydrouracils into 5-alkoxymethylene-2,4-imidazolidinediones <91TL3799>. 5-Aminopyrimidin-4-ones are converted into 2-alkoxyimidazoles by copper(II) salts in a reaction presumed to rely on Lewis acid acidity and oxidative ability of the copper(II) salt. Other Lewis acids and oxidizing agents in methanolic solution are able to carry out the same transformation <93CPB608>. In the same solvent 5-aminouracils are oxidized by thallium(III) nitrate with ring contraction to 2-imidazolidinones (Equation (78)) <93MI 302-01>.



(ii) Pyrazines

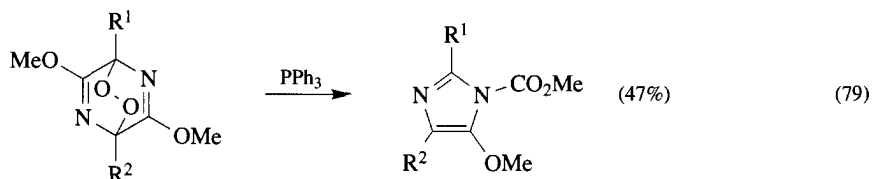
Photochemical transformations of pyrazines into imidazoles are well known (see CHEC-1). Although diphenyl- and methylphenyl-substituted azidopyrazines give only resins when photolyzed, 2-azido-3,6-dialkylpyrazines in ethanol are converted into imidazoles and 1-cyanoimidazoles. The latter species lose the cyano group on further irradiation. The reaction appears to be much more versatile and gives higher yields under thermolysis conditions (Scheme 192) <83JHC1277, 90JHC711>.



Scheme 192

Photochemical rearrangement of tetrahydro-2-pyrazinones to imidazol-5-ones (62%) in aqueous solution is believed to proceed through enediimine and isoimidazole intermediates, in analogy with the mechanism of rearrangement of 5,6-dihydropyrazines to imidazoles <82JOC3145>.

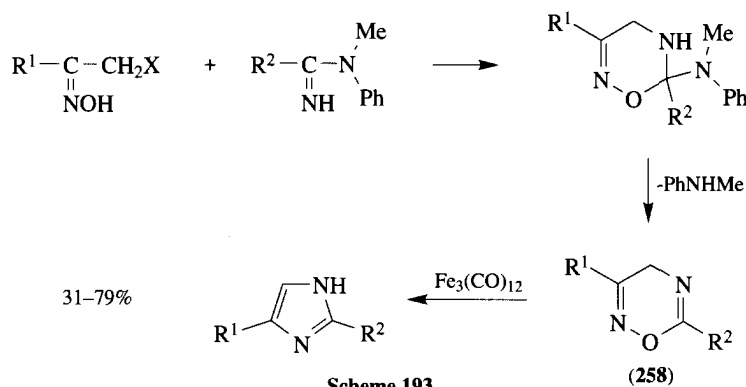
Deoxygenation of pyrazine endoperoxides with triphenylphosphine induces ring contraction to imidazoles (Equation (79)) <83CC399>.



(iii) Other six-membered heterocycles

When 1,2-dihydro-1,2,4-benzotriazines are heated in the presence of traces of water they ring contract to give low yields of benzimidazoles <88JCS(P1)3381>.

Good yields of 2,4-disubstituted imidazoles are obtained when 4*H*-1,2,5-oxadiazine intermediates (**258**) are deoxygenated by iron carbonyls (Scheme 193) <83CL341>.



1,3,5-Triarylhexahydro-1,3,5-triazines react with oxalyl chloride to form 1,3-diaryl-4,5-imidazolidinediones, presumably via sequential reactions of two units of the monomer ($\text{ArN}=\text{CH}_2$) with oxalyl chloride <93T10609>.

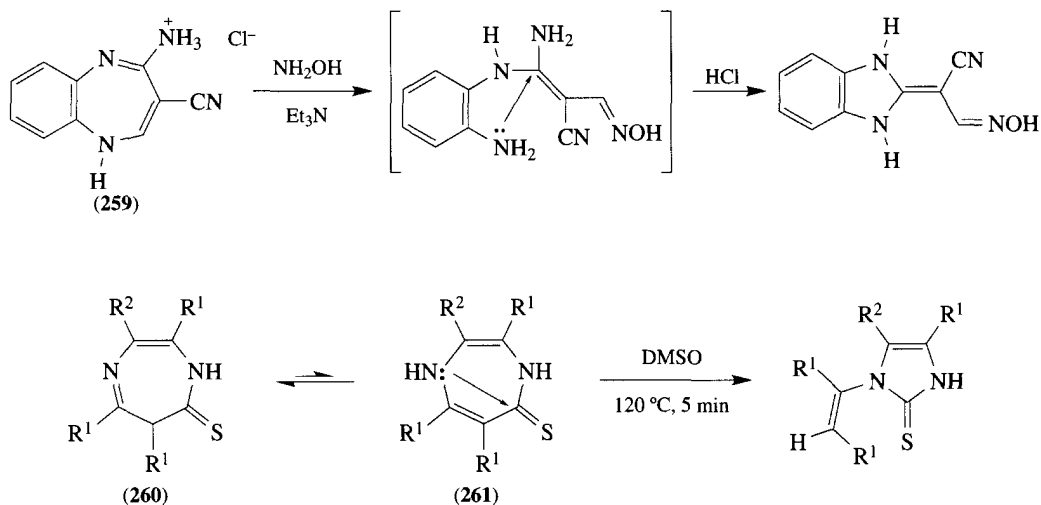
(iv) Seven-membered rings

Acid-catalyzed contractions of 1,5-benzodiazepines into benzimidazoles are well known <87JHC885>. A new preparation of benzimidazolidine has utilized the reaction of hydroxylamine with amino-1*H*-1,5-benzodiazepine-3-carbonitriles (**259**) <89JHC277>. Thermal rearrangement of 1*H*-1,4-diazepine-7(6*H*)-thiones (**260**) gives 1-vinylimidazole-2(3*H*)-thiones. The contraction presumably takes place with the tautomer (**261**) (Scheme 194) <92BSF566>.

3.02.8.3 Syntheses of Specific Classes of Imidazoles

3.02.8.3.1 Imidazole and benzimidazole oxides

Direct *N*-oxidation of these heterocycles invariably fails (see Section 3.02.7.2.8), making ring synthetic methods the only viable alternative <93CHE127>. Although there has been considerable interest in the chemistry of compounds of this type, there are no new synthetic approaches of a general nature. The most common approach is to react α -oximinoketones with aldehydes and primary amines. With formaldehyde, however, the 2-unsubstituted 1-oxides rearrange to 2-imidazolones. Variations on this theme allow synthesis of 1-hydroxyimidazole 3-oxides. Thus, treatment of an α -dicarbonyl compound with an aldehyde and hydroxylamine, or reaction of the aldehyde oxime or aldehyde with a 1,2-dioxime are common approaches <89S773>. Similarly, α -hydroxyamino-



Scheme 194

oximes in the *anti*-configuration react with aldehydes to give 1-hydroxyimidazoline 3-oxides which may be aromatized. See Sections 3.02.8.1.2(i), 3.02.8.1.3(i),(iv).

Similar methods are commonly and successfully applied to benzimidazole oxide preparation, but in these instances an *o*-aminonitrobenzene is the key substrate. Reductive methods convert *o*-acylaminonitrobenzenes into 2-substituted benzimidazole 1-oxides, and cyclization of analogous alkylaminonitrobenzenes with acid, base or UV irradiation, or reactions of *o*-nitroaniline with aldehydes have also proved successful. The 1-hydroxybenzimidazole-3-oxides can be made from a suitable benzoquinone dioxime with an aldehyde <90JPR345>, but the compounds are much more generally accessible from conversions of benzofuroxan oxides (see Sections 3.02.8.1.1(i), 3.02.8.2.2(iv)) <85H(23)1625, 87JHC165, 88JCS(P1)681>.

Less common methods of synthesis include nitrosation of suitable alkenes in acetonitrile solution (see Section 3.02.8.1.3(ii)) <84TL1319>, cyclization of *N*-alkoxy ureas <87S1058>, and specific approaches to benzimidazole oxides from quinoxaline oxides, and to imidazole oxides from oxadiazine and pyrazine oxides <93CHE127>.

3.02.8.3.2 Nitroimidazoles

In view of the interest in these compounds as pharmaceuticals, a brief survey of synthetic approaches is included here. As there are no general ring-synthetic approaches it is necessary to have regiospecific methods of introducing a nitro group to the preformed imidazole ring.

Electrophilic nitration can give 4-nitro (and sometimes 4,5-dinitro) products, but if there is a 1-substituent mixtures of 4- and 5-nitro products are formed <80AHC(27)241>. Reports of direct nitration in the 2-position may not be correct. Nitrodehalogenation is possible, but only at the 4-position <79AJC1727>. A report suggesting that a 2-nitroimidazole was formed when 2,4-diiodoimidazole was nitrated is flawed because the substrate was in fact 4,5-diiodoimidazole (see Section 3.02.5.3.2) <70CHE614>.

Nucleophilic introduction of nitro functions seems to be confined to reactions of diazonium salts which offer a useful entry, particularly to 2-nitroimidazoles (from the diazonium fluoroborates; see Section 3.02.7.1.6). This method, though, depends on the ease of synthesis, isolation, and stability of aminoimidazoles. The 4- and 5-amino isomers in particular are frequently unstable in air, and aminoimidazoles are usually made either by ring synthetic methods or by reduction of nitro compounds. Oxidation of amino groups to nitro is seldom a useful option.

The paucity of data on conversions of lithioimidazole into nitroimidazole suggests that this approach is not a valid option <85H(23)417>, but in view of the way in which all ring carbons of imidazole can now be specifically metallated, reactions with reagents like N₂O₄ may merit reexamination (see Section 3.02.7.1.11).

Thermal rearrangements of 1-nitroimidazoles to the 2- or 4-isomers offer an alternative approach which has as yet been little studied (see Section 3.02.7.2.5).

3.02.8.3.3 Fluoroimidazoles

Few examples are known of ring syntheses which produce fluorine-substituted imidazoles (but see Section 3.02.8.1.1(i)), and it is usual to add the fluorine to the preformed heteroaromatic ring <93AHC(57)291>.

Methods which involve decomposition of diazonium fluoroborates are common, with the Balz–Schiemann photolytic method offering the best results usually (30–40% yields; see Section 3.02.7.1.6) <84JOC1951>, but again these approaches are entirely dependent upon the availability of the amino-imidazole precursors.

There are some examples of nucleophilic displacement of a suitably activated bromine by fluoride, but there have been instances where such reactions are unsuccessful <93AHC(57)291>. Electrophilic methods do not include direct fluorination, but metallic derivatives provide carbanions which react with fluorine sources. Thus, 2- and 4-fluoroimidazoles have been made from the lithioimidazoles, for example, perchloryl fluoride converts 2-lithio-1-methylimidazole into the 2-fluoro derivative in more than 50% yield. Access to 4- and 5-fluoroimidazoles is even more convenient from the trimethylstannyl derivatives using fluorine or caesium fluoroxysulfate as the “electrophile”. Mercury groups react in much the same way, but they are more difficult to prepare and purify <86BSF930>.

3.02.9 APPLICATIONS AND IMPORTANCE

In addition to the material covered in CHEC-I there has been coverage of the biological significance of imidazoles <93PHC143>. Along with the triazoles, imidazoles are probably the most important family of compounds used for fungal infections <87JMC1054, 88JHC1439>, and their involvement in catalytic processes at the active sites of enzymes has been well documented (see Sections 3.02.5.2.2; 3.02.5.2.7).

2-Aminobenzimidazoles have potent biological activity (e.g., mebendazole, oxfendazole, benomyl) <83S861, 88JMC260>, and other benzimidazoles are anticonvulsants, sedatives, immunosuppressants, antitumour agents, and antihistaminics <85JMC1934, 92JHC1033>.

Recognition of the ATP-imidazole cycle has prompted an attempt at chemical simulation programmed to continuous production of daughter imidazoles from an immobilized imidazole template (6-chloropurine anchored to polystyrene). However, although the first cycle split off a 30% yield of 1-benzyl-2-phenylimidazole, subsequent cycles were much less productive <90JOC4006>.

There is considerable interest in studies of the nitroimidazoles which act as sensitizers of hypoxic tumor cells to radiation, and which are used in the treatment of human cancer <90JHC1877, 93JCS(P1)2681>. Of particular importance are the studies of reductive metabolism of the compounds, which is presumably related to their preferential toxicity to hypoxic rather than aerobic cells (see Section 3.02.7.1.7(ii)) <84JOC932, 87JA4308, 88JMC323, 89H(28)849, 92JCS(P1)2779>. Electron affinities of the nitroimidazoles are therefore of importance in their effectiveness as radiosensitizers. This makes the 2-nitro isomers the most reactive, and the 4-isomers the least reactive because of their greater solution stability (see Section 3.02.2, 3.02.3.2) <89CJC1666>. The 4-nitroimidazoles are gaining pharmacological significance as immunosuppressants, potential radiosensitizers, radiotherapy synergists, and aldehyde dehydrogenase inhibitors <85AF1220>. Difficulties with the nitroimidazoles are related to the fact that useful pharmacological properties cannot always be separated from mutagenic ones; indeed both may have the same metabolic intermediate. A substituent in the 4-position of 5-nitroimidazoles seems able to decrease this mutagenicity <87JMC150>. Some nitroimidazoles are of use in the treatment of infections caused by anaerobic protozoa and bacteria. Reduction metabolites are again probably the active agents <B-83MI 302-01, 89H(28)849>.

ACKNOWLEDGEMENT

My sincere thanks go to Elizabeth Grant who so expertly deciphered my handwriting, accurately and speedily typed the manuscript and references, and transformed my reaction schemes into a professional format. I also owe a debt to the Division of Sciences and the Chemistry Department of Otago University for financial assistance which made it possible to visit the Science Libraries at Auckland and Canterbury Universities.

3.03

Isoxazoles

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3.03.1 INTRODUCTION

Five-membered ring systems containing one oxygen and one nitrogen atom adjacently are isoxazoles, isoxazolines, and isoxazolidines and are collectively referred to as isoxazole systems. The parent ring system (unsaturated), isoxazole is historically old and an isolated compound, but not identified until 1888 <1852LA(81)96, 1888CB1149>. Claisen was the first to identify isoxazole and named as “monazole” <1888CB1149>. Hantzsch modified the name “monazole” to “isoxazole” <1888LA(249)1>. The partially saturated systems, isoxazolines are known in the literature from 1898. Only from 1960 has more attention been paid to these systems in the following order: 2-isoxazolines > 4-isoxazolines > 3-isoxazolines. Even though the first isoxazolidine derivative (fully saturated) was known in 1918, the first isoxazolidine was prepared in 1942. Brown, Delpierre, and Huisgen were the pioneers in the studies of isoxazolidine from 1960. Studies since the mid-1980s on isoxazole systems are extensive, due to their versatility in chemical synthesis of a variety of compounds as well as in their usefulness in several fields such as agriculture, medicine, and industry. Reported literature has been discussed systematically, but extensively or comprehensively, depending upon the scope of the series: *Comprehensive Heterocyclic Chemistry* <84CHEC-I(6)1>, *Advances in Heterocyclic Compounds* <93AHC(56)9, 93AHC(56)50, 93AHC(56)213, 93AHC(57)1, 93AHC(57)292, 93AHC(58)123, 93AHC(58)216, 94AHC(60)27, 94AHC(60)155, 94AHC(60)261>, *The Chemistry of Heterocyclic Compounds* <91HC(49)1>, *Comprehensive Organic Chemistry* <79COC(4)993>, and *Progress in Heterocyclic Chemistry* <89PHC186, 90PHC146, 91PHC166, 92PHC150, 93PHC185, 94PHC190, 95PHC179>. In addition, since the mid-1980s an enormous number of references have been reported in the literature. Other general reviews are mentioned in the appropriate sections.

3.03.1.1 Scope

This chapter details the nomenclature, theoretical studies, experimental methods, thermodynamics, reactions and reactivity, synthesis, and summarizes applications in the following order:

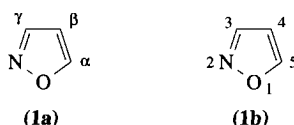
- (i) isoxazoles plus benzisoxazoles;
- (ii) isoxazolines plus benzisoxazolines;
- (iii) isoxazolidines without and with substituents on the ring(s) of all three systems and their salts/complexes.

In order to provide a survey of all available literature, repetitions have been avoided and some sections are grouped together, wherever necessary.

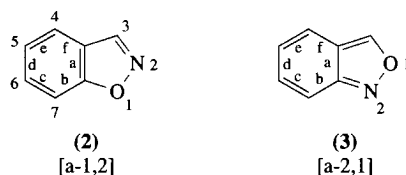
3.03.1.2 Structure and Nomenclature

3.03.1.2.1 Isoxazoles

The trivial name for the title five-membered fully unsaturated heterocycle as “isoxazole” was originally proposed by Hantzsch as it is the isomer of “oxazole” discovered first. The trivial name follows the Hantzsch–Widman system of nomenclature: the prefix “iso” represents isomer, “oxa” represents the oxygen atom, “aza” represents the nitrogen atom (when two or more heteroatoms are present in a ring, the lesser valence atom takes higher priority); the suffix “ole” denotes the ring size as five-membered; altogether the derived name is “isoxazole”. This name has been accepted in IUPAC and has been used in *Chemical Abstracts*. In *Chemical Abstracts*, the other systematic name, 1,2-azole, is also used. Until 1950, the positions in the ring (**1a**) were indicated as α , β , and γ . Later, the positions in the ring were numbered by starting from the oxygen atom (**1b**) and this is the form of labeling mainly used.

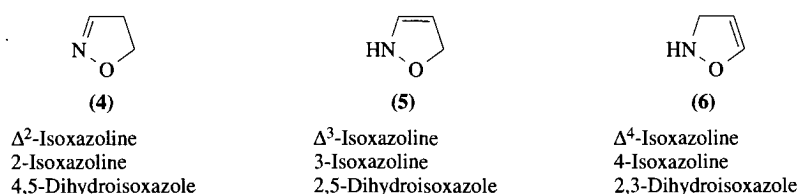


The nomenclature of benzfused or of any fused system or spiral system follows the Hantzsch–Widman system of nomenclature. In these fused systems, the first ring or benzene ring is the base component of the second ring system, isoxazole. Thus the complete name becomes “benzisoxazole.” The bonds in the base component are labeled as a, b, c, d, e, etc. Atoms in the hetero-ring component are numbered as 1–7 as shown in (2) and (3). Two classes of benzfused systems, that is, 1,2-benzisoxazole (or indoxazene) (2) and 2,1-benzisoxazole (or anthranil) (3) exist.



3.03.1.2.2 Isoxazolines

Partially saturated isoxazoles form three isomers, depending upon the position of the double bond. The trivial name is isoxazoline. In earlier literature, “isoxazoline” with the prefix Δ and with a numerical superscript denoting the position of the double bond was used. From 1950 the prefix Δ was deleted, with just the Arabic numeral being used. In the revision of Hantzsch–Widman nomenclature by IUPAC, “oline” is dropped for the partially saturated nitrogen containing ring, and instead the prefix “dihydro” is used (83PAC409). Dihydroisoxazole is the name used in *Chemical Abstracts*. Nevertheless, in the literature and in this chapter the “isoxazoline” nomenclature is used. Therefore the three isomers are named as 2-isoxazoline (4), 3-isoxazoline (5), and 4-isoxazoline (6). Substitution follows the normal numbering as in isoxazole (1b). The nomenclature of benzfused or any fused system or spiral system follows the Hantzsch–Widman system of nomenclature.



3.03.1.2.3 Isoxazolidines

Fully saturated isoxazole systems are named as isoxazolidines or 1,2-oxazolidine or tetrahydroisoxazole (7). Isoxazolidine is the name used in *Chemical Abstracts*. Both names, isoxazolidine

and tetrahydroisoxazole are used in the literature. Substitution follows the normal numbering as in isoxazole (1b).



(7)

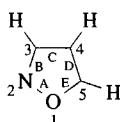
Isoxazolidine
1,2-Isoxazolidine
Tetrahydroisoxazole

3.03.2 THEORETICAL METHODS

3.03.2.1 Isoxazoles

Theoretical studies on isoxazoles focus on electron density, reactivity, aromaticity, molecular geometry, basicity, and dipole moments.

The molecular orbital and semiempirical molecular orbital methods were used to evaluate π -electron density distribution on the isoxazoles. The results served to investigate the reactivity of the heterocyclic ring. The results were consistent for the low aromaticity of the isoxazole ring as well as for the electrophilic substitution at the preferred 4-position. Frontier orbital theory, by the magnitude of the HOMO electron density of each atomic center, explains the position selectivity of electrophilic substitution on the isoxazole ring. The HOMO coefficients calculated by *ab initio* SCF wave functions of double zeta quality and by PRDDO allow prediction of the priority order of electrophilic substitution for the isoxazole: C4 > C5 > C3 and are consistent with experimental data. The use of all electron calculation methods, and other methods such as MO-LCAO, HMO, PPP-SCF, PPP-SCF combined with configuration interaction, aided the calculation of π -electron densities, bond orders, frontier electron densities, and localization energy (Table 1) (8). This led to the prediction of the chemical reactivity of isoxazole, even though some contradictory values of the charge distribution were obtained. The low π bond order of the N—O in comparison with other ring bonds, and the largest localized dipole due to the N—O bond, makes the N—O bond susceptible for hydrolysis. This is consistent with experimental reactivity.



(8)

Table 1 Isoxazole (8): π bond order and π electron densities.

O	N	A	B	C	D	E	C-3	C-4	C-5	Method
1.85	1.28	0.285	0.795	0.546	0.817	0.342	0.87	0.99	1.02	HMO
1.719	1.189	0.412	0.772	0.580	0.776	0.458	1.019	1.014	0.968	MO-LCAO
1.686	1.357	0.371	0.512	0.741	0.603	0.751	0.907	1.063	0.986	PPP-SCF-CI
		1.361	1.957	1.501	1.955	1.498				MO-SINDO1

In general, the earlier concept is to have alternate double bonds in a ring, as a necessary criterion for aromaticity. Graph theoretical and topological resonance are alternate approaches to aromaticity. The semiempirical MO method, SINDO, has been developed for 40 mono- and polycyclic ring systems. The magnitude of the ring current is determined by its weakest link in the ring, that is, by the bond with the lowest bond order. Isoxazole has the lowest bond order value 1.361, which is in the range of moderately aromatic compounds (1.548–1.332) <83JOC1344>. Methods ranging from Huckel to *ab initio* calculations for energy-based criteria for aromaticity employed one-electron eigenvalues. The results for heteroaromatic compounds especially did not correlate well with experimentally derived criteria such as, π ring current contribution to the magnetic susceptibility or chemical reactivity. A modified procedure combining both the natural (NLMO)

and Boys orbital localization methods, was used for a set of ten five-membered ring heteroatoms. The Boys procedure gave better overall correlation $\langle 90\text{IJQ}843 \rangle$.

The theoretical values of bond lengths and bond angles obtained describing the molecular symmetry of isoxazoles and the methods used are summarized (Tables 2 and 3) (8) $\langle 91\text{HC}(49)1 \rangle$.

Table 2 Isoxazole (8): bond lengths (Å).

<i>A</i>	<i>B</i>	<i>C</i>	<i>D</i>	<i>E</i>	<i>C</i> (3)— <i>H</i>	<i>C</i> (4)— <i>H</i>	<i>C</i> (5)— <i>H</i>	<i>Method</i>
1.38	1.30	1.43	1.36	1.36				VESCEF
1.38	1.30	1.44	1.35	1.36				Improved LCAO
1.277	1.328	1.418	1.355		1.112	1.108	1.112	CNDO/2
1.301	1.351	1.449	1.387	1.373	1.082	1.077	1.083	MNDO SCF-MO
1.383	1.316	1.436	1.349	1.373	1.082	1.076	1.083	STO-3G

Table 3 Isoxazole (8): bond angles (°).

<i>ONC</i> (3)	<i>NC</i> (3) <i>C</i> (4)	<i>C</i> (3) <i>C</i> (4) <i>C</i> (5)	<i>C</i> (4) <i>C</i> (5) <i>O</i>	<i>C</i> (5) <i>ON</i>	<i>C</i> (3) <i>C</i> (4) <i>H</i>	<i>C</i> (4) <i>C</i> (5) <i>H</i>	<i>NC</i> (3) <i>H</i>	<i>C</i> (5) <i>C</i> (4) <i>H</i>	<i>C</i> (4) <i>C</i> (3) <i>H</i>
111.1	107.2	106.0	109.5	106.2					
110.0	108.0	107.0	108.0	107.0					
105.8	111.5	104.2	109.2	109.3	127.2	133.6	120.7	128.6	
127.8									
105.3	112.3	103.0	110.6	108.8	128.5	133.4	118.6	128.5	
129.1									

The low basicity ($\text{p}K_{\text{a}} = -2.3$) of isoxazole has been rationalized using the technique of partitioning energy in the MNDO method. Mainly because of the mutual electrostatic field effect between both O and N atoms, the π electron charge density of the oxygen is unable to participate to delocalize the positive charge at the vicinal N atom. The calculated heat of formation for isoxazole ($19.2 \text{ kcal mol}^{-1}$) using the MNDO-SCF-MO method is consistent with experimental results $\langle 81\text{JHC}1189 \rangle$.

Several approaches and methods are used to calculate the value of dipole moment for simple isoxazole. All theoretical methods gave the calculated value, ranging from $2.45\text{--}3.6 \mu$ except EHT (7.63μ) and the observed value, ranging from $2.81\text{--}3.1 \mu$. A comparison of the calculated value with the obtained value is a good verifying strategy for the validity of the theoretical method used. The Huckel method seems to be in good agreement with the experimental values. In general, the calculated values show disparity from the experimental values either due to the use of extended *sp* basis set without polarization function or to the use of minimal basis set $\langle 91\text{HC}(49)1 \rangle$.

Using LCAO-SCF-MO and CNDO-CI methods, the first ionization potentials for isoxazole was calculated and are (8.78 eV) $\langle 69\text{BSB}407 \rangle$ and (9.78(π), 11.25(π), 12.27 (*n*)eV) $\langle 72\text{JCPB}860 \rangle$. Photoelectron spectroscopy for isoxazole gave 10.17 and 11.29 eV for the vertical and 9.99 and 11.13 eV for the adiabatic values $\langle 70\text{ANC}1064 \rangle$. Using population analysis data, vertical ionization energy of isoxazoles is calculated and compared with other heterocycles. Isoxazoles show a considerable similarity with furan and the corresponding azoles. Combination of the first-order perturbation theoretical approach with the technique of photoelectron angular distribution measurements on isoxazoles showed three bands. From top to the bottom, the bands are assigned as π , π , and *n* bands while those of oxazoles are identified as π , *n*, and π $\langle 82\text{BCJ}3915 \rangle$.

Theoretical studies are also done to interpret the synthesis reactions and mechanism of reactions. The regioselectivity of 1,3-dipolar cycloaddition reaction between substituted trimethylstannyl-ethynes and nitrile oxides yielding isoxazoles, was interpreted by the application of frontier electron theory $\langle 93\text{CPB}478 \rangle$. By the combination of experimental and molecular orbital (*ab initio*) studies, a multistep mechanism is proposed for unimolecular radical chemistry of isoxazoles in the gas phase $\langle 92\text{OMS}(27)317 \rangle$.

3.03.2.2 Benzisoxazoles

A CNDO/2 study of the substituted 1,2-benzisoxazole 2-oxides elucidated the features of its electronic structure and explained their reactivity. Charge densities fail to account for the observed reactivity. Both electrophilic and nucleophilic reactions appear to be orbital controlled $\langle 87\text{T}785 \rangle$.

3.03.2.3 Isoxazolines

Ab initio MO calculations on 3-formyl- δ 2-isoxazoline-BF₃-complex suggests that *s-trans* conformation is preferred over *s-cis* conformation. Nucleophiles attack the stable *s-trans* conformer from the opposite side of the C-4 substituent, giving the respective *anti* adducts <93T7637>. The regioselectivity of the 1,3-dipolar cycloadditions of mesitonitrile oxide with benzo[b]thiophene *S*-oxide and *S,S*-dioxide yielding only 2,3-dihydrobenzo[b]thieno[2,3-d]isoxazolines, is discussed in terms of frontier MO interactions on the basis of photoelectron spectra and CNDO/S calculations <82JOC2461>.

3.03.2.4 Isoxazolidines

The 1,3-dipolar cycloaddition of nitrones to *N*-arylmaleimides gave predominantly the *anti*-isoxazolidines and was rationalized by (*Z*)/(*E*) isomerization of nitrones. AM2 calculations of the nitrones and MM2 calculations of the isoxazolidine adducts, were performed <92M999, 93M1019>.

3.03.3 EXPERIMENTAL STRUCTURAL METHODS

An extensive data on all experimental methods are summarized and discussed <91HC(49)1>. Experimental studies related to the structural aspects alone are discussed in this section. Other aspects such as evidence for mechanism, conformation, configuration are discussed under thermodynamic aspects (Section 3.03.4). Depending on the amount of literature reported, experimental methods are either categorized or grouped together.

3.03.3.1 Isoxazoles

3.03.3.1.1 Spectroscopy

Several spectroscopic methods are used in the study of isoxazole systems and are categorically discussed.

(i) Nuclear magnetic resonance spectroscopy

In the literature on synthesis and reactions, almost all provide NMR data along with other structural evidences, even though they are not categorized under "NMR" or "experimental methods" keyword search in *Chemical Abstracts*. The presence of two vicinal heteroatoms causes dissymmetry in the ring nucleus, thus affects the chemical shifts of both proton and carbon nuclei in the ring. The differences in the chemical shifts almost always enable one to elucidate the structure of an unknown isoxazole, on the basis of NMR alone. Of course one needs to consider the effects of substituents on the chemical shift.

Proton NMR data of unsubstituted isoxazole, neat or dissolved in various solvents have been summarized (Table 4) (9). It is obvious that all protons absorb in aromatic region, even though H-4 at the higher field (δ 6.31–6.75) than H-3 (δ 8.15–8.46) and H-5 (δ 8.39–8.69). Proton NMR data for a selected few alkyl, aryl, and alkyl/aryl substituted isoxazole derivatives are summarized (Table 5) (9). In the literature from the early 1990s ¹H NMR is used as one of the structural evidences for diversely substituted isoxazole derivatives <90JOC1227, 91BSF272, 92JHC1325, 92MI 303-01, 93JCS(P1)939,

93MI 303-01, 93MI 303-02, 95PJC579), for complexes of metals (83JMR(54)99, 93MI 303-03) and of transition metals (89JOM287).

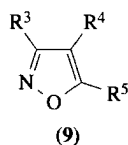


Table 4 Isoxazole (9): ^1H NMR chemical shifts (δ) and coupling constants.

<i>H</i> -4	<i>H</i> -3	<i>H</i> -5	J_{3-4}	J_{4-5}	J_{3-5}	Solvent
6.31	8.19	8.44	1.6	1.6		Liq. cryst.
6.40	8.40	8.61	1.7	1.7	0.5	Neat
6.41	8.34	8.51	1.5	1.5		CDCl_3
6.32	8.19	8.44	1.6	1.6		CCl_4
6.28	8.15	8.39	1.78	1.69	0.27	CS_2

Table 5 Alkyl/aryl isoxazole (9): ^1H NMR chemical shifts (δ).

R^3	R^4	R^5	R^3	R^4	R^5	<i>H</i> -3	<i>H</i> -4	<i>H</i> -5	Solvent
Me	H	H	2.26				6.29	8.79	Neat
H	Me	H		2.0		8.23		8.35	Neat
H	H	Me			2.36	8.21	6.05		Neat
Me	H	Me	2.13		2.31		5.89		Neat
H	Me	Me		1.86	2.26	8.08			Neat
Me	Me	H		2.22	1.97			8.06	CDCl_3
Ph	H	H					6.62	8.48	Neat
H	Ph	H				8.43		8.58	CCl_4
H	H	Ph				8.29	6.44		Neat
H	Me	Ph				8.12			Neat
Ph	H	Me					6.20		CCl_4
Ph	Et	H						8.18	Neat

As mentioned under ^1H NMR, in ^{13}C NMR for the unsubstituted isoxazole, C-4 ring carbon atoms absorb at 104.5 ppm, C-3 at 150.0 ppm and C-5 at 158.9 ppm (75CJC1677, 76OMR(8)226). A downfield shift of 8–10 ppm results from the introduction of a methyl group on the ring carbon to which it is linked. Carbon-13 NMR data for a selected few alkyl, aryl, and alkyl/aryl substituted isoxazole derivatives are summarized (Table 6) (9). Use of ^{13}C NMR data is used as one of the structural evidences for diversely substituted isoxazole derivatives (91BSF272, 93JCS(P1)939, 93MI 303-01, 95PJC579).

Table 6 Alkyl/aryl isoxazole (9): ^{13}C NMR chemical shifts (ppm).

R^3	R^4	R^5	R^3	R^4	R^5	<i>H</i> -3	<i>H</i> -4	<i>H</i> -5	Solvent
H	H	H				150	104.5	158.9	$(\text{CD}_3)_2\text{CO}$
Me	H	H				159.2	105.7	159.2	Neat
H	H	Me				150.9	101.4	169.2	Neat
Me	H	Me				160.0	102.7	169.4	Neat
Me	Me	H	9.6	6.3		159.3	113.6	154.8	CDCl_3
Me	Me	Me	10.7	6.6	10.0	159.9	109.0	164.2	CDCl_3
Ph	H	Me			11.6	160.3	100.1	169.6	CDCl_3

Data reported earlier for ^{15}N and ^{14}N NMR chemical shifts, and coupling constants for isoxazoles are discussed, along with results of correlation studies using theoretical calculations (91HC(49)1). The values of chemical shifts under different experimental conditions, for isoxazole, alkylisoxazoles, and benzisoxazoles are summarized (Table 7) (9) (83HCA1537, 84OMR(22)215). As expected, introduction of a methyl group at the C-3 position in the ring shields ^{15}N resonance by 9 ppm in $\text{DMSO}-d_6$ and 10 ppm in CDCl_3 , which are similar to imidazoles and pyrazoles. Using INEPT and DEPT

pulse sequences, ^{15}N —H spin coupling constants ($2J^{15}_{\text{N-H}}$ (3 Hz), $3J^{15}_{\text{N-H}}$ (1.3–1.8 Hz), and $4J^{15}_{\text{N-H}}$ (<1)) with *syn* conformation have been measured for isoxazole and its methyl derivatives <83HCA1537>. In order to examine the structural changes on the magnitude of the shifts, for the ^{18}O induced isotope the shifts in the ^{15}N NMR spectra were measured. A shift of 0.159 ppm was reported for isoxazole and 0.027 ppm for nitrile oxide. This large isotope shift in isoxazole was attributed to the aromatic nature and shorter N—O bond length of isoxazole as opposed to the oximes <87JA4357>.

Table 7 Isoxazoles (9): ^{15}N NMR chemical shifts (ppm).

R^3	R^4	R^5	Chemical shifts (reference)	Solvent
^{15}N isoxazole			339.6 (MeN $^+\text{Cl}^-$)	Neat
H	H	H	−2.7 (MeNO $_2$)	DMSO
H	H	H	+2.2 (MeNO $_2$)	DMSO- d_6
H	H	H	+0.6 (MeNO $_2$)	CDCl $_3$
H	H	Me	−2.4 (MeNO $_2$)	CDCl $_3$
H	H	Me	+0.1 (MeNO $_2$)	DMSO- d_6
Me	H	Me	−9.2 (MeNO $_2$)	DMSO- d_6
Me	H	Me	−12.0 (MeNO $_2$)	CDCl $_3$
Benzo[d]isoxazole			−3.3	DMSO
Benzo[d]isoxazole			−3.2	D $_2$ O
Benzo[c]isoxazole			+7.5	DMSO

The chemical shifts in ^{17}O NMR for isoxazole and its methyl derivatives are provided (Table 8) (9). The electronegativity of atoms linked directly to oxygen atoms has major influence on the chemical shifts of ^{17}O . The substituents at various positions of the ring also have influence to some extent <84OMR(22)55>.

Table 8 Isoxazoles (9): ^{17}O NMR chemical shifts (ppm).

R^3	R^4	R^5	Chemical shifts
H	H	H	350
Me	H	H	344
H	H	Me	356
Me	Me	H	338
Me	H	Me	350
Me	Me	Me	340

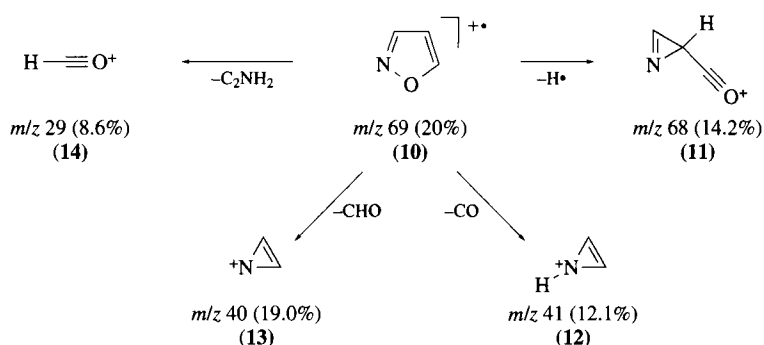
Flourine-19 NMR chemical shifts for CF $_3$ - and C $_6$ F $_5$ -substituted isoxazoles are reported <83ZOR223>. A quantitative evaluation of the reaction mixture was accomplished using the different signals (C(4)—CF $_3$, 14 ppm; C(5)—CF $_3$ −22 ppm; ref. TFA) for the CF $_3$ groups in the isomers of 4- and 5-trifluoromethyl isoxazoles <83ZOR221>. Mercury-199 NMR chemical shift in 3-cyano-4-methylmercurio-5-phenylisoxazole was found to be at −344 ppm (q, $J^{199}_{\text{Hg-H1}} = 138.7$ Hz) from neat dimethyl mercury <84JOM(269)115>.

(ii) Infrared spectroscopy

A systematic and thorough study has been done on isoxazole and isoxazole- d_3 using IR and Raman spectroscopy. IR spectra have been recorded in vapor and liquid phases as well as in solutions. A full assignment of absorption frequencies have been based on its planar structure, Cs symmetry group, in comparison with the spectra of other heterocycles (furan and pyran) and theoretical calculations. The assignment of stretching vibrations in unsubstituted isoxazoles are as follows (in cm $^{-1}$): $\nu\text{C}(5)$ —H 3161, $\nu\text{C}(4)$ —H 3131, $\nu\text{C}(3)$ —H 3089, $\nu\text{C}=\text{N}$ 1557, $\nu\text{C}=\text{C}$ 1429. Using IR data, the structures of substituted isoxazoles <91BSF272, 95PJC579>, poly(quinolinyne-isoxazole) polymers <86MI 303-01>, and metallic complexes <82AJC1829, 83SA(A)903, 83JCC177, 84JOC2772, 84POL261, 86MI 303-02, 89JOM(372)287, 89POL935, 93MI 303-03>. In 4-benzoyl-2,3,5-trimethylisoxazolium methosulfate, the lack of coplanarity between the benzoyl group and the isoxazole ring was deduced from IR carbonyl frequency (1887 cm $^{-1}$), which is a higher value than expected from a diarylketone <83H(20)1035>.

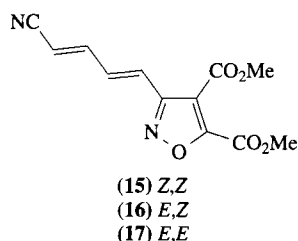
(iii) Mass spectroscopy

Mass spectroscopy is used widely in isoxazole systems to understand the fragmentation pathways, elucidate the structure, differentiate the isomers, and to interpret the reaction mechanism and tautomerism. MS data for unsubstituted isoxazole was reported for the first time in 1972 and it revealed the fragmentation pathway (Scheme 1). Advanced techniques in MS, such as electron impact (EI/MS) giving metastable ion, mass-analyzed ion kinetic energy (MIKE) spectra giving molecular ion and FAB giving fragmentation ion in combination with theoretical calculations (MNDO/3) on the heat of formation of some of the predictable ions or ions formed in the fragmentation of isoxazoles are discussed <91HC(49)1>. The characteristic chemical behavior of isoxazole, that is, the lability of the N—O bond is well reflected in the fragmentation pattern especially in alkyl isoxazoles via the azirine (13) and acyl ion (14). MS data for unsubstituted isoxazole (1) are given at 50 eV: 70(5), 69(M⁺, 100), 68(71), 42(17), 41(60), 40(95), 39(25), 38(22), 37(9), 30(7), 29(43), 27(12), 26(13). Reported MS results for structural elucidation are <84JOC4419, 84MI 303-01, 84OMS(19)72, 91BSF272, 92JHC1325, 92RCM667>.



Scheme 1

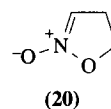
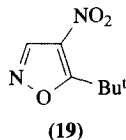
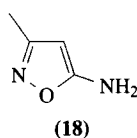
A comparative MS study on the three geometrical isomers (15)–(17) of dimethyl 3-(4'-cyano-buta-1',3'-dienyl)isoxazole-4,5-dicarboxylate with dimethyl 3-phenyl- and dimethyl 3-formyl-isoxazole-4,5-dicarboxylate revealed that all three isomers underwent an identical fragmentation pattern. And it was supported by a metastable ion <84OMS(19)250>. A FAB/MS study on isoxypenicillin and its metabolites <85CPB383> and a GC-MS study on isoxicam and its metabolites are reported <84MI 303-01>. MS studies on some new 3,5-disubstituted 4-isoxazolecarboxylic acids revealed that fragmentation occurs via azirine intermediates <90RCM513>. The EI and field desorption spectral data on some macro cyclic–acyclic polyether-ester compounds containing isoxazole are reported and discussed <82OMS(17)34>. Isoxazoles yielded iminopropadieneone ions by dissociative ionization (flash vacuum pyrolysis) and yielded neutral cumulenes by neutralization experiments in a tandem mass spectrometer <92RCM667>. Using high-pressure mass spectrometry, the proton affinity for isoxazole was found to be 202.3 kcal mol^{−1}, which is the least among the azoles studied (e.g., oxazole 207.8 kcal mol^{−1}, and imidazole 222.1 kcal mol^{−1}). These results are consistent with the *ab initio* calculation for the enthalpy of protonation. A correlation between lone-pair *n* orbital energies and proton affinities was also observed <86JOC1105>.



(iv) Ultraviolet spectroscopy

In the UV region, isoxazoles only show absorption for the $\pi \rightarrow \pi^*$ transition, like the other five-membered heterocycles. For unsubstituted isoxazole the absorption maximum occurs at 211 nm

($\log \epsilon = 3.6$) in both aqueous and ethanolic solutions. Isoxazoles do not obey Beer's law, as evidenced by the absorption in ethanolic and cyclohexane solutions and they exhibit hypochromism. These behaviors are attributed to the high dipole moment $\langle 68\text{SA(A)}1975 \rangle$ and to anti-parallel sandwich type self-association, via dipole-dipole interaction $\langle 77\text{MI } 303-01 \rangle$. Remarkably, triphenyl isoxazole obeys Beer's law, in contrast to 3,5-diphenylisoxazole or isoxazole. It is attributed to the absence of self-association due to steric hindrance $\langle 68\text{SA(A)}1975, 77\text{MI } 303-01 \rangle$. Methylisoxazoles in aqueous solution show a range of absorption maxima from 210–230 nm, depending on the substituent position. The strongest bathochromic shift is produced by the methyl group at C-4 (2–10 nm) when compared to positions C-5 (5–6 nm) and C-3 (1–2 nm). More pronounced bathochromic shift is exhibited when a fully conjugated phenyl group is present (C-4 ~ 47 nm, C-5 ~ 49 nm, C-3 ~ 30 nm), unless otherwise the coplanarity between the phenyl ring and isoxazole ring is prevented. The influence of functional groups on bathochromic shift ($-\text{CHO} \sim -\text{CONHNH}_2 < -\text{COOH} \sim -\text{CONH}_2 < -\text{COOR} \sim \text{R}_2\text{CO}$) depends on the extent of conjugation of the substituent(s) on the isoxazole ring. Solvents have influence on the position and number of absorption maxima. For example, isoxazole (18) show different absorption maxima, 227 nm (3.68) in cyclohexane, 239 nm (3.96) in water, 254 nm (4.09) in 2N H_2SO_4 $\langle 61\text{T51} \rangle$ and isoxazole (19) show three absorption maxima (213 nm (3.80), 261 nm (3.77), 322 nm (2.20)) in isooctane and two absorption maxima (269 nm (3.72), 337 nm (2.36)) in water $\langle 64\text{G915} \rangle$. UV data is used in elucidating the structure of an array of substituted isoxazoles $\langle 95\text{PCJ579} \rangle$ and complexes of metals $\langle 83\text{JCC177}, 83\text{SA(A)}903, 93\text{MI } 303-03 \rangle$.



(v) *Electron spin resonance spectroscopy*

In the past, ESR studies on isoxazole(s) revealed the formation and structure of radical as well as the stereochemical information of metallic complexes. It has been reported that the metal appears to be 4-coordinate square planar in bis complexes and hexacoordinate in tetrakis complexes $\langle 83\text{SA(A)}903, 89\text{POL935} \rangle$.

(vi) *Microwave spectroscopy*

Microwave spectroscopy (MWS) is used to collect the information on molecular geometry, electron distribution, barrier to internal rotation and molecular force field. Often, the results from MWS have been compared with theoretical calculations. The MWS of 4-methylisoxazole has been measured in the region 8–40 GHz. Internal rotation analysis is done along with the results of ^{14}N NQR spectroscopy (NQRS) $\langle 87\text{ZN(A)}501 \rangle$.

(vii) ^{35}Cl *Nuclear quadrupole resonance spectroscopy*

NQRS data along with the corresponding symmetry parameters η , indicate the electronic distribution in the vicinity of the nucleus considered. ^{35}Cl NQR spectra of substituted phenylisoxazole and isoxazolines along with the results of atom charges and orbital population calculations (MNDO/3) proved that a chlorine atom present at the 4-position on an isoxazole ring transmits the influence from the phenyl ring at position 3, to the phenyl ring at position 5 on the isoxazole ring through the system of π bonds $\langle 94\text{MRC573}, 94\text{MI } 303-01 \rangle$.

3.03.3.1.2 X-ray analysis

X-ray analysis has aided in establishing the structure of isoxazoles $\langle 92\text{JCS(P2)}121, 92\text{JHC1325}, 93\text{JCS(P1)}939 \rangle$ and transition metallic complexes $\langle 89\text{JOM(372)}287 \rangle$ unequivocally.

3.03.3.1.3 Other methods

Other methods (fluorescence, phosphorescence, radioluminescence, reflectance, circular dichroism spectroscopy) used in the past in the study of isoxazoles are discussed <84CHEC-I(6)1, 91HC(49)1>. HPLC, GC, TLC densitometry and other chromatographic separation techniques are used in qualitative and quantitative estimation of isoxazole derivatives <84MI 303-02, 91DIS(B)4848, 91CB2481, 95MI 303-01>.

3.03.3.2 Isoxazolines

3.03.3.2.1 2-Isoxazolines

In 2-isoxazoline systems, both chemical shifts and coupling constants from ^1H NMR data enable the structure elucidation <84CPB2450, 87JCS(P2)523, 94JCR(S)383, 94T479> as well as to determine the mode of formation of regio- and stereoisomers from 1,3-dipolar cycloaddition <89MRC872, 92RCM667, 93JCS(P1)75, 93JOC4524>. Three well-separated signals are obtained for unsubstituted 2-isoxazoline (H-4 δ 2.9 (m, 2H), H-5 δ 4.1 (m, 2H), H-3 δ 7.1 (m, 1H)) <72JCS(P1)1701>. This pattern becomes complex in substituted 2-isoxazolines. Most of the substituted isoxazolines are 3-substituted. Simple ^{13}C NMR or with DNOE or NOE experiments the stereo- and regiochemistry of reaction products from 1,3-dipolar cycloaddition <89MRC872, 91MRC706, 92RCM667, 93JOC4524, 94JCR(S)383>. For 2-isoxazoline systems IR is used mainly for deducing the structures <92RCM667>. Bands in the range 1560–1640 cm^{-1} have been assigned to $\text{C}=\text{N}$ and 841–936 cm^{-1} to $\text{N}-\text{O}$ <83MI 303-01, 83MI 303-02, 83MI 303-03, 83MI 303-04, 83MI 303-05, 83NKK1678>. The UV spectroscopic method is less useful for 2-isoxazolines except for substituted 2-isoxazolines with groups such as phenyl <92RCM667>. Unlike isoxazoles and isoxazolidines, 2-isoxazolines are *less* extensively studied by MS. In the systems where MS is used, it is to mainly to find out the molecular weight of the products. The fragmentation pattern varies depending on the nature and position of the substituent: 5-monosubstituted, 3,5-disubstituted, 4,5-disubstituted, 5,5-disubstituted 2-isoxazolines are reported <83KGS738>. X-ray diffraction analysis has been well exploited to confirm the structure and stereochemistry of 2-isoxazolines <83CC1460, 83T2231, 83TL5501, 84T177, 87JCS(P2)523, 93JCS(P1)75>. Electrochemical behavior of 3-methyl-4-(substituted-benzeneazo)-2-isoxazolin-5-ones has been reported <94JCR(S)383, 93PIA(A)35>.

3.03.3.2.2 2-Isoxazoline N-oxide

Several ^1H NMR spectra are reported for 2-isoxazoline *N*-oxide (**20**) systems in earlier literature, whereas ^{13}C NMR spectra and MS spectra are only a very few. In IR spectra, the characteristic intense band at 1600–1660 cm^{-1} is attributed to the $\text{C}=\text{N}^+$ bond. UV spectra for a large number of 3-nitro derivatives are reported ($\lambda_{\text{max}} = 320 \text{ nm}$) <91HC(49)1>.

3.03.3.2.3 3-Isoxazolines

The structure of the natural product, 2-(2-carboxyethyl) 3-isoxazolin-5-one was determined by spectroscopic methods and chemical degradation techniques <84CPB2450>.

3.03.3.2.4 4-Isoxazolines

Proton NMR is the most useful method to deduce the structure and regiochemistry of 4-isoxazolines. Ring protons are not heavily influenced by the substituents, thus follow the chemical shift order: H-3, H-4, H-5 from higher to lower field. Only a very few ^{13}C NMR data for 4-isoxazolines are reported <84JCR(M)1531>. MS data for 4-isoxazoline derivative is reported to corroborate structural assignments. The general instability of the ring is reflected in the MS fragmentation pattern <84JCR(M)1531>.

3.03.3.3 Isoxazolidines

3.03.3.3.1 Spectroscopy

(i) Nuclear magnetic resonance spectroscopy

Proton NMR is a useful method for determining the structure and stereochemistry of isoxazolidines. Proton NMR spectra of a free base isoxazolidine is reported (H-4 (δ 2.14), H-3 (δ 3.11), H-5 (δ 3.81), H-4 (δ 4.87)). With irradiation of NH frequency, a broad singlet at about δ 5.0 appears without affecting other proton signals <68MI 303-01, 72JCS(P1)1701>. Isoxazolidine hydrobromide salt in a downfield shift of ^1H NMR spectrum: δ 2.5 (q, $J = 7$ Hz, 2H, H-4), δ 3.7 (t, $J = 7$ Hz, 2H, H-3), δ 4.3 (t, $J = 7$ Hz, 2H, H-5), δ 4.8 (s, 2H, HOD) <80JA1649>. In many substituted isoxazolidines, the coupling constants of vicinal protons provide a clear indication of stereochemistry of substituents. In general, the coupling constants of *cis* are higher than that of *trans* <83JOC486, 84H(22)2187, 89H(29)547, 92M999>. By NOEDS, the configurations of isoxazolidinium salts have been determined. It provided a good explanation for the reactivity of the compound, that is ring opening in the five-membered ring as a function of steric requirement in the isoxazolidine systems <88MRC974>. Carbon-13 NMR complements ^1H NMR data for determination of structure, regio-, and stereochemistry of some isoxazolidine adducts <83JHC519, 83JOC486, 83JOC4043, 89PS(42)135, 92M999>. Fluorine-19 NMR data for 2-methyl-4-aryl-5-(perfluoro hexylsulfonyl) isoxazolidines have been reported <84JFC(25)453>. Phosphorus-31 NMR data on variously substituted *N*-phenyl-4-(or 5-)phosphoisoxazolidines enabled the determination of structure and conformation <80IZV715>.

(ii) Mass spectroscopy

Depending upon the substituents, a number of cleavage patterns occur in isoxazolidines, and so as the fragments. The molecular ions are detectable. The MIKE technique on the structure of the products aided deduction of the substituent effect on the bimolecular reaction mechanism of isoxazolidinium salt with LiAlH_4 <83JHC1207>.

(iii) Electron spin resonance spectroscopy

ESR spectroscopic studies, have been found to be useful in detecting the formation of aminyl oxides, on oxidation of 5-(hydroxyamino)isoxazolidines <86CB36>.

3.03.3.3.2 X-ray analysis

In *cis*-2-(2'-cyanoethyl)-3-phenyl-5-cyanoisoxazolidine, the cyano and phenyl group are *cis* with respect to each other and with respect to the nitrogen of the heterocyclic ring. It was evidenced by the ORTEP diagram and full x-ray analysis data <84JCS(P1)47>.

3.03.4 THERMODYNAMIC ASPECTS

3.03.4.1 Isoxazoles

Isoxazoles are insoluble in dilute acids but in HCl gas some isoxazoles form crystalline salts.

3.03.4.1.1 Conformation

A discussion of conformational studies on few isoxazoles by the use of theoretical methods (PCILO, CNDO/2, Dewar σ - π , and EHT), revealed ring and side chain rotation at C-5 position <91HC(49)1>. Theoretical studies on a series of isoxazolyl dihydropyridines ($\text{R}^1 = \text{Me, Et, iso-Pr, } n\text{-C(5)H(11)}$; $\text{R}^2 = \text{Ph, Me}$; $\text{R}^3 = \text{H, D}$; $\text{R}^4 = \text{Me or Et}$) enabled the estimation of the relative energy and barrier to rotation, for different conformers as a function of both the ring juncture between the

heterocyclic rings and the esters in the 3- and 5-positions of the dihydropyridine. A controversial prediction of minimum energy conformer to be *O-exo-ap*, *ap* and *O-exo-sp*, *sp* by molecular mechanics and quantum mechanics calculations, respectively. Both methods indicate that barrier rotation about the heterocyclic ring juncture should be low, but both methods appear to overestimate the difficulty of ester rotation. A single-crystal x-ray diffraction of (3,5-dimethyl isoxazolyl) dihydropyridine shows the *O-endo* ring juncture and *sp*, *sp* ester conformation. But 2D NOE NMR spectroscopy indicate the presence of both conformers <90JMC2255>. X-ray analysis and ¹H NMR results of (*RS*)-3-hydroxy-4,5,6,7-tetrahydroisoxazolo[5,4-*c*]pyridine-7-carboxylic acid (7-HPCA) and of (*RS*)-3-hydroxy-4,5,6,7-tetrahydroisoxazolo[5,4-*c*]pyridine-5-carboxylic acid (5-HPCA) provide evidence that carboxylate groups are in equatorial position, in preferred conformations <85JMC673>.

3.03.4.1.2 Isomerism

MNDO results evidence the gas-phase thermal isomerization of isoxazole to oxazole via nitrile ylide or keteneimine with similar activation energies, through an azirine intermediate and the rate limiting step is the first step which is in good agreement with experimental results <90JPO611>. The effects of conformation, *R-Z* photoisomerization and light wavelength on the photolysis of 3,3,5-trimethyl-4(5*H*)-isoxazolone are discussed <91RTC31>. A quantum-chemical analysis on the isomerization of isoxazole and other five-membered isoxazoles, via singlet and triplet states is reported <86KGS173>. A photochemical isomerization of isoxazole to oxazole is reported <91H(32)1765>.

3.03.4.1.3 Tautomerism

The kinetics of enolization and degradation studies on *N*-(5-methyl-4-isoxazolyl)-4-amino-1,2-naphthoquinone in aqueous solutions over a pH range of 7.30–12.25, at 35°C and constant ionic strength ($\mu = 0.5$) using reversed-phase HPLC along with theoretical pH rate profile supports the tautomerization to 2-hydroxy-*N*-(5-methyl-4-isoxazolyl)-1,4-naphthoquinone 4-imine <95JPS783>.

3.03.4.2 Isoxazolines

3.03.4.2.1 Conformation

A combination of force-field calculation, LIS measurements, LIS simulation, and CD spectroscopy has been used to assign the conformation and configuration of the cholecalciferol-isoxazoline adducts <93LA595>. The configuration and conformation of all pentacyclic isoxazolines obtained as products from the reaction between benzonitrile oxide and norbornene-azetidinone fused 3,1-oxazines, were determined by ¹H NMR, ¹³C NMR, and DNOE experiments <89MRC872>.

3.03.4.2.2 Tautomerism

A spectroscopic survey of the tautomerism of 3-hydroxyisoxazolines indicates the occurrence of the NH form as a predominant or exclusive one <90T1975>.

3.03.4.2.3 Reaction rate factors and mechanism

The decarboxylation rate of 3-carboxybenzisoxazoles depends on the substituent and strongly on the solvent, which is evidenced by the use of the empirical Kamlet–Taft–Abraham solvatochromic parameter set in a multilinear correlation analysis based on LSER, along with a theoretical computational set of molecular parameters <94JCS(P2)1641>. The effect of temperature and evaluation of thermodynamic parameters for the polarographic behavior of 3-methyl-4-(2' substituted benzeneazo)-2-isoxazol-5-ones are reported <94MI 303-02>.

In flash vacuum photolysis and pyrolysis experiments on isoxazole derivatives, IR is used to monitor the reaction and to elucidate the reaction mechanisms $\langle 84JOC2772 \rangle$. Evidence is found for the formation of azirine during the transformation of isoxazole to oxazole.

3.03.4.3 Isoxazolidines

3.03.4.3.1 Conformation

Proton NMR (sometimes low temperature NMR or NOE) is the major reliable method for conformational analysis of isoxazolidines $\langle 82JOC4397, 84OMR(22)399 \rangle$. It is generally agreed that conformers created by isoxazolidine derivatives are promoted by the pyramidal inversion of the ring nitrogen atom. Earlier literature on invertomers is thoroughly reviewed $\langle 91HC(49)1 \rangle$. Using PES, the ratios of axial and equatorial conformers of isoxazolidine (3 : 1), 2-methylisoxazolidine (1 : 4), 2-*t*-butylisoxazolidine (1 : 10) are reported $\langle 78TL841 \rangle$. By the use of NMR, the conformations of tetrahydroisoxazolo[2,3-*d*][1,4]benzodiazepinone isoxazolidines are reported $\langle 82JCS(P1)2701 \rangle$. The NMR LIS technique is used to evaluate the epimeric mixtures of 5-regioisomeric isoxazolidines $\langle 84OMR(22)399 \rangle$. An envelope conformation with a pseudoequatorial N-Me group was found for 2-methyl-3,3,3,4,5-tetracarbomethoxy isoxazolidines from x-ray and NMR data $\langle 82IZV2050 \rangle$.

3.03.4.3.2 Tautomerism

NMR data indicated that 2-acyl-3-hydroxyisoxazolidines exist in the cyclic form in *weak* polar solvents, but in polar solvents ~10–15% exist in the open chain form, $BzNHCH_2CHO$ $\langle 85KGS1137 \rangle$.

3.03.5 REACTIVITY AND REACTIONS

Discussion in this section follows a general format:

- (i) reactions only on the ring, with and without ring cleavage;
- (ii) reactions involving both ring and side chain;
- (iii) reactions only on the side chain in isoxazole systems followed by isoxazoline (2-, 3-, and 4-isomers) systems and isoxazolidine systems.

3.03.5.1 Isoxazoles

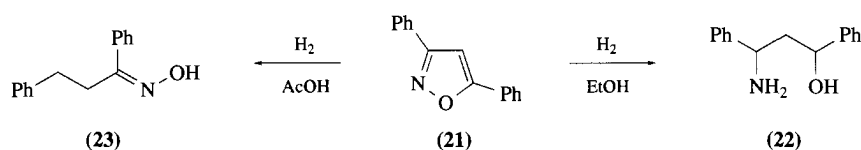
Heteroatoms, the nitrogen atom and the oxygen atom reflect electron-withdrawing effects and electron-donating effects, respectively, in the isoxazole ring. As neutral molecules, isoxazoles undergo electrophilic substitution rather more readily at the 4-position, than benzene. Effects of substituents can modify their behavior. Substituents at the 5-position apparently have more activating and deactivating effects than substituents at the 3-position. In natural product synthesis, isoxazoles are used as latent synthons, such as masked new heterocyclic rings, masked fused rings, masked aromatic rings, and masked aldol and related moieties $\langle 87S857 \rangle$. The capability of isoxazole undergoing reactions are diverse: protonation; quaternization; complexation; oxidation; reduction; carbanionic condensations; thermolysis; photolysis; transformations into other heterocyclic ring systems; and reactions with electrophiles, nucleophiles, and Grignard reagents $\langle 84CHEC-I(6)1, 91HC(49)1 \rangle$.

3.03.5.1.1 Reactions only on the ring

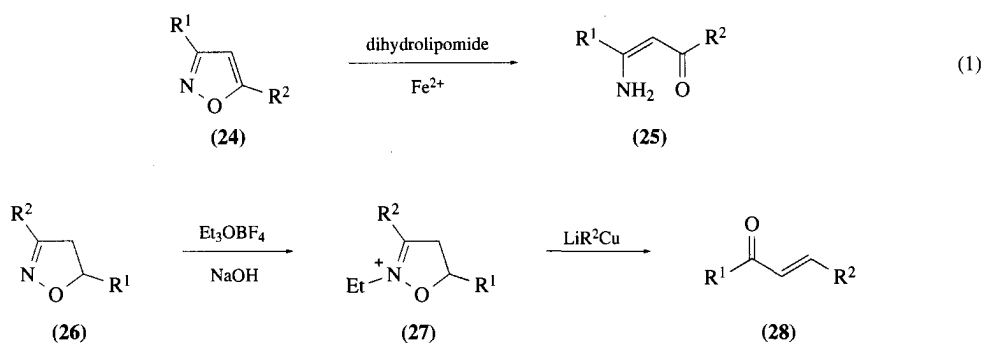
(i) Reactions with ring cleavage

Irrespective of the substituents, the N—O bond of the isoxazole ring is cleaved under well-controlled conditions; usually hydrogenolysis. Several reaction conditions are cited $\langle 87S857 \rangle$.

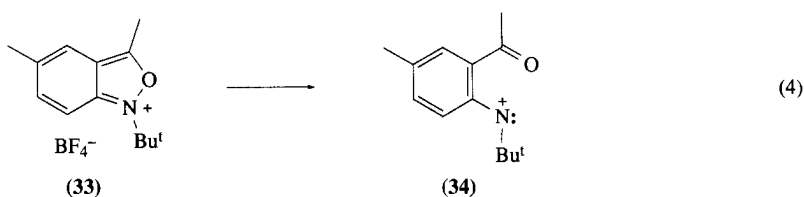
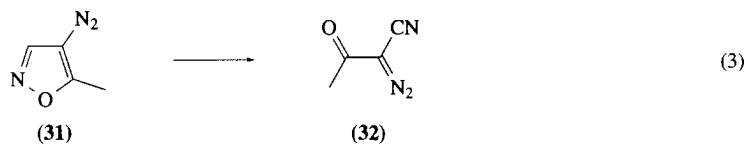
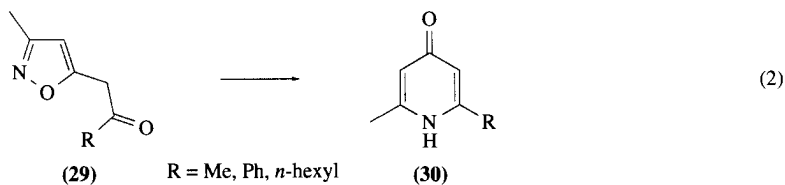
Solvent-dependent hydrogenolysis of 3,5-diphenyl isoxazole (21) in the presence of palladium on charcoal resulted in open-chain products (22) and (23) (Scheme 2) <87T3983>. Another reactive method, used to form β -amino ketones (25) from 3,5-disubstituted isoxazoles (24), is a combinatory use of dihydrolipomide and ferrous ammonium sulfate (Equation (1)) <85JOC1140>. The action of molybdenum hexacarbonyl on the isoxazole ketones (29) cleaved the N—O bond and resulted in pyridones (30) (Equation (2)) <94H(38)853>. Nonreductive ring cleavage is accomplished by quaternization of isoxazole derivatives (26), followed by treatment with lithium dialkylcuprates to give vinylogous amides (28) (Scheme 3). The diazonium salt (31) of 4-amino-5-methyl isoxazole, readily underwent N—O bond cleavage to form a diazoketone (32) (Equation (3)) <87BSB229>. The photolysis of 1-*t*-butyl 3,5-dimethyl-2,1-benzisoxazolium tetrafluoroborate (33) leads to the formation of nitrenium ion (34), via N—O bond cleavage (Equation (4)) <94TL4943>. A number of rearrangement reactions in isoxazoles lead to the formation of other heterocycles. Most of them involve cleavage of the N—O bond. Photochemical rearrangement of 4-(aminomethyl)-3,5-diphenyl isoxazoles yielded diverse heterocycles and open-chain products, such as <91G329>. Thermolytic rearrangement of benzisoxazolo quinone afforded alkylidene butenolides <91TL5825>.



Scheme 2



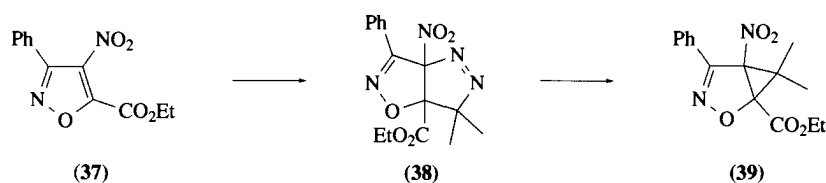
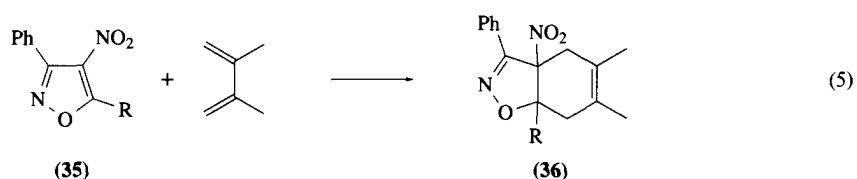
Scheme 3



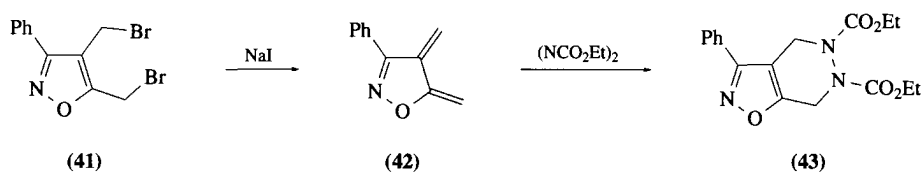
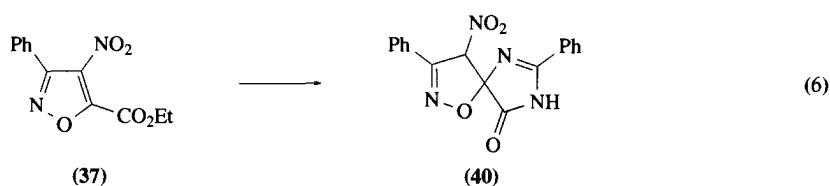
(ii) Reactions without ring cleavage

(a) *Cycloaddition.* Isoxazoles with electron-withdrawing substituent(s) readily undergo cycloaddition reaction.

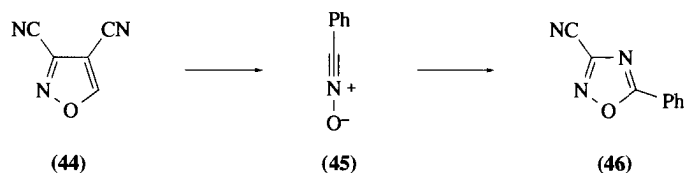
The nitroisoxazole (35) underwent Diels–Alder reaction with 2,3-dimethyl butadiene to form the adduct (36) (Equation (5)) <90JOC1227>. The nitroisoxazole ester (37) with 2-diazopropane yielded the bicyclic cyclopropane (39), via an unstable adduct (38) (Scheme 4) <87CC1077>. The same ester (37) reacted with benzamidine to afford a spiroannulated product (40) (Equation (6)) <87JCS(P1)1005>. A Diels–Alder cycloadduct (43) was produced from 4,5-bis(bromoethyl)-3-phenyl isoxazole (41), on treatment with sodium iodide and subsequently with azodicarboxylate (Scheme 5) <91TL4603>. On heating 3,4-dicyanoisoxazole (44), the nitrile oxide (45) is generated. And (45) was trapped by benzonitrile to form the cycloadduct (46) (Scheme 6) <91IZV1916>.



Scheme 4



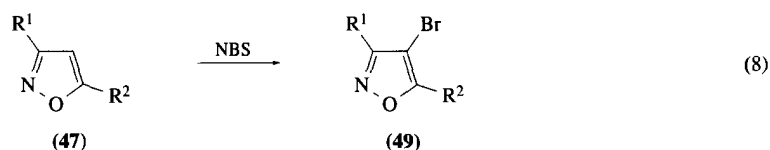
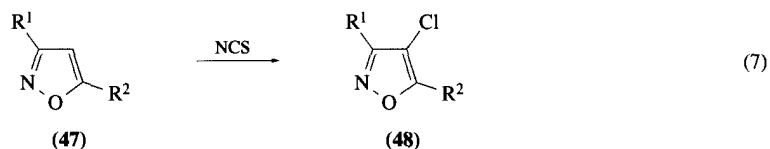
Scheme 5



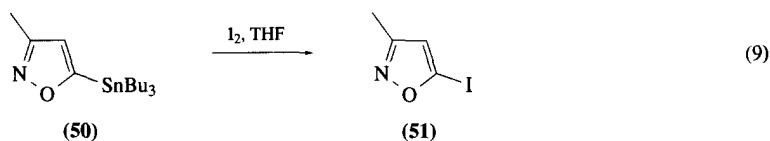
Scheme 6

(b) *Halogenation.* Isoxazoles undergo halogenation more readily than pyridine, but less so than pyrrole and furan. Chlorinating agents for isoxazole, such as sulfur chloride, aqueous chloroform containing 20% HCl, sodium hypochlorite, *N*-chlorimide, and the appropriate reaction conditions are described <93AHC(57)292>. *N*-chlorimide reagents were used to prepare the 4-chloro derivatives (48) of 3- and 5-substituted isoxazoles (47) (Equation (7)). As expected, 4-bromination (49) is

accomplished successfully in many 3- and 5-substituted isoxazole derivatives (47) with NBS <90JHC337> as well as with bromine in carbon tetrachloride or in chloroform (Equation (8)). Other brominating agents, such as bromine in sulfuric acid, acetic acid, nitric acid, or pyridine are cited. Substitution effects and neighboring group participation in bromination of isoxazoles are discussed <93AHC(57)292>.

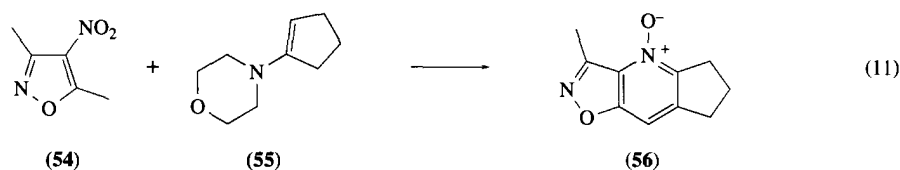
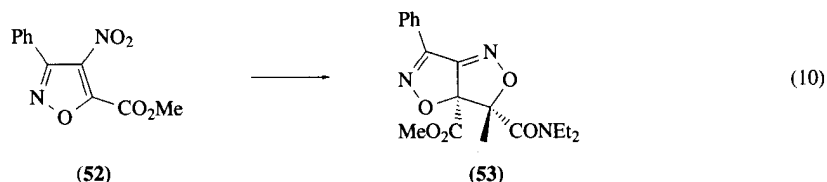


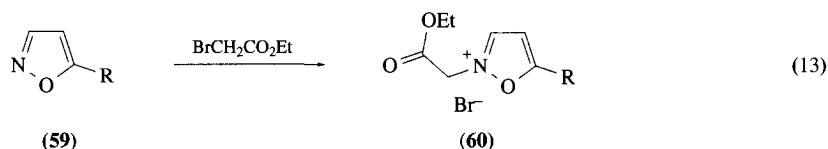
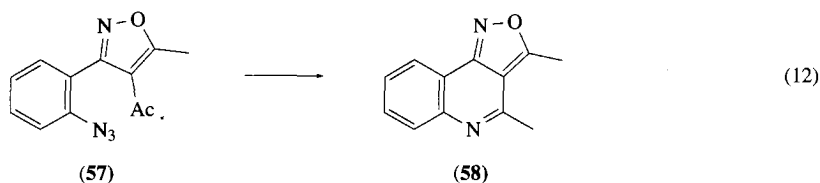
Iodination of isoxazoles are accomplished by using iodine in nitric acid, only if the 4-position is free. Unlike NCS and NBS, NIS is not a successful iodinating agent for isoxazole. The 3-methyl-5-tributylstannyl isoxazole (50) reacted with iodine in THF to give the iodo derivative (51) (Equation (9)) <91T5111>.



(c) *Nitration.* Unsubstituted isoxazole undergoes nitration with greater difficulty, 3- and 5-substituted (alkyl or phenyl) isoxazole undergo nitration considerably easier. Earlier work on nitration, substitution effects on nitration have been discussed <84CHEC-1(6)1, 91HC(49)1>. The use of nitric acid in acetic anhydride resulted in the 4-nitration as the predominant product and phenyl ring nitration as the minor product <89H(29)1965>. However, nitration of 5-methyl-3-phenyl isoxazole-4-carboxylic acid afforded only 3-nitrophenyl as the product <93AHC(58)216>.

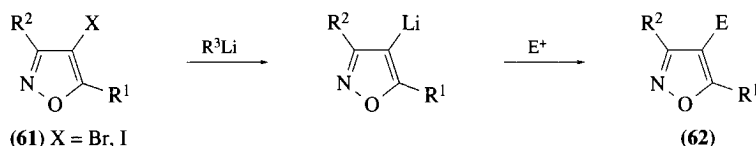
(d) *Other reactions.* If and when the nitro group is present in the 4-position of the isoxazole ring, it participates in the new ring formation; from the isoxazole (52) and 1-(diethylamino)propyne, the novel isoxazolo[4,5c]isoxazole (53) was formed (Equation (10)) <91TL6223> from 3,5-dimethyl-4-nitro isoxazole (54) and morpholinocyclopentene (55), pyridine *N*-oxide (56) was formed (Equation (11)) <91H(32)1913>. Intramolecular aza-Wittig reaction was facilitated by triphenyl phosphine to transform 3-*O*-azidophenyl isoxazole (57) to isoxazolo isoquinolinone (58) (Equation (12)). *N*-Alkylation of 5-substituted isoxazole (59) with ethylbromoacetate resulted in the isoxazolium bromide salt (60) (Equation (13)). Isoxazolium salts are very useful in making the synthon, β -ketoamide <83JOC1149>.



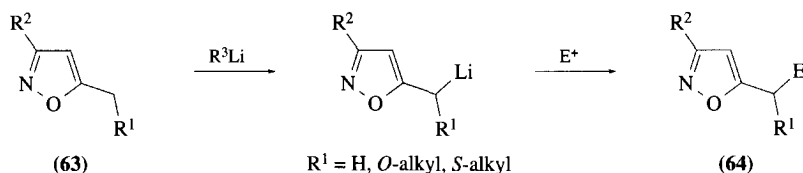


(iii) Lithiation

Lithiation of isoxazoles is discussed separately as a unique section. Because it may involve only ring or only side chain or both ring and side chain, depending upon the substrates, type of base used, and reaction conditions used. Unsubstituted isoxazoles can be deprotonated at the C-3 position, but often lead to the cleavage of the labile N—O bond. Lithiation of simple alkyl isoxazoles is a useful methodology for synthesizing molecules with elaborate and complex structures. 3-Substituted isoxazoles do undergo lithiation at the 5-position, but ring fragmentation rapidly follows even at -60°C . Interestingly the cleavage products are very useful in organic synthesis $\langle 93\text{AHC}(56)213 \rangle$. When both the 3- and 5-positions are substituted (61) lithiation occurs at the 4-position leading to 3,4,5-trisubstituted isoxazoles (62) (Scheme 7). However, the nature of the substituents determine the products. When the 5-substituent is methyl, alkoxyethyl, or the alkoxythiomethyl group (63), side chain metallation (64) becomes predominant (Scheme 8). The presence of substituents at the 3-position which favor *ortho* lithiation, then 4-lithiation occurs with *n*-butyllithium. When LDA is used as a base, lateral or side chain metallation becomes exclusive $\langle 83\text{JOC}4307 \rangle$. Even with *C*-alkyl substituents, a clean 4-lithiation can be accomplished by the use of halogen-metal exchange reactions. Successful 4-substitution was achieved from both bromo and iodo isoxazoles $\langle 84\text{JMC}1245, 91\text{H}(32)1757 \rangle$. In 3,5-dimethoxyisoxazole, metallation and alkylation occurs at the same position. Factors influencing regiocontrol have been discussed $\langle 85\text{H}(23)571, 85\text{H}(23)585 \rangle$.



Scheme 7

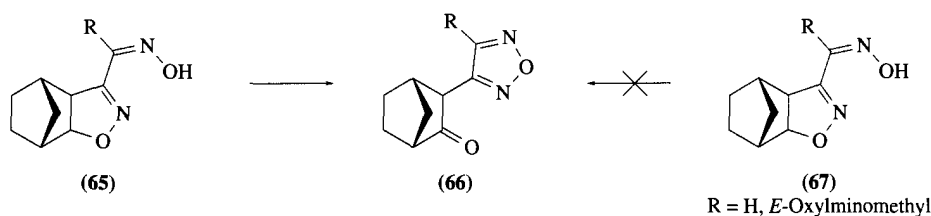


Scheme 8

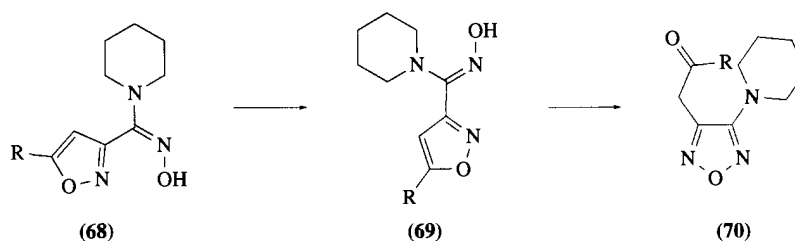
3.03.5.1.2 Reactions on both ring and substituents

In general, reactions under this category involve both the isoxazole ring as well as the substituent ring or chain and thus result in forming new heterocycles. Oximation reaction and consequent

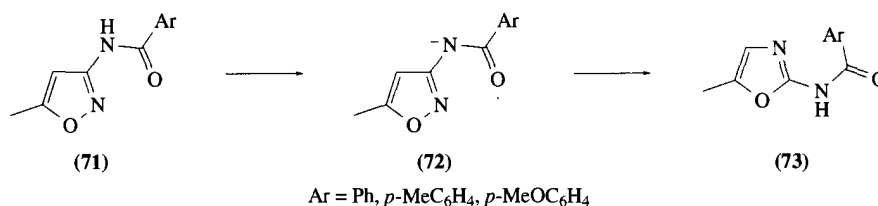
rearrangements in isoxazole derivatives lead to the transformation of isoxazoles into other heterocycles. It is also attributed to the function of their geometry <83JCS(P1)483, 85T5181, 85T727>. The influence of oxime geometry on the base-promoted rearrangement is revealed. Thus, (*Z*) isomers (**65**) are treated with aqueous KOH at room temperature, are afforded the cycloadducts of the dimer or trimer of fulminic acid and norbornene, and rearranged to (**66**). On the contrary, the (*E*)-isomer (**67**) did not form (**66**) under similar conditions of an aqueous base (Scheme 9) <85T5181>. Another example of the importance of oxime geometry is reported: acid-promoted isomerization of (*E*) *N,N*-disubstituted amidoximes (**68**) into their (*Z*) isomers (**69**), which in turn rearranged into (**70**) under basic conditions (Scheme 10). A thermally induced rearranged product (**73**) was formed from 3-arylamino isoxazole (**71**) via the anion (**72**) (Scheme 11) <91H(32)1765>. Isoxazole (**74**) is rearranged to pyrrole (**75**) by the reaction with dbu in ether. This rearranged pyrrole further stabilizes the negative charge in the rearranged enolate (**76**) under ethanolic KOH or sodium methoxide (Scheme 12) <86JCS(P1)927>. In dioxane water, (*Z*)-aryl hydrazones of 3-benzoyl-5-phenyl isoxazole (**77**) is rearranged into phenacyl triazole (**78**) (Equation (14)) <87JCS(P2)537, 88JCS(P2)1683>. Aryl hydrazones of 5-phenacyl isoxazoles (**79**) is rearranged into the 5-oxidopyridazinium betaines (**81**) via the intermediate (**80**) (Scheme 13) <83TL1285>.



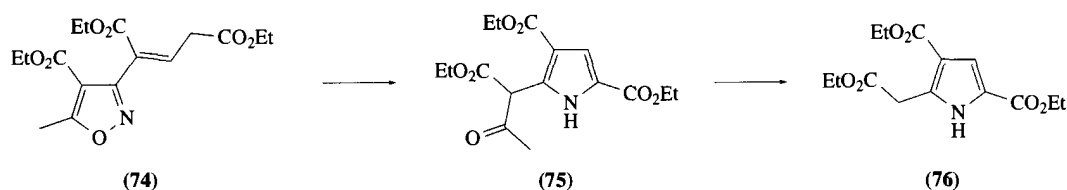
Scheme 9



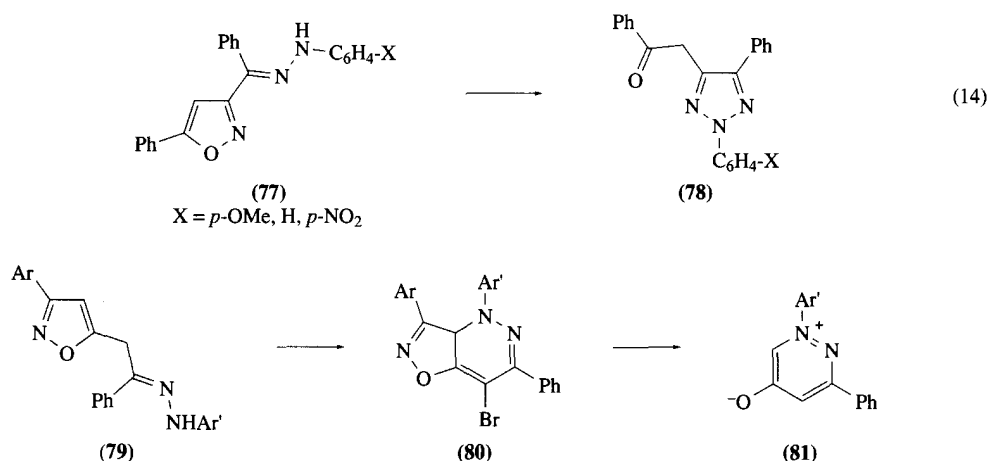
Scheme 10



Scheme 11



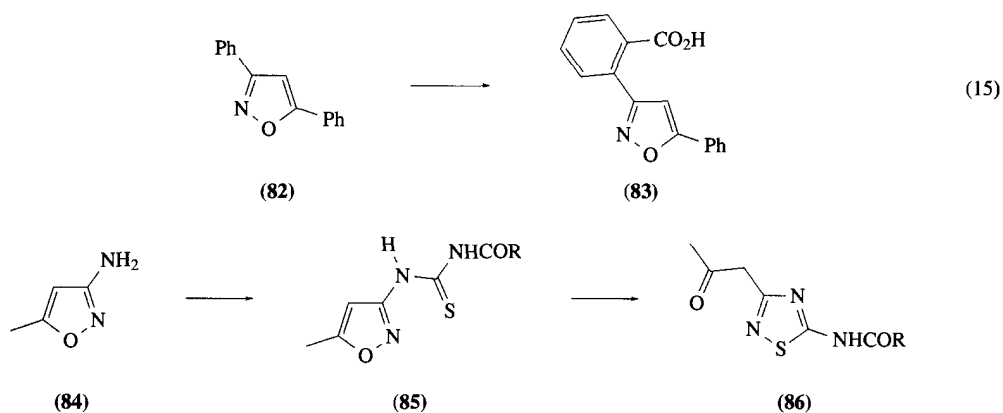
Scheme 12



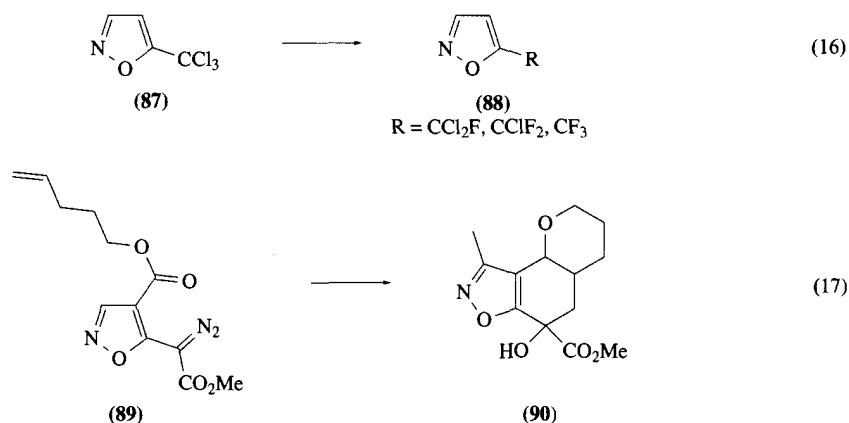
Scheme 13

3.03.5.1.3 Reactions only on substituents

Reactions discussed under this section involve only the substituents (a ring or a chain) on the isoxazole ring. A regioselective carboxylation was catalyzed by palladium on 3,5-diphenylisoxazole (82) to yield the acid (83) (Equation (15)) <89CPB1694>. Aminoisoxazole (84) reacts with ethoxycarbonyl isothiocyanate to afford the thiourea (85), which was subsequently easily rearranged into thiadiazole (86) (Scheme 14). By a chlorine-fluorine exchange reaction, 5-(trichloromethyl)isoxazole (87) has been converted into a series of fluorine compounds (88) (Equation (16)) <93PHC185>. Extrusion of nitrogen from diester (89) was catalyzed by dirhodium tetraacetate to afford the tricyclicisoxazole (90) via a transient fluoro [3,4-d]isoxazole (Equation (17)) <89H(29)1003, 91CB2481>.



Scheme 14

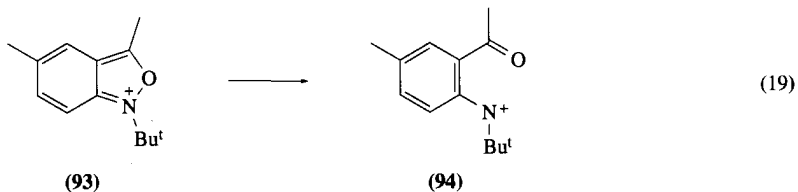
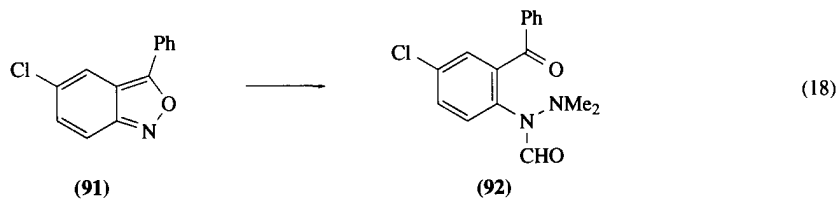


3.03.5.2 Benzisoxazoles

Reported reactions on benzisoxazole systems result either in N—O bond cleavage or rearranged products.

3.03.5.2.1 [2,1]Systems

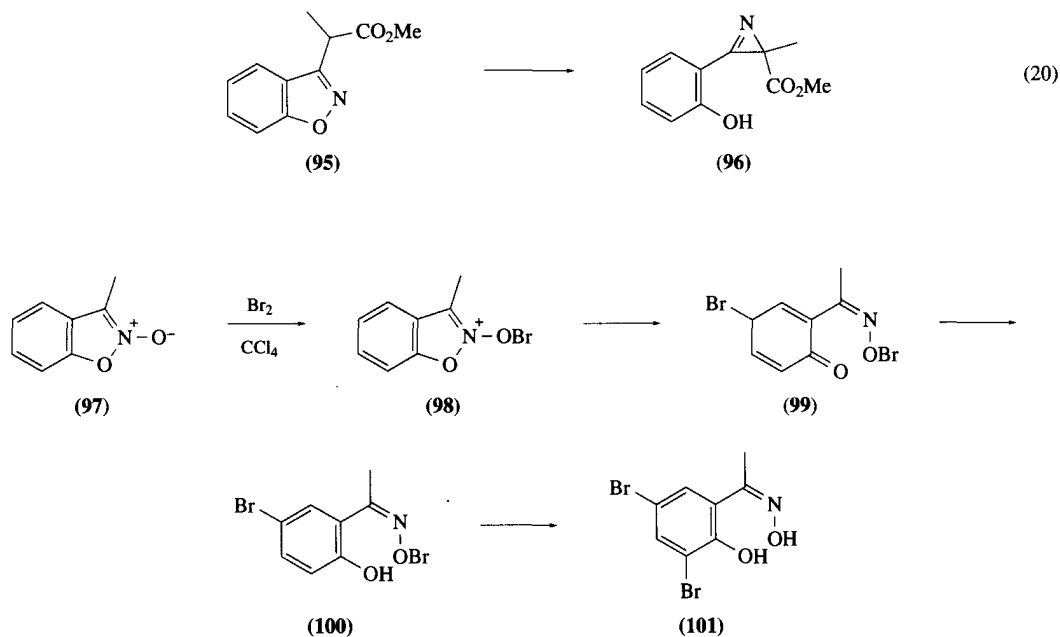
2,1-Benzisoxazoles (**91**) on treatment with Vilsmeier reagent (DMF/ POCl_3) resulted in ring cleavage product (**92**) (Equation (18)) <87TL955>. By photolysis of 1-*t*-butyl-3,5-dimethyl-2,1-benzisoxazolium tetrafluoroborate (**93**), nitrenium ion (**94**) is produced (Equation (19)) <94TL4943>.



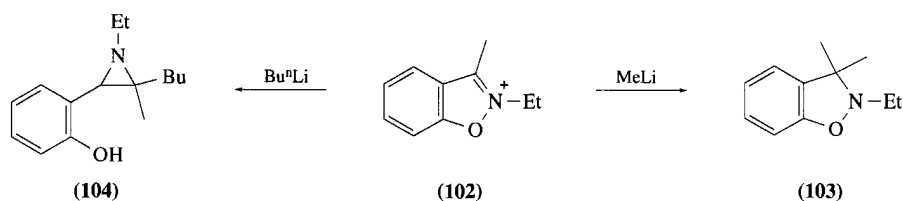
3.03.5.2.2 [1,2]Systems

(i) Reactions on the ring

1,2-Benzisoxazole ester (**95**) underwent ring contraction to the azirine (**96**), with sodium methoxide (Equation (20)) <88JCS(P1)1013>. Bromination of 1,2-benzisoxazole 2-oxides (**97**) underwent N—O cleavage to give dibromo oximes (**101**) (Scheme 15) <87JCS(P1)695>. Lithiation on quaternized benzisoxazole (**102**) resulted in dialkylation of isoxazole ring (**103**) with MeLi and in N—O bond cleavage (**104**) with Bu^nLi (Scheme 16) <88JCS(P1)767>.



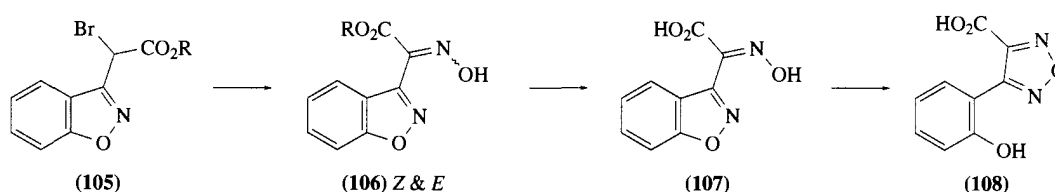
Scheme 15



Scheme 16

(ii) Reactions on the substituent(s)

The α bromoester (105) reacted with sodium nitrite in methanol, yielded the corresponding α hydroxy ester, as the major product along with a mixture of both (*E* and *Z*) oxime esters (106). Treatment with hydrochloric acid on the oxime esters (106) afforded an isomeric mixture of both (*E* and *Z*) hydroxyimino carboxylic acids (107) (Scheme 17) <83JHC385>.



Scheme 17

(iii) Reactions on the ring and the substituent(s)

The isomeric mixture of both (*E* and *Z*) hydroxyiminocarboxylic acids (107) reacted with 2N sodium hydroxide at room temperature to yield the rearranged product (108) <88JHC285>.

3.03.5.3 Isoxazolines

3.03.5.3.1 2-Isoxazolines

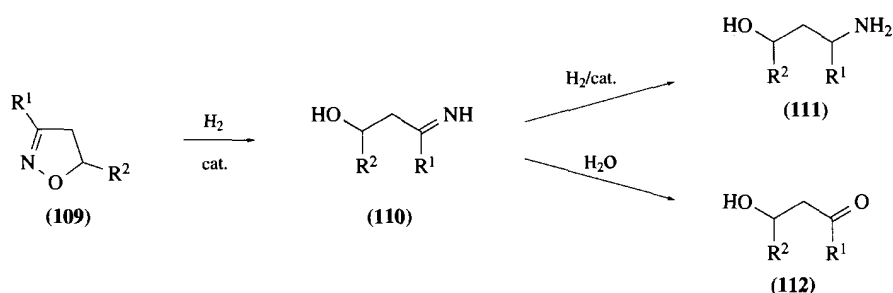
The chemical behavior of 2-isoxazolines is similar to cyclic ethers of oximes.

(i) Reactions only on the ring

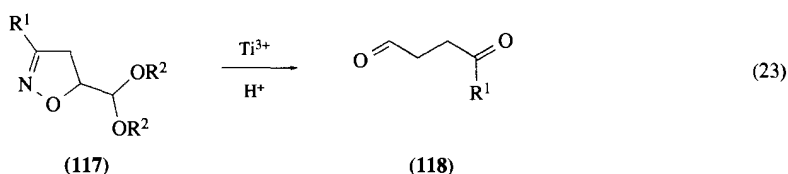
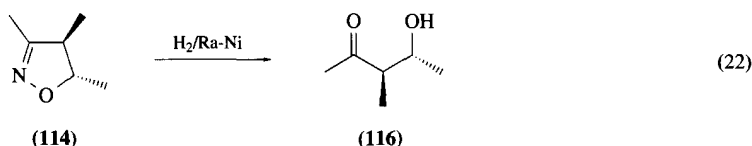
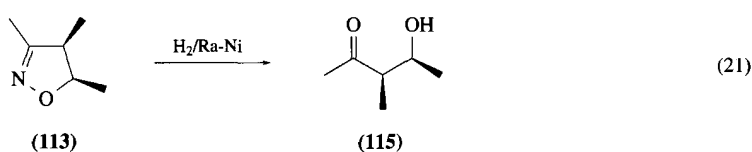
(a) *Reactions with ring cleavage.* The heterocyclic 2-isoxazoline ring is very stable under several conditions such as heating, acids or alkali, or even oxidizing agents, unless it has a ring destabilizing substituent(s) on the ring. However, the N—O bond or C(5)—O bond of the ring can still be cleaved by hydrogenolysis, by nucleophiles, photochemically, or thermolytically.

Cleavage of the N—O bond. Hydrogenolysis of the N—O bond is accomplished by either catalytic hydrogenation or treatment with LAH. Generally catalytic hydrogenolysis of 2-isoxazoline (109) results in β hydroxy imine (110) and in γ amino alcohol (111) or (110) and β hydroxy ketone (112) depending upon the conditions (Scheme 18) <91HC(49)1>. Irrespective of the solvent used (alcohol, glacial acetic acid, aqueous acetic acid, presence or absence of hydrochloric acid), the use of platinum as a catalyst, always resulted in the corresponding aminoalcohol. The use of Raney nickel as catalyst in an aqueous methanolic or acetic acid medium, is proven to be the best to isolate β hydroxyketone (112) <83TL1337, 84JOC2762>. The diastereospecificity is exemplified in the hydrogenolysis of 3,4,5-trisubstituted isoxazolines (*cis*-(113) and *trans*-(114)) by the use of Raney nickel. *Cis*-(113) resulted in *erythro* aldol (115) and *trans*-(114) resulted in *threo* aldol (116) (Equations (21) and (22))

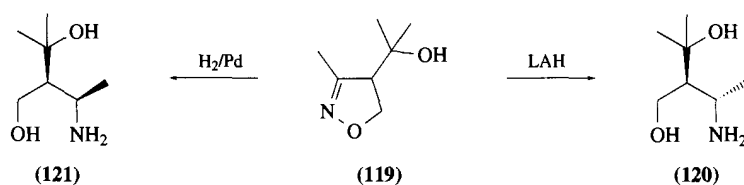
<83JA5826>. By the use of titanous chloride in methanol (pH 3–4), 2-isoxazoline-5-acetal (**117**) afforded γ ketoaldehydes (**118**) (Equation (23)) <83T2231>.



Scheme 18



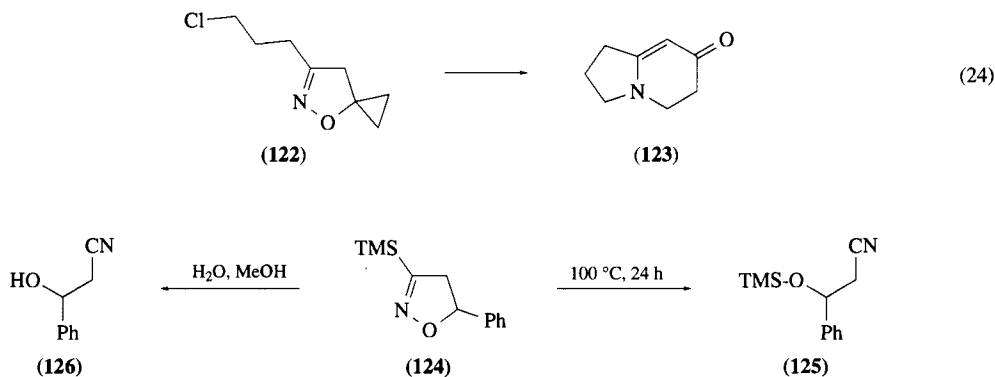
Several stereoselective reducing agents have been used to cleave the N—O bond of isoxazoline. Reductive cleavage method is a well-exploited route to obtain amino alcohol, aziridine, or both, depending upon the reaction conditions <91HC(49)1>. LAH is found to be the most selective agent. Ring opening of 3-methyl-4- α hydroxypropyl-2-isoxazoline (**119**) under reductive cleavage conditions with LAH, afforded γ amino alcohols (**120**) and (**121**) 95 : 5 of *trans* : *cis*, respectively (Scheme 19). Whereas under catalytic hydrogenolysis conditions with hydrogen/palladium reversed the stereoselection to 3 : 97 of *trans* : *cis*, (**120**) : (**121**) <91HC(49)1>.



Scheme 19

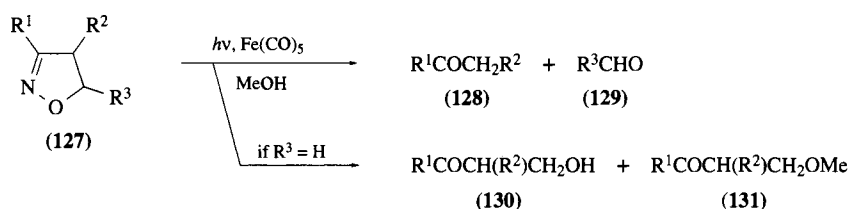
In general, above $300^\circ C$, thermolysis of 3-aryl substituted 2-isoxazolines lead to ring cleavage. Flash vacuum pyrolysis of the spiroxazoline (**122**) resulted in the fused heterocycle (**123**) (Equation (24)) <89JCS(P1)125>. Thermal ring opening of trimethylsilyl 2-isoxazoline (**124**) afforded

trimethylsilyl ethers (**125**) of the corresponding β -hydroxy nitriles (**126**) (Scheme 20). Such ring opening was demonstrated under hydrolytic conditions yielding the corresponding alcohols (**126**) $\langle 82S719, 83H(20)511 \rangle$. Thermolysis of 3,5-diphenyl-2-isoxazoline with diiron enecarbonyl resulted in acetophenone and benzaldehyde $\langle 83CL51 \rangle$.



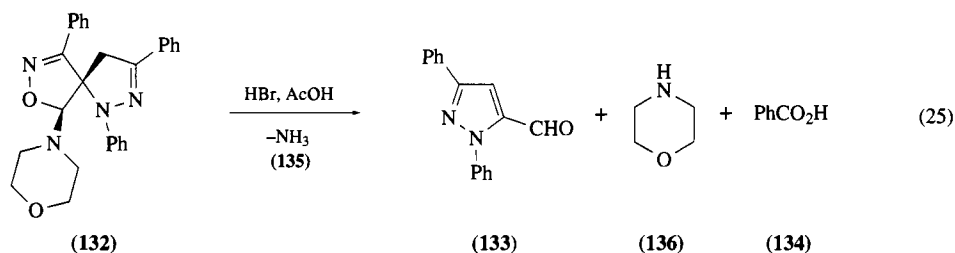
Scheme 20

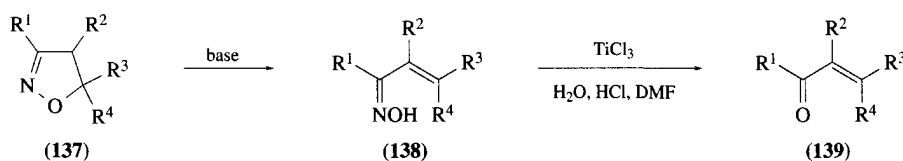
An extensive and a systematic photochemical studies had been done on 2-isoxazoline. Photolysis of 2-isoxazolines always result in a mixture of products, depending upon the nature of the substituents. Three possible different pathways of photolytic cleavage are reviewed $\langle 91HC(49)1 \rangle$. Ultraviolet irradiation of 5-unsubstituted 2-isoxazoline (**127**) in the presence of iron pentacarbonyl, resulted in ring fragmentation products (a ketone (**128**) and aldehyde (**129**)) as well as N—O bond fission products ((**130**) and (**131**)) (Scheme 21). The plausible mechanism involves N-donor complexation with photochemically generated pentacarbonyl, prior to N—O and C(3)—C(4) bond fissions $\langle 83CL51 \rangle$.



Scheme 21

Cleavage of the C—O bond. In 2-isoxazoline the cleavage of the C(5)—O bond is accomplished under strong acidic or basic conditions, even though it is less common than cleavage of the N—O bond. Under strong acidic treatment, spiro(isoxazoline-4,5-pyrazoline) (**132**) is fragmented completely leading to a mixture of products (**133**)–(**136**) (Equation (25)) $\langle 83JCR(M)1317, 83JCR(S)140 \rangle$. The reaction of 2-isoxazolines (**137**) under strong basic conditions underwent C(5)—O cleavage, to afford α,β -ethylenic oximes (**138**) and subsequently α,β -enones (**139**) (Scheme 22) $\langle 84CB2875 \rangle$.

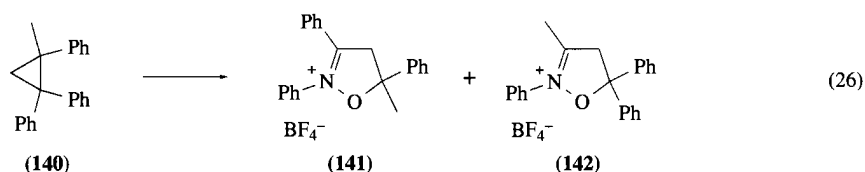




Scheme 22

(b) Reactions without ring cleavage

Quaternization. 2-Isloxazolines are also weak bases, but slightly higher than that of corresponding isoxazoles. Quaternization of 2-isloxazoline was easily accomplished by treatment with excess trimethyl (or triethyl)-oxonium tetrafluoroborate in dichloromethane at room temperature <83LA906>. Several other conditions to accomplish quaternization of 2-isloxazolines are discussed <91HC(49)1>. In some cases, quaternization is achieved not directly from 2-isloxazolines. For example the cyclopropane (140) with nitrosonium tetrafluoroborate afforded a mixture of isloxazolium salts (141) and (142) (Equation (26)) <89CL457>.



Substitution at the ring atom. In 2-isloxazolines (143), nucleophilic substitution occurs at the 3-position (144) if there is an electron-withdrawing group (nitro or sulfonyl) at the 3-position (Equation (27)). Successful nucleophilic substitutions are entered in Table 9 <84JOC4595, 84T601>. Substitution by chlorine or bromine atom at the 3-position of isloxazoline is a reversible process with HCl or HBr <84TL487>. Repeated electrophilic substitution at the 4-position is accomplished by treating 2-isloxazoline with LDA/THF in HMPA/−78°C and subsequently with alkyl iodide. The resulted products are 3-phenyl-4,4-dialkyl-2-isloxazolines <84T673>. None was found on substitutions at the 4- or 5-positions in the last decade, but prior literature is reviewed <84CHEC-I(6)1, 91HC(49)1>.

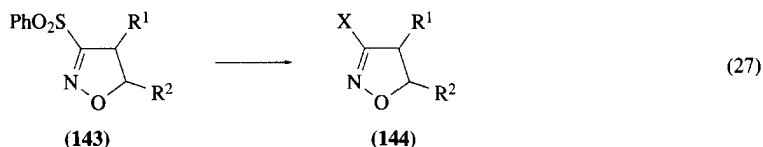
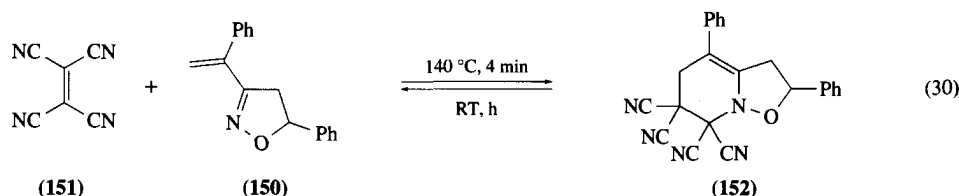
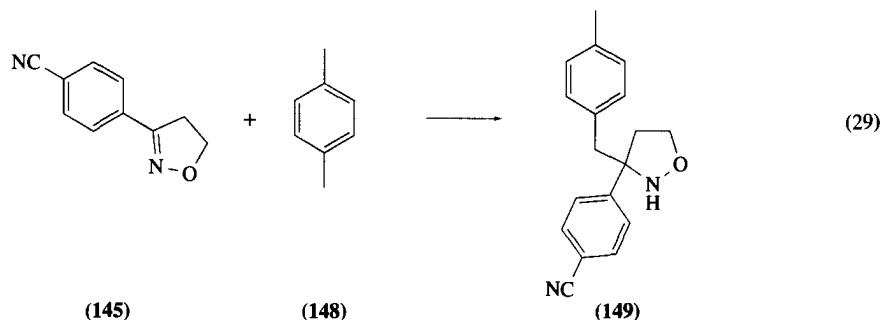
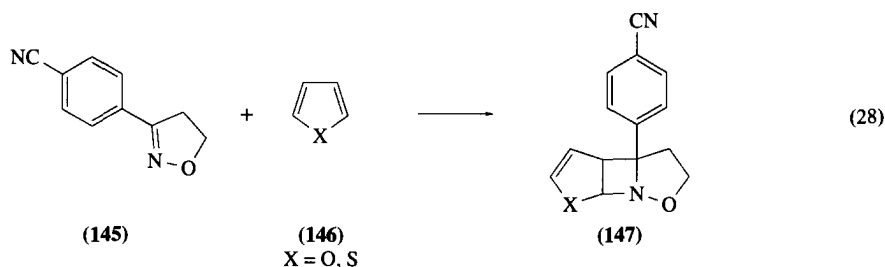


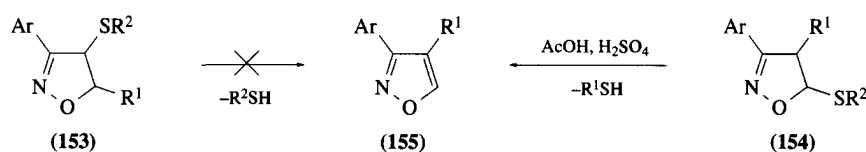
Table 9 Nucleophilic substitution in 2-isloxazoline.

R ¹	R ²	Nucleophile	X	Ref.
H	Ph	CH ₂ =CHMgBr	CH ₂ =CH	84JOC4595
H	CHNHCOCCH ₂ Ph	MeLi	CH ₃	84T601
H	CMe ₂ OH	MeLi	CH ₃	84T601
H	CH(NPh)COOH	NaCN	CN	83JOC1796
Ph	Ph (<i>cis</i>)	PhLi	Ph	83JOC1796
Ph	Ph (<i>trans</i>)	PhLi	Ph	83JOC1796

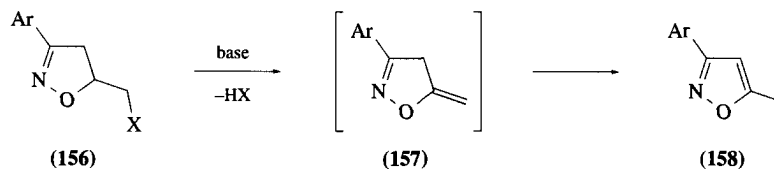
Addition reactions of the C=N double bond. Addition through the C=N double bond of isloxazoline is the common route to synthesize isloxazolidines and is discussed in Section 3.03.6.3. 2-Isloxazoline (145) underwent [2 + 2] cycloaddition with furan or thiophene (146) to yield the photocycloadduct (147) (Equation (28)) <83CL1357>. At this juncture it is worth mentioning that the same isloxazoline (145) with *p*-xylene (148) by hydrogen abstraction yielded the isloxazolidine (149) (Equation (29)) <83TL2299>. Conjugated isloxazoline C=N double bond as in (150) creates 1-aza-1,3-diene system. It (150) is forced to undergo a Diels–Alder reaction with tetracyano ethylene (151) to give the cycloadduct (152) (Equation (30)) <84JOC4595>.



Aromatization to isoxazoles. The higher stability in isoxazoles favors the conversion of 2-isoxazoline to isoxazole. It is achieved either by dehydrogenation or by elimination. Only elimination reactions have been reported since the mid-1980s. 4-Alkyl (or aryl)thio-2-isoxazolines (**153**) are stable in a boiling mixture of acetic-sulfuric acids unlike their 5-regioisomer (**154**). Under similar conditions, 5-regioisomer (**154**) yielded 3,4-substituted isoxazole (**155**) with a loss of thiol (Scheme 23) <83T683, 84T441>. 3-Aryl-5-halomethyl-2-isoxazolines (**156**) underwent dehydrogenation to give 3-aryl-5-methyl isoxazole (**158**) via unstable 3-aryl-5-methylene-2-isoxazoline (**157**) (Scheme 24) <91HC(49)1>.

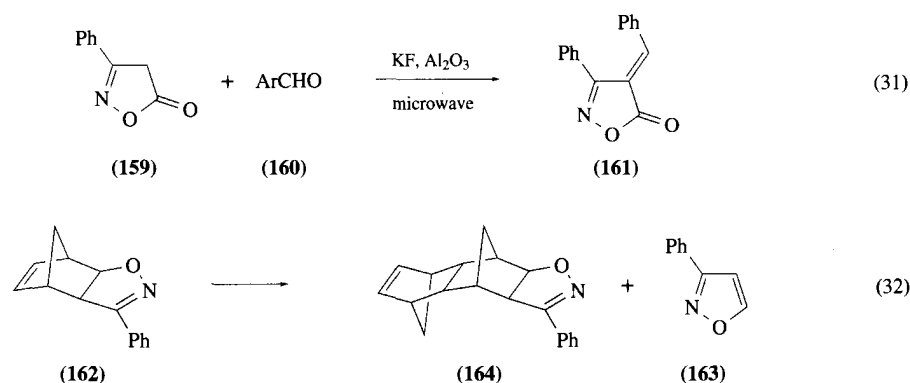


Scheme 23



Scheme 24

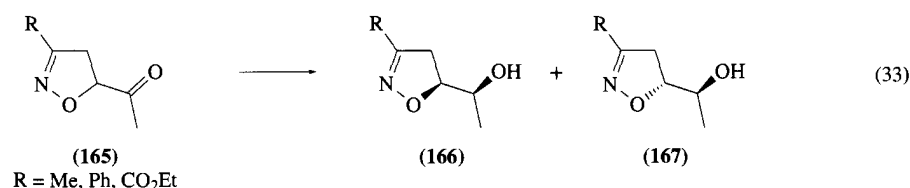
Other reactions. Microwave irradiation of 3-phenyl-2-isoxazolin-5-one (**159**) in the presence of KF on alumina, without any solvent, reacted with aromatic aldehydes (**160**) to afford 4-(arylmethylene) derivatives (**161**) (Equation (31)) <93SC16>. The fused bicyclic-isoxazoline (**162**) underwent a thermal retro-Diels-Alder reaction and resulted in a mixture of 3-phenyl isoxazole (**163**) and norborneneadduct (**164**) (Equation (32)) <90MRC1023>.



(ii) Reactions on the substituents

The stability of the 2-isoxazoline ring towards a variety of reagents under normal conditions facilitates the manipulation of the substituents.

Hydrogenation. With the use of Pd/C, a selective catalytic hydrogenation of the C=C double bond in the substituent chain, was achieved without affecting the N—O bond in the ring $\langle 84T441 \rangle$. The isoxazoline nucleus in ethyl 5-phenyl-2-isoxazoline-3-carboxylate, activates the carboxylic ester group in the 3-position. This facilitates a smooth reduction of the ester group into its carbinol, 3-hydroxymethyl-5-phenyl-2-isoxazoline with sodium borohydride at room temperature $\langle 84JOC4595 \rangle$. The reduction of 5-acyl-2-isoxazolines with L-selectride yields $>95\%$ of the *syn*-alcohol. Whereas Grignard reagents added to 5-formyl-2-isoxazolines yield *anti*-5-hydroxyalkyl compounds with 80–95% selectivity $\langle 91JCS(P1)2613 \rangle$. Racemic 5-acetyl isoxazolines (**165**) are reduced by baker's yeast to give (**166**) and (**167**) (with enantiomeric excess) (Equation (33)) $\langle 88TL6167 \rangle$.



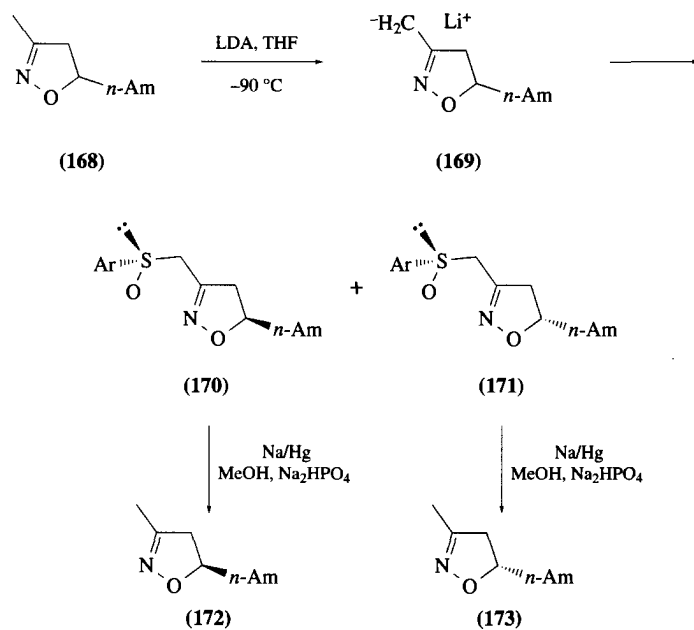
Lithiation. MeLi is successfully added to carbonyl or ester groups $\langle 84JOC4595 \rangle$. Lithiated isoxazoline (**169**) from (**168**) with (*S*)-methyltoluene-*p*-sulfinate afforded a mixture of the two diastereomeric isoxazolines (**170**) and (**171**). They can be easily separated by chromatography. Desulfurization of individual isomers was achieved by sodium amalgam, providing the pure enantiomers (**172**) and (**173**) (Scheme 25) $\langle 84CC551 \rangle$.

Nucleophilic addition. Due to the conjugation of the endocyclic C=N double bond in 4-methylene-4,5-dihydroisoxazoles (**174**) Michael-type nucleophilic addition can occur to give (**175**) $\langle 95SL1208 \rangle$. However, addition and/or addition–elimination products (**175**) and (**176**) can be obtained (Scheme 26). The results depend upon the substituent at the 5-position as well as due to the experimental conditions. The addition–elimination path way can occur only if 5-amino substituted isoxazolines are reacted with nucleophiles in a protonating medium $\langle 95SL1208 \rangle$.

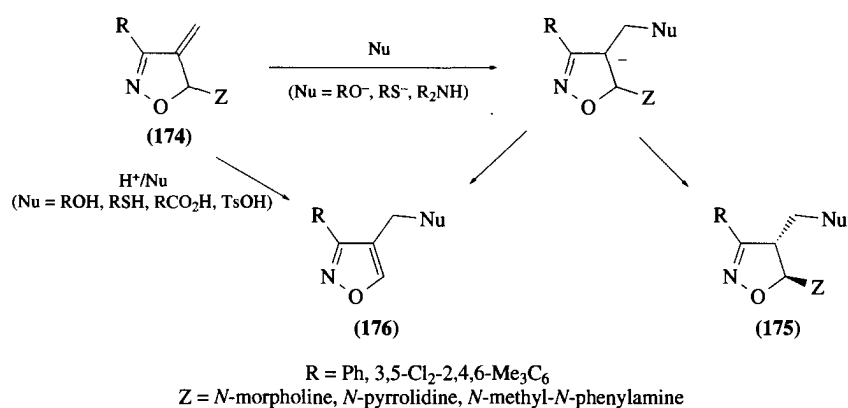
Cycloaddition. 4-Methylene-4,5-dihydroisoxazoles (**174**) are good dipolarophiles towards a variety of 1,3-dipoles (e.g., aryl nitrile oxide (**177**)) to form a spiral compound (**178**), which is not easily accessible by other routes. The resulted 1,3-dipolar cycloaddition product (**178**) is regio- and stereoselective $\langle 95SL1208 \rangle$. The exocyclic double bond of (**174**) is sluggish towards the diene systems, but with the activated diene, 2,5-dimethyl-3,4-diphenyl-2,4-cyclopentadienone (**179**) yielded the Diels–Alder product (**180**) (Scheme 27) $\langle 95SL1208 \rangle$.

3.03.5.3.2 2-Isoxazoline N-oxides

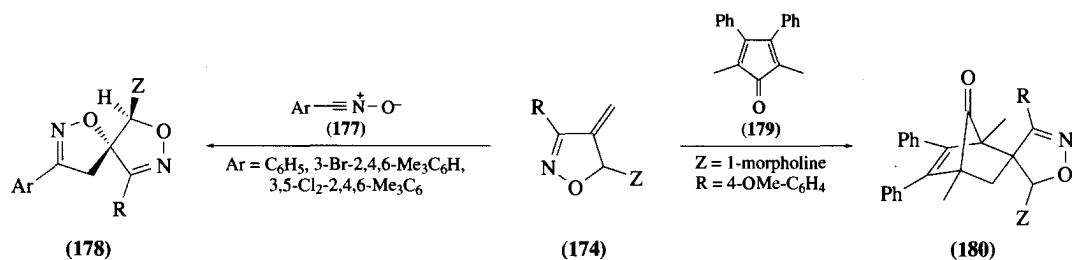
2-Isoxazoline *N*-oxides reflect in their characteristics both as a heterocyclic isoxazoline ring as well as cyclic nitronic ester. As a nitronic ester they can undergo 1,3-dipolar cycloaddition with even



Scheme 25

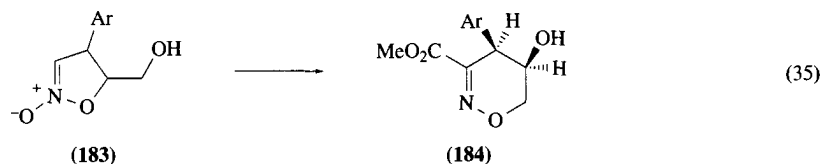
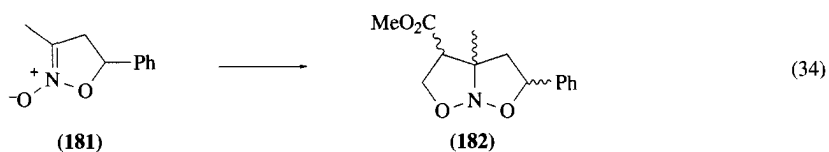


Scheme 26



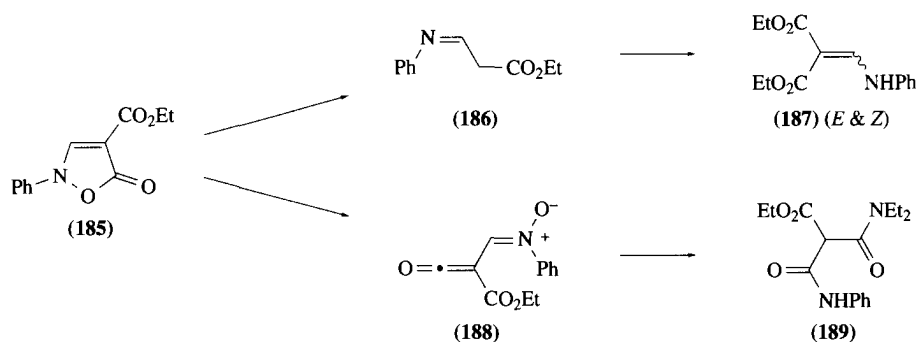
Scheme 27

less active alkene. The reaction of 2-isoxazoline *N*-oxide (181) with methyl acrylate yielded the isoxazolidines (182) as a mixture of all four possible geometrical isomers (Equation (34)) <89H(29)2245>. The action of titanium(IV) chloride on the methane sulfonate of the 2-isoxazoline *N*-oxide ($\text{Ar} = p\text{-bromophenyl}$) (183) resulted in the dihydro-1,2-oxazine (184) (Equation (35)) <92CPB1921>.

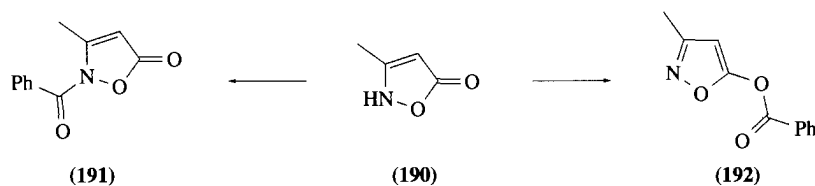


3.03.5.3.3 3-Isoxazolines

As mentioned earlier, not much work has been done on 3-isoxazolines. Quaternization of the nitrogen atom in 3-isoxazoline is accomplished with methyl iodide $\langle 83\text{LA}906 \rangle$. Photolysis of isoxazolinone (185) in the presence of diethylamine, resulted in (*E*) and (*Z*) isomers of (187) via (186) along with diamide (189) via (188) (Scheme 28). The proposed mechanism is discussed $\langle 93\text{AJC}477 \rangle$. The reaction between 3-methyl-3-isoxazolin-5-one (190) and benzoyl chloride afforded a mixture of *N*-(191) and *O*-benzoyl derivatives (192) (Scheme 29) $\langle 86\text{CPB}3153 \rangle$.



Scheme 28

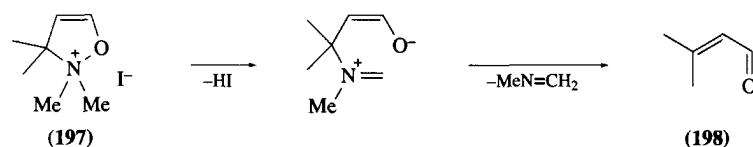
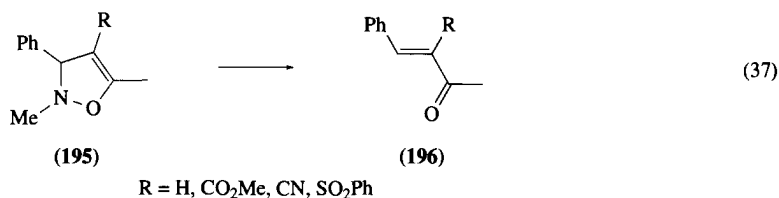
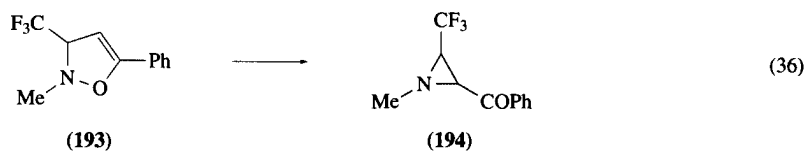


Scheme 29

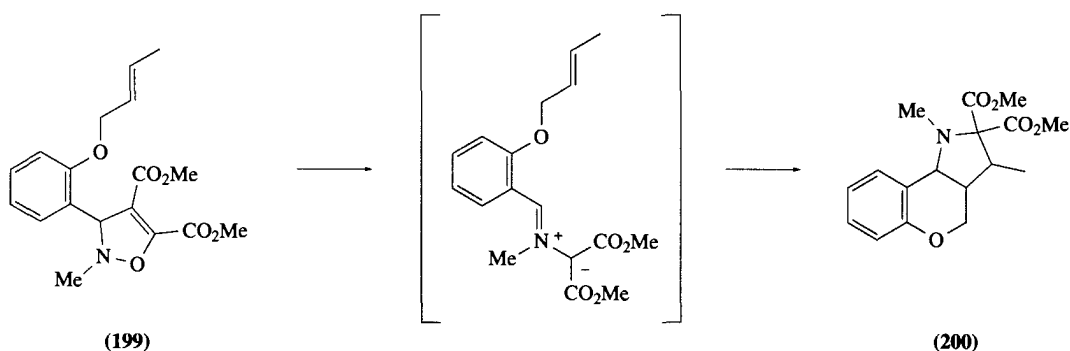
3.03.5.3.4 4-Isoxazolines

On heating, the 4-isoxazoline (193) afforded the rearranged product aziridine (194) (Equation (36)) $\langle 88\text{JFC}(39)39 \rangle$. A heavily substituted 4-isoxazoline on thermolysis, afforded a stable conjugated compound $\langle 84\text{JCR}(\text{M})1531, 84\text{JCR}(\text{S})150 \rangle$. The 4-isoxazoline (195), on treatment with *m*-chloro-perbenzoic acid yielded unsaturated carbonyl compounds (196) (Equation (37)) $\langle 87\text{TL}913, 88\text{JOC}2238 \rangle$. The quaternary salt (197) was obtained from 2,3,3-trimethyl-4-isoxazoline and methyl iodide. It underwent the N—O bond cleavage and gave the unsaturated aldehyde (198) (Scheme 30) $\langle 92\text{T}123 \rangle$.

4-Isoxazolines (**199**) with a double bond in a suitable position of the side chain can be trapped intramolecularly. Two isomers resulted (**200**) (Scheme 31) <84CL797>.



Scheme 30



Scheme 31

3.03.5.4 Isoxazolidines

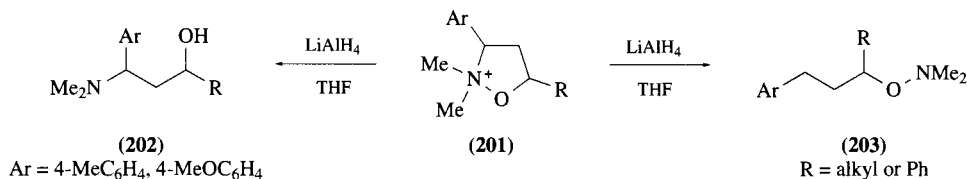
Isoxazolidines reflect their properties as cyclic hydroxyl amines. Consistent with their cyclic hydroxylamine structure, isoxazolidines behave as nucleophiles and thus can be alkylated or acylated. Isoxazolidines are also strong bases (pK_a 5.05). They undergo several reactions such as quaternization, hydrogenolysis, oxidation, thermolysis, photolysis, decomposition by bases, etc. <84CHEC-1(6)1, 91HC(49)1>. With the exception of a few, all other reactions result in ring fission products.

3.03.5.4.1 Reactions without N—O or C—O cleavage

The ring nitrogen of *N*-unsubstituted, *N*-alkyl or *N*-aryl substituted isoxazolidines are stable under mild conditions. As strong bases, they form quaternary salts.

3.03.5.4.2 Reactions with ring cleavage

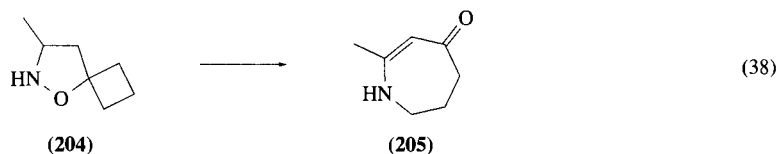
A large variety of reducing agents promote N—O cleavage on monocyclic, bicyclic, or polycyclic free base as well as quaternary salts. The use of Rh/C on isoxazolidines yielded 3-aminoalcohols <84TL3533>. In some alkoxy substituted isoxazolidines, the hydrogenation was proven to be difficult. But with the use of Pd/C catalyst under pressure in methanolic HCl proven to be successful <83JA1686>. Some 3,5,5-triaryl derivatives (**201**) with LAH affords the aminoalcohol derivatives (**202**) <83JHC1207, 83T683> and other 3,5-diaryl or 3,5,5-triaryl derivatives yield *N,N,O*-trisubstituted hydroxyl amines (**203**) (Scheme 32) <83JHC1207, 84T1901>. LAH-induced ring contraction occurs in isoxazolidinone to afford the aziridines <91IJC(B)1135>.



Scheme 32

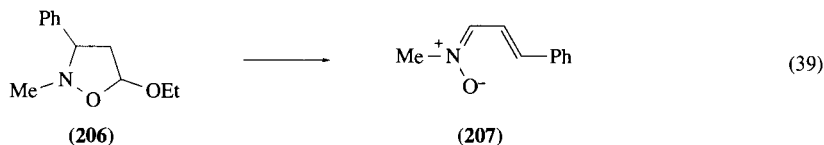
N-Substituted isoxazolidines are easily oxidized to 2-isoxazolines. Several oxidizing agents are discussed <91HC(49)1>. None were found to be reported since the mid-1980s.

Isoxazolidine ring is very unstable upon heating and forms a variety of thermolytic products, depending upon the cleavage pattern. Flash vacuum pyrolysis of spiroisoxazolidine (**204**) lead to the rearranged, ring expanded product, azapin-4-one (**205**) (Equation (38)) <92T5283>.



The photochemical behavior of the isoxazolidine ring is not extensively studied. Depending upon the experimental conditions, 5-nitroxazolidines undergo photolysis to yield either 4-isoxazolines by the elimination of nitrones or to β lactam derivatives, by ring opening followed by reclosure <84JOC282>.

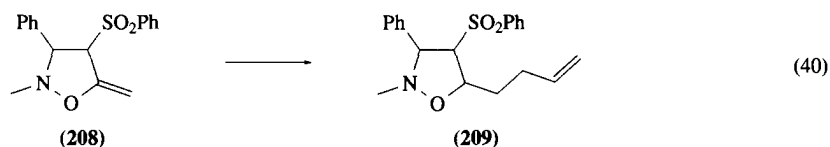
Only strong acidic conditions make the isoxazolidine ring unstable, either leading to ring opening (via N—O cleavage) products or to the formation of isoxazoline ring (via elimination). Isoxazoline (**206**) was decomposed into nitron (**207**) in hot sulfuric acid (Equation (39)) <92T9473>. In several cases, in mild acidic conditions, *N*-substituted isoxazolidines are transformed into *N*-unsubstituted isoxazolidines. For example, *N*-methyl thiomethyl isoxazolidines are demethylated to *N*-unsubstituted thiomethyl isoxazolidines <84ACS(B)423>.



Both *N*-substituted (alkyl/aryl) and *N*-unsubstituted isoxazolidines are fairly stable to base under mild conditions. Strong base-promoted ring fission or decomposition results are reported <84JOC282, 84TL5355>.

3.03.5.4.3 Reactions on the side chain

The exocyclic carbon atom in the methylene isoxazolidine (**208**) reacted with allyl bromide to give the isoxazolidine (**209**) (Equation (40)) <88JCS(P1)2639>.



3.03.6 SYNTHESIS

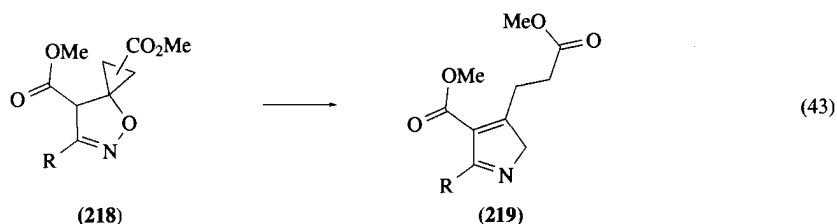
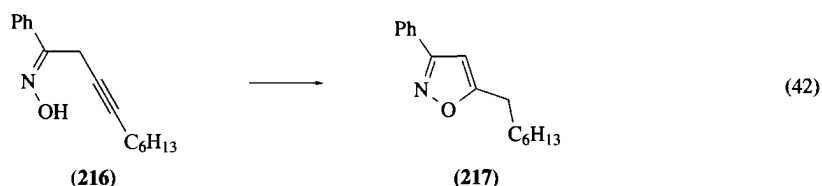
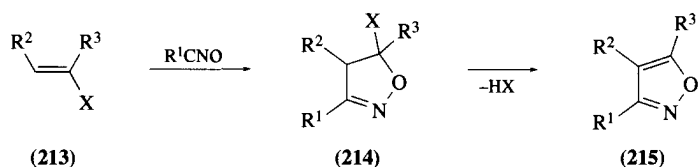
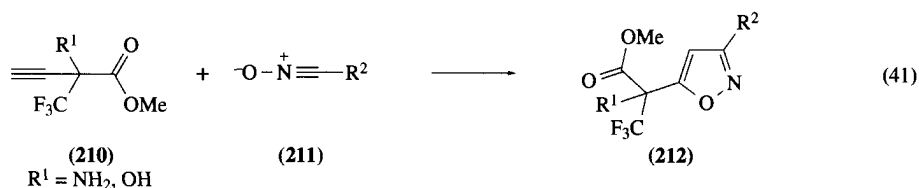
Synthesis of isoxazoles, isoxazolines, and isoxazolidines are discussed in the literature on the basis of reacting component number, type of components, and type of bond formation.

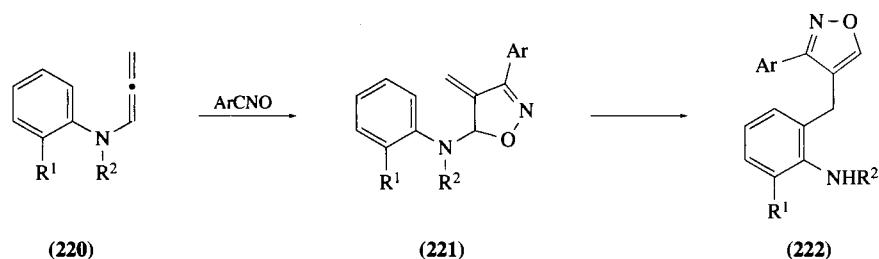
3.03.6.1 Isoxazoles

Synthesis of fully unsaturated systems with and without substituents is accomplished mainly through three general methods:

- (i) cycloaddition of alkynic derivatives (**210**) with nitrile oxide (**211**) yielding 3,5-substituted isoxazoles (**212**) (Equation (41)) <87BCJ1948, 90H(31)633, 93H(35)591>;
- (ii) transformation of isoxazolines (**214**) to isoxazoles (**215**) (Scheme 33) <92H(34)1703>;
- (iii) inter- or intramolecular condensation of oxime (**216**) with alkyne (**216**) or carbonyl double bond giving (**217**) (Equation (42)) <93CC17, 93TL75, 94S989>.

A less commonly used method is via unusual rearrangements. Unusual rearrangement of spiro-oxazoline (**218**) to isoxazole (**219**) (Equation (43)) <92T3323> and Claisen rearrangement of (**220**) to isoxazole (**222**) via the isoxazoline (**221**) (Scheme 34) <91JCS(P1)1843> and other rearrangement reactions <89H(29)1443, 94MI 303-03> are reported. A novel one-pot synthesis of 3,5-disubstituted isoxazoles from terminal alkynes and nitric acid has been reported <93JA4401>.





Scheme 34

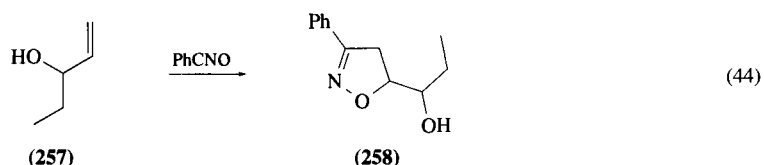
3.03.6.2 Isoxazolines

2-Isoxazolines are the most prepared and widely studied among the three isomers. 3-Isoxazolines and 4-isoxazolines are relatively recently discovered and are difficult to prepare.

3.03.6.2.1 2-Isoxazolines

An elaborate and a systematic review on the synthesis of 2-isoxazoline via 1,3-cycloaddition of nitrile oxides with alkenes is provided. Their mechanism, reactivity, regio- and stereoselectivity are discussed <94AHC(60)261>. The most commonly used nitrile oxide is benzonitrile oxide and less commonly used ones are alkynitrile oxide, phenylthionitrile oxide, and benzoylnitrile oxide. Table 10 reveals the reaction of intermolecular 1,3-cycloaddition of benzonitrile oxide (**223**) with an array of alkenes (**224**)–(**238**) yielding the corresponding 2-isoxazolines (**239**)–(**256**). By the virtue of this reaction, the resulted 2-isoxazolines with substituents (with and without functional groups) on 3,5-positions are common. 1,3-Dipolar reaction of nitrile oxide with C-60 and C-70 fullerenes are reported <94CB581, 94JA7044>. Intramolecular cycloaddition of nitrile oxide yielded spiral or fused bicyclic, or tricyclic, or tetracyclic 2-isoxazolines <87S471, 87T2369, 87TL4097, 89JCS(P1)289, 89JCS(P1)979, 89PHC186, 90H(30)817, 90JOC5505, 90TL743, 91CB1181, 91JOC896, 91TL4259>.

2-Isoxazolines are also obtained from oximes <90JHC275>. 3-Phenyl-2-isoxazoline is yielded from the reaction, the hydroximoyl chloride ($\text{PhCCl}=\text{NOH}$) with tri-butyl (vinyl)tin <91CC884>. The reaction of α -chlorobenzaldoxime with the alcohol in the presence of ethyl magnesium bromide is the first example of stereocontrolled 1,3-dipolar cycloaddition to allyl alcohol bearing a chiral center at C-1 (**257**). It resulted mainly in the *syn* adduct (**258**) (Equation (44)) <91TL6367>. Benzylideneacetone oxime $\text{PhCH}=\text{CHCMe}=\text{NOH}$ afforded isoxazoline on reaction with phenylselenenyl chloride <93PHC185>. A ring contraction of 2,6-di-*t*-butyl thiopyrylium ion with hydroxylamine to yield isoxazoline is reported <94AHC(60)155>.



The isoxazoline is also obtained from other reactions with pyridinium nitrate and pyrrolidine <89JHC1569>. Silyl nitronate (**259**) ($\text{R} = \text{H, Me, Et, Ph}$) with *N*-acrylyl-(2*R*)-bornane-10,2-sultam (**260**) yielded a mixture of adducts. Further treatment with *p*-toluene sulfonic acid afforded the diastereomeric isoxazoline (**261**) (Equation (45)) <91PHC166>.

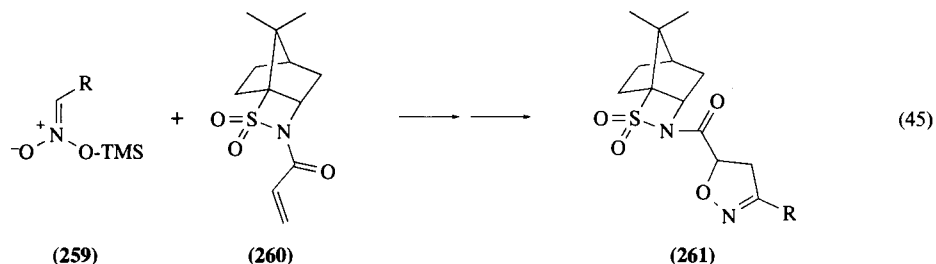


Table 10 2-Isoxazoline synthesis from benzonitrile oxide (**223**).

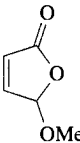
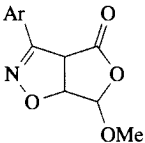
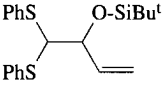
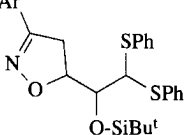
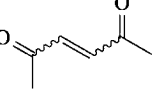
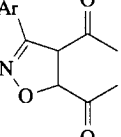
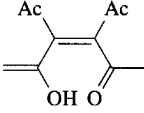
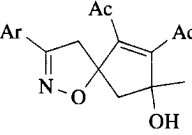
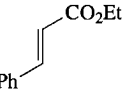
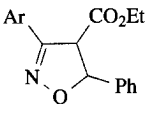
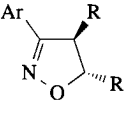
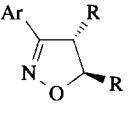
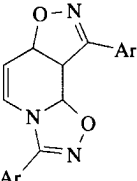
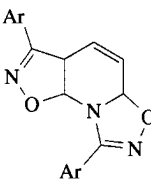
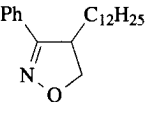
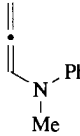
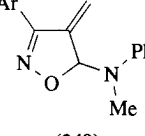
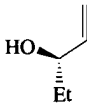
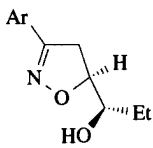
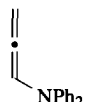
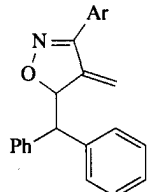
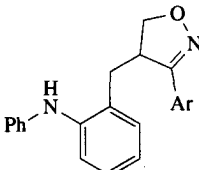
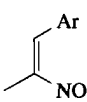
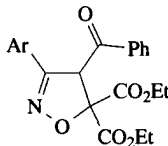
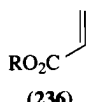
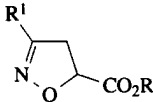
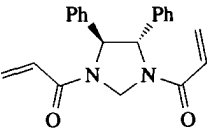
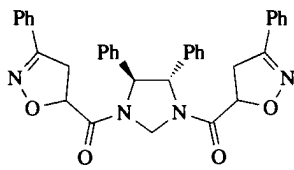
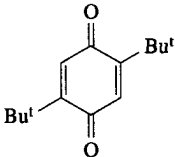
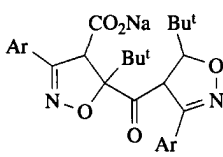
		89PHC186
(224)	(239)	
		90PHC146
(225)	(240)	
		90PHC146
(226)	(241)	
		90PHC146
(227)	(242)	
		91PHC166
(228)	(243)	
		91PHC166
(229)	(244)	
		
	(245)	
		91PHC166
(230)	(246)	
		
	(247)	
		92PHC150
(231)	(248)	
		91JCS(P1)1843
(232)	(249)	
	Ar = 3,5-dichloromesityl	

Table 10 (continued)

		95PHC179
(233)	(250)	
		95PHC179
(234)	(251)	
		
	(252)	
		91BSF562
(235)	(253)	
	Ar = <i>p</i> -MeC ₆ H ₄	
		94PHC190
(236)	(254)	
	R ¹ = Ph, CO ₂ Me	
		94PHC190
(237)	(255)	
		94PHC190
(238)	(256)	

2-Isoxazoline *N*-oxides cannot be synthesized directly by the oxidation of 2-isoxazoline. Several methods to obtain 2-isoxazoline *N*-oxide are discussed (91HC(49)1). The most commonly exploited route is by using nitroalkene, under a base promoted *O*-alkylating condition. The reaction of nitroalkene with diethyl chloromalonate afforded the 2-isoxazoline *N*-oxide (91BSF562). Dibromonitro

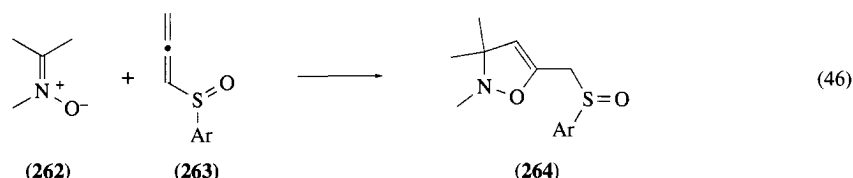
acetonitrile reacted with tetramethylene and afforded isoxazoline *N*-oxide <88H(27)2059>. In the presence of alumina, benzyl bromide condenses with ethylnitro acetate to mainly yield the *trans*-hydroxyisoxazoline *N*-oxide <91JOC6258>.

3.03.6.2.2 3-Isoxazolines

Synthesis of 3-isoxazoline is accomplished only from quaternary salts: oximation of flavylum salts, nucleophilic attack on and basic treatment of 2-isoxazolium salts. Earlier literature on the synthesis of 3-isoxazoline is systematically comprehended <84CHEC-I(6)1, 91HC(49)1>.

3.03.6.2.3 4-Isoxazolines

In general, synthesis of 4-isoxazolines is accomplished via three routes: 1,3-dipolar cycloaddition of nitrones to alkynes or by the oximation of α,β -ethylenic ketones, α -alkynic ketones and aldehydes or from the selective reduction of isoxazolium salts. The nitron (262) underwent tandem cycloaddition-[2,3]sigmatropic rearrangement with allenyl sulfoxide (263). And it resulted in 4-isoxazoline (264) (Equation (46)) <89TL663>.



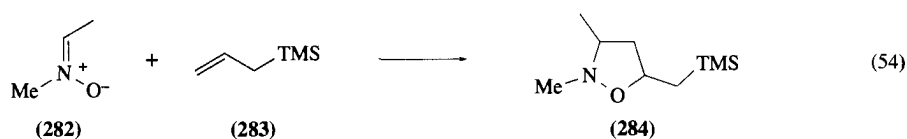
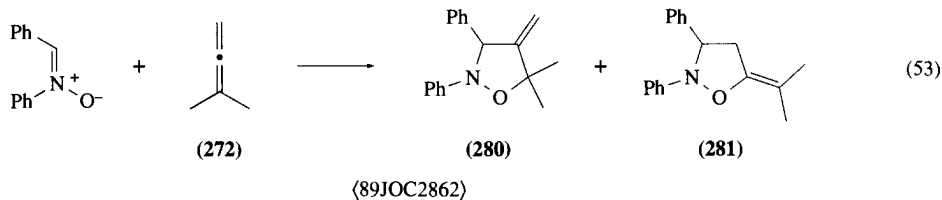
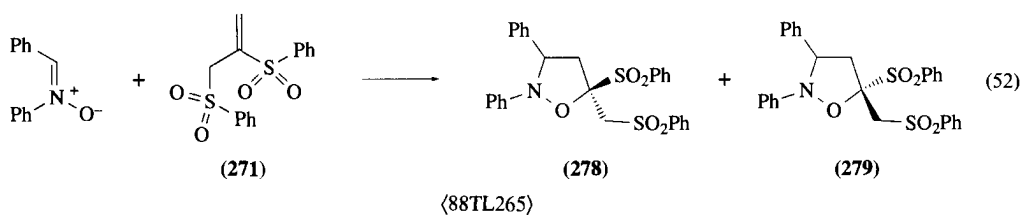
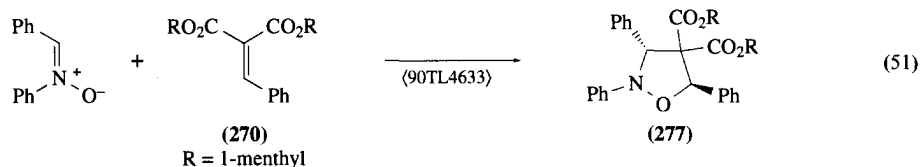
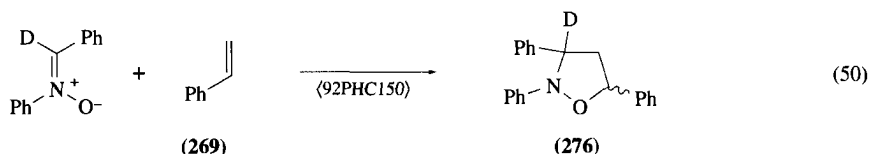
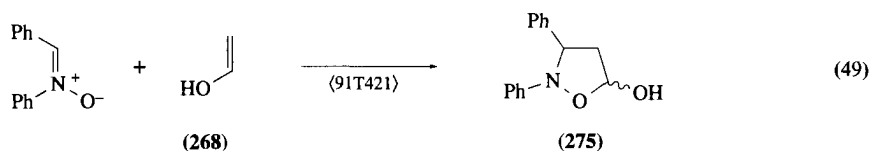
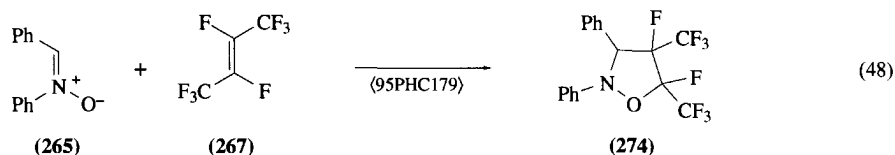
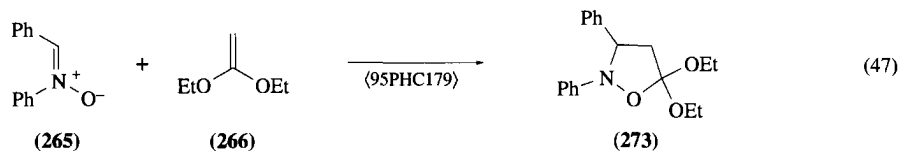
3.03.6.3 Isoxazolidines

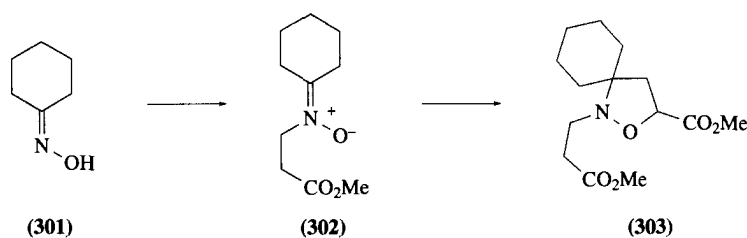
Synthesis of isoxazolidines are accomplished by 1,3-dipolar cycloaddition of nitron or nitron esters to alkenic compounds. At this juncture, it is worth mentioning that the attempted synthesis from isoxazoles by reduction always resulted in N—O bond cleavage products. Numerous references for 1,3-cycloaddition of nitron or nitron esters to alkenic compounds are reported <87CC1325, 87CC1327, 87T1835, 87T4051, 87TL2383, 87TL2649, 88H(27)17, 88RTC142, 88TL265, 88TL307, 88TL2417, 88TL5313, 89JOC2862, 89JOC4430, 89TL117, 89TL609, 89TL2289, 90JOC1901, 90TL559, 90TL1191, 90TL4633, 91BCJ2388, 91JCS(P1)2888, 91JOC2154, 91JOC2775, 91T421, 91T4007, 91T4477, 91T4495, 91TL279, 92CC1268, 92CPB2014, 92H(34)2253, 92T10399, 92TL7889, 93CB787, 93JOC4539, 94JCS(P1)1661, 94JOC5687, 94SC1669>. The results of this reaction, 1,3-dipolar cycloaddition of nitron to alkene, depends upon both electronic and steric effects. The nature of the substituents on both nitron and the dipolarophile bond determines the outcome of the reaction. In general, (*E*) nitrones are more reactive than their (*Z*) counterparts. Solvent effects are moderate and polar solvents slightly decrease the rate. The cycloaddition of nitrones to monosubstituted alkenes (generally unsymmetrically substituted dipolarophiles) can form two possible regioisomers, 4-substituted isoxazolidine and 5-substituted isoxazolidine.

Irradiation of *N*-hydroxypyrrolidine in the presence of the sensitizer 1,4-dicyanophthalene, produces the corresponding nitron <87TL2649>. Conversion of secondary amines into nitrones occurs by selenium oxide-catalyzed oxidation with hydrogen peroxide <87TL2383>. The reaction of *N*-methylhydroxylamine with (*E*) and (*Z*) aldehydes yields nitrones <87T4051>. Similarly, *N*-butylhydroxylamine with aldehyde yielded nitrones <93CB787>. Nitron and its tautomeric azomethine ylide are formed from desilylation of triflate with caesium fluoride <89JOC4430>. Tautomerization of oxime (generally by heating) yields nitron <88TL2417, 88TL5313, 90JOC1901, 90TL559, 90TL1191, 91JOC2154, 91JOC2775, 91T4007, 91T4495, 91TL279, 93JOC4539, 94SC1669>. Palladium-catalyzed [2,3]sigmatropic shift enabled the conversion of benzaldoxime *O*-allyl ether into the nitron <91TL279>.

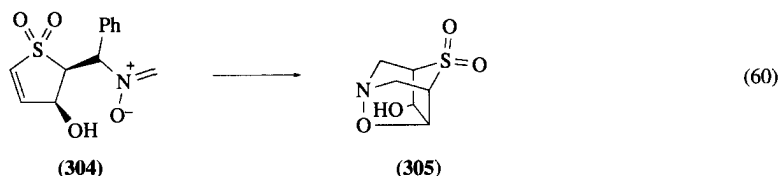
Discussion on synthesis of selected examples in this section is arranged as follows: most common methods for monocyclic, bi/tri/tetracyclic, spiral isoxazolidines and less common methods for all known isoxazolidines. Monocyclic isoxazolidine with a variety of substituents (273)–(281) are synthesized mostly from *C,N*-diphenyl nitron (265) with the corresponding alkenes (266)–(272) via intermolecular 1,3-dipolar cycloaddition (Equations (47)–(53)). Monocyclic isoxazolidines are also

obtained from alkyl nitrones. *C,N*-dimethyl nitrone (**282**) reacts with trimethylsilyl triflate (**283**) to give high yields of isoxazolidine (**284**) (Equation (54)) <92H(34)2253>. Aliphatic nitrones (**285**) react with silyl enol ether (**286**) to yield a variety of isoxazolidines (**287**) with stereospecificity (Equation (55)) <92CC1268>.

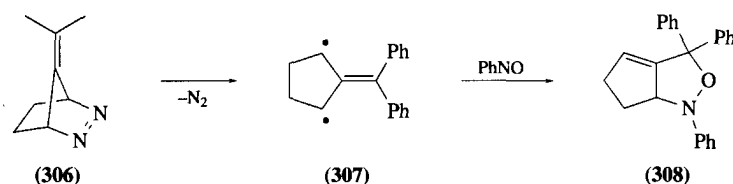




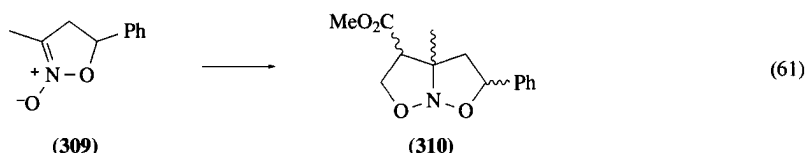
Scheme 36



The azo compound (306) underwent thermolysis or photolysis to yield the trimethylenemethane radical (307), which was subsequently trapped by nitrosobenzene as isoxazolidine (308) (Scheme 37) <91TL4283>. A reaction of isoxazoline *N*-oxide (309) with methyl acrylate yielded the cycloadduct (310) as a mixture of all four possible geometric isomers (Equation (61)) <89H(29)2245>. Reduction of 3,5-dimethyl-4-nitroxazolium salt with sodium borohydride or lithium aluminum tributoxyhydride or of 3,5-dimethyl-4-acetylisoaxazolium salt with lithium aluminum hydride afforded isoxazolidines <91HC(49)1>. Methyl-substituted benzenes underwent photochemical addition to the C=N double bond of 3-*p*-cyano(or *p*-methoxycarbonyl)-phenyl isoxazolines to afford the isoxazolidine <83TL2279>. The reaction of isoxazolidine-5-one with methyl magnesium iodide yielded 3-aryl-5-hydroxy-2,4,4,5-tetramethyl-isoxazolidine <84AP(317)474>.

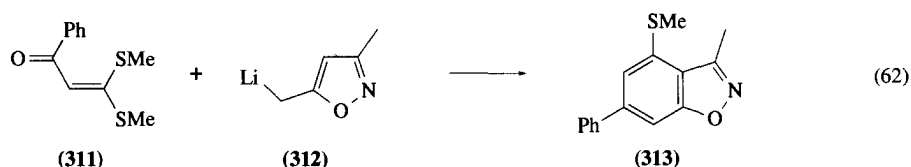


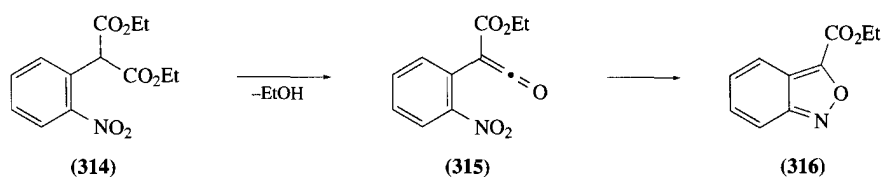
Scheme 37



3.03.6.4 Benzisoxazoles

1,2-Benzisoxazoles could be obtained by cyclization reactions forming N—O, O—C(7), or N—C(3) bonds as well as by heterocyclic rearrangements <84CHEC-I(6)1>. 1,2-Benzisoxazole (313) is synthesized from lithiated 3,5-dimethyl isoxazole (312) and α -oxoketene (311) (Equation (62)) <88TL501>. Thermal transformations of ethyl nitrophenyl ethanoates (314) resulted in cyclization, to afford 2,1-benzisoxazole (316) via the ketene intermediate (315). Its mechanism has been discussed with evidence <95CC2457>.





Scheme 38

3.03.7 APPLICATIONS

Both unsaturated and saturated isoxazole systems have found diverse applications in the area of medicine, agriculture, and other industrial uses. Categorically it has been listed <84CHEC-I(6)1>. A review with 29 references, discusses isoxazole derivatives as hallucinogens, and the mechanisms of their interaction with the nervous system <86MI 303-03>. 3-Phenyl-4-oxo-4,5,6,7-tetrahydrobenz[1,2]-isoxazole showed the reversal of scopolamine-induced memory deficit in mice <90USP4920117>. 4,5,6,7-Tetrahydroisothiazolo[5,4-c]pyridin-3-ol is used on single neurons in the cat spinal cord as γ -aminobutyric acid inhibitor (GABA) <83JMC895>. [*RS*]- α -Amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) is used to assay a novel L-[3H]glutamate binding site in the rodent brain <90MI 303-01> and also in the studies of aplysia neurons <93MI 303-04>. α -S,5S- α -Amino-3-chloro-4,5-dihydro-5-isoxazole acetic acid is found to induce differentiation in tumor cells <92MI 303-02>. Isoxazole derivatives are used as improved fluorescent probes for studying natural and synthetic lipid membranes and related areas <94USP5338854>. Isoxazole derivatives are used as muscle relaxants <94JAP(K)06116146> and for the treatment of hypercholesteremia, arteriosclerosis, and hyperlipimia <93USP5234946>. 3-Amino-5-methylisoxazole is used to prepare the bactericide, sulfamethoxazole <92MIP156789>. 3-*o*-Chloro-5-methyl-4-isoxazolepenicillin tricarprylmethylammonium salt is used as an antibiotic <89MIP148287>. Isoxazole derivatives are used to synthesize steroids such as trilostane and epostane <88USP4755595>.

Dimethyl isoxazole is used in batteries as a co-solvent <88BRP2202670>. Isoxazole additives are used as organic electrolytes of nonaqueous batteries <84JAP(K)59181464>. Isoxazole derivatives are used in photographic emulsion <91JAP(K)03263033> as well as in fiber dyes <81MIP76846, 81MIP76373>.

Isoxazole derivatives are used as herbicides to control weeds such as *Echinochloa crus-galli*, *Setaria viridis*, and *Avena fatua* <92EUP501713>.

3.04

Oxazoles

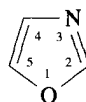
FREDERICK W. HARTNER, JR.
Merck & Co., Inc., Rahway, NJ, USA

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3.04.1 INTRODUCTION

Research on oxazole compounds had its beginnings in the late 1800s and expanded greatly in the 1940s as a consequence of the synthetic effort on penicillin. The first synthesis of the parent compound was reported in 1947 (47JCS96). As their reactivity became known and, in particular, as their usefulness in Diels–Alder reactions, and that of the mesoionic derivatives in 1,3-dipolar cycloaddition reactions, was demonstrated, interest in this class of compounds grew rapidly. Since the 1980s, the application of oxazole (1) and its derivatives as intermediates in organic synthesis, and for the chiral derivatives, as asymmetry transfer agents, has ensured an unremitting interest in oxazole chemistry.

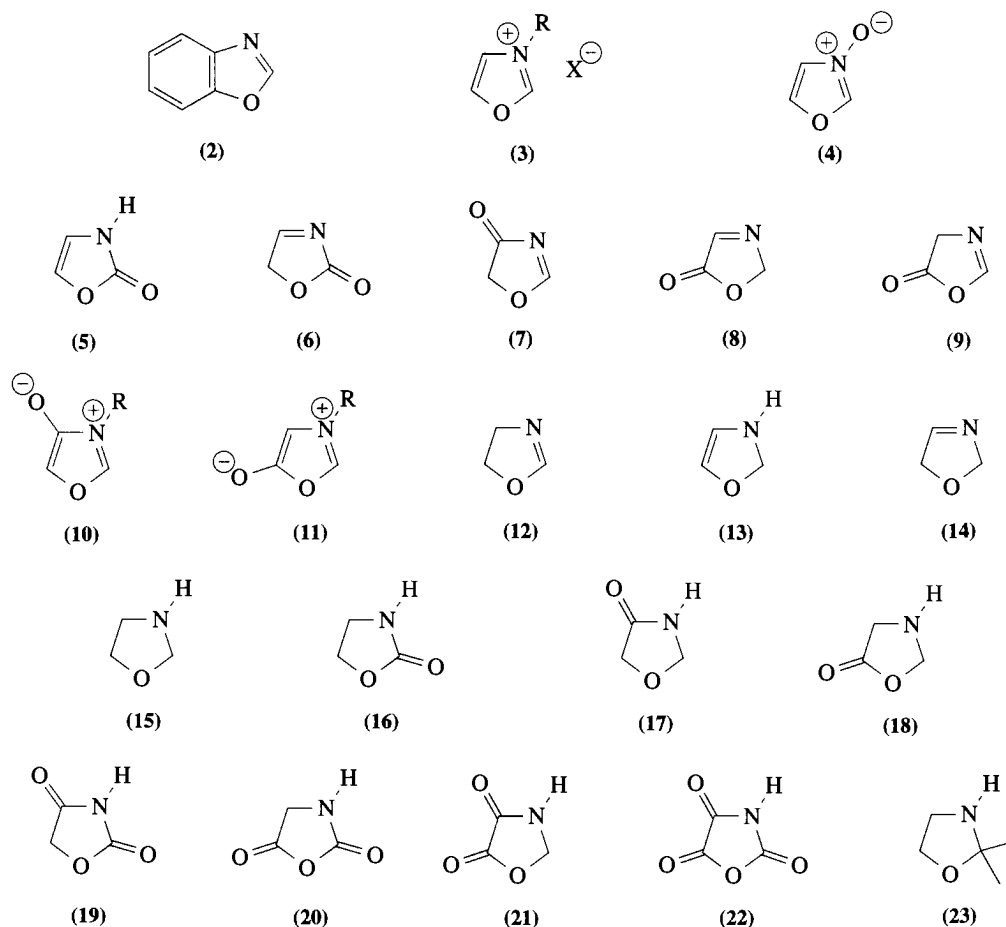


(1)

References to reviews dating prior to 1982 may be found in the first edition of *Comprehensive Heterocyclic Chemistry* (84CHEC-I(6)177). Since then, several comprehensive compilations of oxazole chemistry have been published, including the 45th volume in the series “The Chemistry of Heterocyclic Compounds,” edited by I. J. Turchi (B-86MI 304-01). There are chapters on monocyclic oxazoles, oxazolones, mesoionic oxazoles, the use of oxazoles and dihydrooxazoles in organic synthesis, as well as one covering the spectroscopy of oxazoles. A less extensive summary by

Sainsbury appeared about the same time (B-86MI 304-02). The field has been periodically reviewed by Boyd in *Progress in Heterocyclic Chemistry* (92PHC150). A review of several aspects of oxazole chemistry, including reactions with electrophiles and cycloaddition reactions, was prepared by Hassner and Fischer (93H(35)1441). Two focused reviews include the use of oxazoles to protect and activate carboxylate groups by Wasserman *et al.* (86CRV845) and Lipshutz's summary on the use of oxazoles as intermediates in organic synthesis (86CRV811). Diels-Alder reactions of oxazoles were briefly reviewed along with those of other azadienes by Boger (83T2869, 86CRV781). The chemistry of 2-silyl- and 2-stannyloxazoles and dihydrooxazoles was summarized by Dondoni (85MI 304-01). The use of oxazolones as 1,3-dipolar reactants was reviewed by Lown (B-84MI 304-01). Meyers and co-workers have condensed reports on 4,5-dihydrooxazole chemistry in two thorough reviews (85T837, 94T2297). Oxazolidine chemistry was reviewed by Scolastico (88PAC1689). There are numerous reviews on natural products that include oxazole compounds. There is also an extensive review by Maga on the chemistry of oxazoles and dihydrooxazoles in foods (81MI 304-01).

As in CHEC-I (84CHEC-I(6)177), the naming and numbering of oxazole and its derivatives follow the convention of *Chemical Abstracts*. The fully conjugated compounds are called oxazoles (1), benzoxazoles (2), oxazolium salts (3), and oxazole *N*-oxides (4). Hydroxy-substituted oxazoles exist in the oxo form, and there are five representatives: the 2(3*H*)-, 2(5*H*)-, 4(5*H*)-, 5(2*H*)-, and 5(4*H*)-oxazolones, (5)–(9) respectively. There are two mesoionic structures, the anhydro-4-hydroxy-oxazolium hydroxides (10) and the 5-hydroxy analogues (11), the latter of which are also referred to as the münchnones. Compound (12) is named 4,5-dihydrooxazole instead of Δ^2 -oxazoline or 2-oxazoline, which is commonly used in the general literature. The other dihydrooxazoles include the less common 2,3- and 2,5-dihydrooxazoles, (13) and (14), respectively. The fully saturated compound (15) is called oxazolidine, and its monooxo derivatives are 2-oxazolidinone (16), 4-oxazolidinone (17), and 5-oxazolidinone (18). There are also three oxazolidinediones (19)–(21), and the oxazolidinetriene (22). In the structures that follow, bonds with no terminal label signify methyl groups; thus (23) is named 2,2-dimethyloxazolidine.



3.04.2 THEORETICAL METHODS

3.04.2.1 Structure

A variety of theoretical studies have been reported on heterocyclic compounds that provide further insight into the nature of these chemical entities. Bond lengths and angles and charge densities of oxazole were calculated in a comparison of several *ab initio* and semiempirical computational methods (93MI 304-01, 94T2405). Using the percent deviation from experimental results of eight bond lengths and five internal bond angles as a criterion, density functional (DF) calculations, which are particularly useful for their efficient use of computational resources, gave the closest fit to experiment; of the semiempirical techniques, MNDO was the best. The pattern of net atomic charges found from earlier MO studies (75CRV389) was repeated, although values ranged widely. Values for bond lengths and angles for the DF and MNDO methods are compared with values obtained from microwave spectra in Table 1. Net atomic charges are listed in Table 2.

Table 1 Comparison by method of bond lengths (Å) and angles (deg) of oxazole.

	MNDO	DF	Microwave data
<i>Bond</i>			
O—C2	1.3642	1.358	1.357
C2—N	1.3368	1.301	1.292
N—C4	1.3996	1.383	1.395
C4—C5	1.3905	1.365	1.353
C5—O	1.3678	1.364	1.370
<i>Angle</i>			
O—C2—N	112.40	114.1	115.0
C2—N—C4	105.29	104.6	103.9
N—C4—C5	108.21	108.9	109.1
C4—C5—O	107.73	107.8	108.1
C5—O—C2	106.36	104.6	103.9

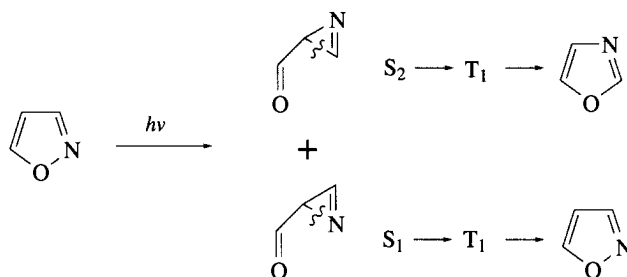
Table 2 Comparison by method of net atomic charges of oxazole.

Atom	MNDO	DF
O	−0.1375	−0.06
C-2	0.0690	−0.11
N	−0.2248	−0.09
C-4	−0.0666	−0.22
C-5	−0.0479	−0.15
H-2	0.1566	0.21
H-4	0.1187	0.21
H-5	0.1325	0.21

3.04.2.1.1 Photochemistry

A mechanistic understanding of the well-known photoisomerization of isooxazoles to oxazoles was developed through results of *ab initio* MO-CI calculations on the parent compounds (81BCJ1293). There are two excited singlet states of the intermediate azirine. If intersystem crossing to a triplet state occurs from the lowest of these two states, the C—N bond breaks and an isooxazole is produced. If intersystem crossing proceeds from the other singlet state, the C—C bond of the azirine ring cleaves and an oxazole is obtained (Scheme 1). The photochemically induced isomerization of

oxazole was also studied by *ab initio* MO-CI calculations <83JA1753>. Through stabilization by conjugation, aromatic substituents, according to their position, controlled the reaction course along four possible pathways.



Scheme 1

3.04.3 EXPERIMENTAL STRUCTURAL METHODS

3.04.3.1 X-ray Diffraction

Bond lengths and angles that are typical for the planar oxazole nucleus were found for 2-aryl-oxazole derivative (**24**) <93AX(C)1532>. These values are compared in Table 3 with those obtained from the x-ray structures of 2-amino-oxazole (**25**) <81AX(B)2090> and derivative (**26**) <86AX(B)478>. Although the presence of the 2-amino group has only a minor effect on the structure of the oxazole ring, there is a lengthening of the two longest bonds of the aryl substituted oxazole by 0.02 Å, indicating an increase in bond localization. The C(2)—NH₂ bond lengths are 1.343 and 1.337 Å, bracketing that in 2-aminopyridine: 1.341 Å <77JMR(27)303>. For compound (**26**) the amino hydrogens are out of the plane by only 0.10 and 0.02 Å, suggesting *sp*² hybridization for the nitrogen.

A few dihydrooxazole-metal complexes have been characterized by x-ray crystallography <92AG(E)430>.

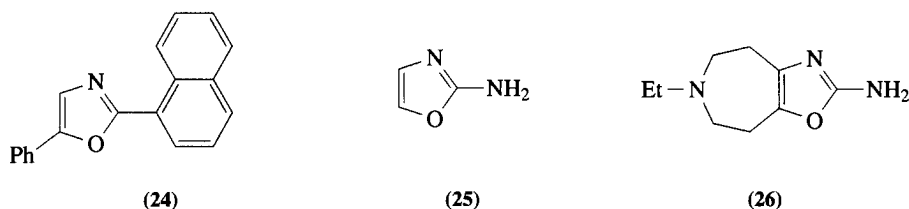


Table 3 X-ray structure data.

	24	25	26
<i>Bond length (nm)</i>			
O—C(2)	1.370	1.356	1.356
C(2)—N	1.299	1.294	1.297
N—C(4)	1.382	1.410	1.405
C(4)—C(5)	1.333	1.310	1.332
C(5)—O	1.375	1.399	1.402
<i>Bond angle (deg)</i>			
O—C(2)—N	112.8	114.6	114.3
C(2)—N—C(4)	104.5	103.2	104.2
N—C(4)—C(5)	110.7	110.7	109.9
C(4)—C(5)—O	107.0	107.5	107.4
C(5)—O—C(2)	105.0	103.9	104.2

3.04.3.2 Microwave Spectroscopy

An analysis of the ^{14}N nuclear quadrupole coupling and methyl internal rotation was reported for the monomethyl oxazoles $\langle 90\text{ZN(A)911} \rangle$. Using the microwave structure of the parent oxazole (see Section 3.04.2.1), parameters were optimized to give methyl to ring C—C distances. The barrier hindering methyl internal rotation was lower for the 2-methyl isomer (719 cal mol^{-1}) compared to the other two isomers (1227 and $1366 \text{ cal mol}^{-1}$ for 4- and 5-methyl oxazole, respectively). It was concluded that the observed difference arose from steric interactions between ring and methyl hydrogens rather than attractions between methyl hydrogens and heteroatom electron lone pairs $\langle 86\text{ZN(A)623} \rangle$. The dipole moments for 2-, 4-, and 5-methyl oxazole were found to be 1.37, 1.08, and 2.16 D, respectively. That of oxazole itself is 1.50 D $\langle 78\text{ZN(A)549} \rangle$.

3.04.3.3 NMR Spectroscopy

For oxazole, the ^1H chemical shifts for H-2, H-4, and H-5 are 7.95, 7.09, and 7.69 ppm, and the H(2)—H(4), H(2)—H(5), and H(4)—H(5) coupling constants are 0.0, 0.8, and 0.8 Hz, respectively $\langle \text{B-84CHEC-I(6)177} \rangle$. The ^{13}C chemical shifts for C-2, C-4, and C-5 are 150.6, 125.4, and 138.1 ppm, respectively. Additional ^1H NMR data on benzoxazole and the methyloxazoles, as well as ^{13}C and ^{14}N NMR data on oxazole and benzoxazole are found in $\langle 84\text{CHEC-I(6)177} \rangle$. Chemical shifts and coupling constants obtained from ^{15}N NMR spectra of a variety of oxazoles, dihydrooxazoles, and oxazolidines were reported $\langle 83\text{HCA1537} \rangle$. A few examples are given in Table 4.

Table 4 ^{15}N NMR spectral data.

Compound, in $(\text{CD}_3)_2\text{SO}$	Chemical shifts (ppm)	^{15}N — ^1H coupling constants		
		$^2J(3,2)$ (Hz)	$^2J(3,4)$ (Hz)	$^3J(3,5)$ (Hz)
Oxazole	−123.7	13.4	10.4	1.2
4,5-dihydrooxazole	−154.5	14.6	Not determined	Not determined
<i>N</i> -methyloxazolidine	−322.7	Not determined	Not determined	Not determined

A sufficient body of ^{13}C NMR data is available to allow predictions of C-4 or C-5 substitution patterns in alkyl or aryloxazoles. The effect of a 2-alkyl or 2-aryl substituent is a deshielding of ≤ 2 ppm at C-4 or C-5. The β effect of C-4 or C-5 substitution on the corresponding C(H) position is likewise small: there is a shielding of 0–6 ppm for a wide range of substituents. Thus, the ^{13}C chemical shift at the unsubstituted carbon of a C(4)—C(5) bond occurs in the following ranges: 119–127 ppm for C-4(H) with C-5(R) and 132–140 ppm for C-5(H) with C-4(R). These observations were used to assign the bisoxazole substitution in the natural products, bengazole A and B $\langle 88\text{JA1598} \rangle$.

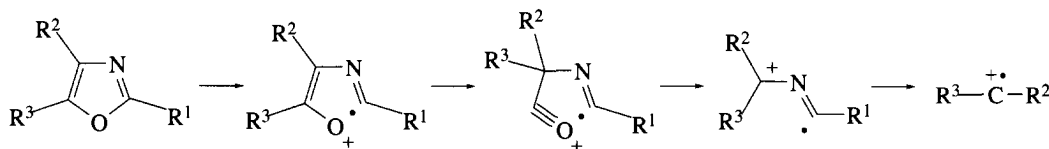
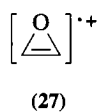
The $^1J(\text{CC})$ spin–spin coupling for oxazole is 70.7 Hz, the largest for 11 five-membered aromatic heterocyclic systems studied $\langle 94\text{MRC62} \rangle$. The value is of the usual magnitude for a carbon carbon double bond and indicates the degree of bond localization in oxazole. The $^2J(\text{CC})$ couplings are 4.2 Hz and 4.4 Hz for C(2)—C(4) and C(2)—C(5), respectively.

A study of the effect of *N*-protonation and aluminum chloride complexation on the ^{13}C NMR spectra of 2-methyl- and 2-phenyloxazole was reported $\langle 85\text{CS266} \rangle$. Chemical shift data show that protonation and complexation cause a deshielding at C-2 and C-5 and an increased shielding at C-4.

3.04.3.4 Mass Spectrometry

In the mass spectrum of oxazole, one of the four major peaks, m/z 42, corresponds to loss of HCN. Using neutralization–reionization MS, it was concluded that this ionic species was an oxirene radical cation (**27**) $\langle 89\text{JA441} \rangle$. Oxazoles in general show sequential loss of CO and a nitrile. Frag-

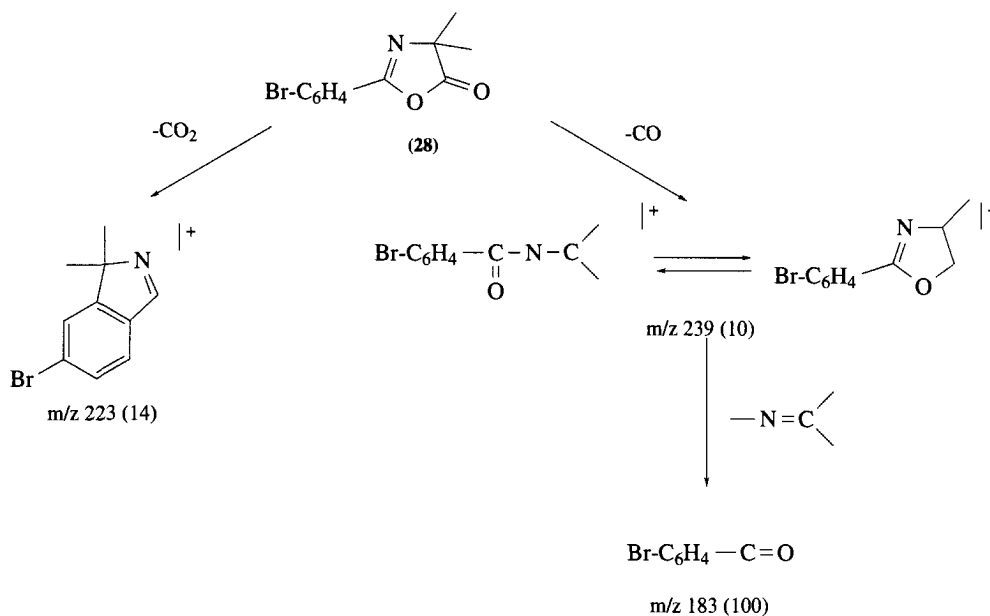
mentation is initiated by migration of the 5-substituent of the radical cation (Scheme 2) <76OMS(11)1047>.



Scheme 2

A reinvestigation of the FAB mass spectra of several heterocycles, including 2-methyl-4,5-dihydrooxazole, showed that, in contrast to the original report, the most abundant peaks in the molecular ion region corresponded to the protonated molecular ion $[M + H]^+$ <90OMS(25)435>.

The mass spectrum of 2-(*p*-bromophenyl)-4,4-disubstituted-5(4*H*)-oxazolones (28) shows fragmentation patterns dependent on the nature of the substituents at the 4-position <88JHC209>. For the dimethyl compound, loss of CO gives an abundant ionic species and further fragmentation gives the base ion (Scheme 3). Loss of CO₂ from the parent compound to give the second largest peak initiates a second major fragmentation pathway.

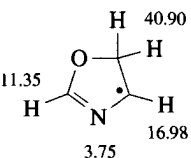
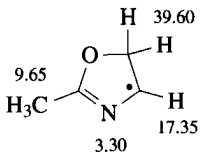
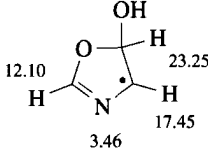
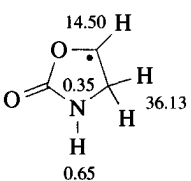
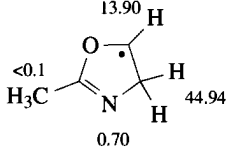
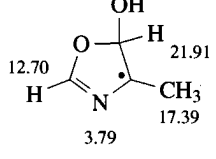
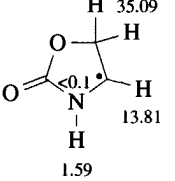


Scheme 3

3.04.3.5 Electron Spin Resonance Spectroscopy

ESR parameters of radicals produced by reaction of OH $\cdot$ or H $\cdot$ with oxazole, 4-methyloxazole, 2-methyl-4,5-dihydrooxazole, and oxazolidinone are shown in Table 5 <90JPC1887>. The radical chemistry is discussed in Section 3.04.5.7.

Table 5 ESR parameters (*g* factors and coupling constants in gauss) of oxazole, dihydrooxazole, and oxazolidinone derived radicals.

3.04.3.6 UV Spectroscopy

The UV absorption maxima of oxazole in MeOH is 205 nm <60CB1389>. Values for other oxazoles are found in <84CHEC-I(6)177>. No studies since 1984 have been reported.

3.04.3.7 IR Spectroscopy

Values for the stretching modes of oxazoles are 1650–1610, 1580–1550, 1510–1470, 1485, and 1380–1330 cm⁻¹ <84CHEC-I(6)177>. No studies since 1984 have been reported.

3.04.4 THERMODYNAMIC ASPECTS

3.04.4.1 Thermochemistry

Several non-density functional (see Section 3.04.2.1) methods and two empirically derived thermochemical databases developed by Benson and Stine/Kramer were used to calculate the heat of formation of oxazole, and the results are compared with the experimental value in Table 6. The range in values was much greater than those calculated for thiazole, showing that oxazole was a good molecule for detecting differences in the computational methods.

Table 6 Comparison by method of heats of formation of oxazole.

Method	ΔH_f° (kcal mol ⁻¹)	Method	ΔH_f° (kcal mol ⁻¹)
Experimental	-3.70 ± 0.12	MNDO	-8.24
Stine/Kramer	-3.58	6-31G	-9.25
MP2/6-31G	-4.13	Benson	6.48
PM3	-1.48	AM1	12.46

Protonation enthalpies for the *N*- and *O*-protonated forms of oxazole were also calculated by the DF and MP2/6-31G methods <86JOC1105>, and are compared with an experimentally determined

value for the *N*-protonated form in Table 7. Relative energies for *N*- and *O*-protonated 2-methyl-oxazole in a polarizable dielectric were calculated by the CNDO/2 method <85CS266>. The *N*-protonated form was favored by 71.8 kcal mol⁻¹.

Table 7 Protonation enthalpies of oxazole (kcal mol⁻¹).

	<i>LSD/6-31G</i>	<i>MP2/6-31G</i>	<i>Experimental</i>
<i>N</i> -protonation	-215.2	-212.0	-207.8
<i>O</i> -protonation	-154.9	-155.1	

3.04.4.2 Basicity

The pK_a of oxazole, 0.8, is considerably less than that of pyridine, 5.22. The substitution of alkyl groups on the ring increases the basicity; the pK_a of 2,4,5-trimethyloxazole is 3.51, similar to that of 4-chloropyridine, 3.84.

Basicity has also been assessed through calculation of the average local ionization energy, a measure of the electrostatic field around a molecule that is derived through SCF MO theory <91JOC2934>. Of particular interest are the points on the molecular surface at which, on average, the least amount of energy is required to remove an electron. These locations are also expected to be the most reactive toward electrophiles. For oxazole, the calculated locations and energies in eV are: N, 13.12; C₄—C₅ (closer to C₄), 13.27; and O, 17.24. For a variety of azines and azoles, an excellent correlation was demonstrated between pK_a's and the local ionization energies at the nitrogen atoms.

Of relevance to the problem of drug design is hydrogen bond basicity. The hydrogen bonding capability, log *K*_β, of oxazole has been compared with 91 other proton acceptors using a UV technique <89JCS(P2)1355>. Hydrogen bond basicity was also shown to correlate with electrostatic potential local minimum along the axis of the nitrogen lone pair in a series of heterocycles <94JCS(P2)199>. The experimental and calculated basicities for oxazole, 2,4,5-trimethyloxazole, and pyridine are shown in Table 8. A proton affinity ladder of 47 compounds has also been determined using variable-temperature pulsed high-pressure mass spectrometry <91JA4448>. For oxazole and pyridine, the proton affinities, in kcal mol⁻¹, are 213.3 and 227.6, respectively.

Table 8 Hydrogen bond basicities (log *K*_β).

<i>Compound</i>	<i>Experimental</i>	<i>Calculated</i>
Oxazole	1.67	1.91
2,4,5-trimethyloxazole	2.65	2.59
Pyridine	2.52	2.51

Information about the bonding of oxazole in transition metal complexes was obtained from a study of a series of oxazole, thiazole, and pyridine gold(III) complexes of the type [AuCl₃(L)] <91JCS(D)307>. The oxazoles were bound through nitrogen. Equilibrium and rate constants for the reaction of the complexes with added chloride were obtained. From the derived rate constants for the reaction of [AuCl₄]⁻ with the ligands it was observed that the oxazoles (and thiazoles) were poorer nucleophiles than pyridines of similar basicity. This difference was attributed to a lesser π acceptor ability of the five-membered ring heterocyclic ligands in the transition state.

3.04.4.3 Aromaticity

The chemistry of oxazole is consistent with a high degree of bond localization and little or no aromatic character. This was pointed out through several examples in <84CHEC-1(6)177> and is also illustrated by the value of ¹*J*_{cc} (Section 3.04.3.3) and the cycloaddition reactions discussed in Section 3.04.5.6.

Several theoretical studies concerned with the quantitation of aromaticity that have been reported during the past decade also revealed the lack of aromaticity of oxazole. A ring current index was

developed from the idea that the bond with the lowest bond order would determine the magnitude of the ring current $\langle 83JOC1344 \rangle$. For oxazole, the lowest bond order occurs for the C(5)—O bond. Most heterocyclic compounds were higher on the index than oxazole; isoxazole and pyrazole were lower. Another index was devised based on a statistical evaluation of the deviations in peripheral bond orders $\langle 85T1409 \rangle$. Oxazole was lowest on the aromaticity scale of 29 heterocyclic compounds.

The technique of principal component analysis was applied to a set of 12 characteristics associated with aromaticity, including the two above, using a variety of heterocyclic compounds $\langle 89JA7 \rangle$. Three principal components, t_{11} – t_{13} , were found that accounted for most of the variance of the data. Characteristics associated with classical aromaticity, such as the two mentioned above, were dominated by the first component and those associated with magnetic properties, such as the molar susceptibility, were dominated by the second. The t_{11} score for oxazole was low, of 16 compounds, only furan was lower. On the other hand, the t_{12} score was one of the higher scores.

3.04.4.4 Tautomerism

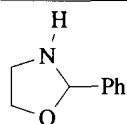
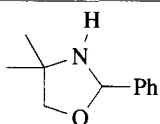
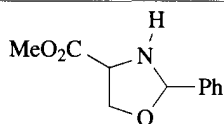
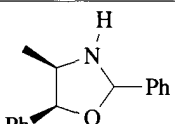
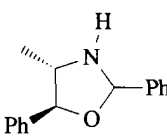
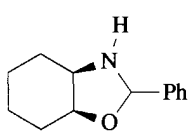
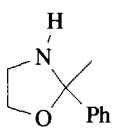
3.04.4.4.1 Substituent tautomerism

Oxazolones and their sulfur counterparts exist predominately as the keto rather than enol forms; for the nitrogen analogues, the aminooxazole structure prevails. The subject of substituent tautomerism was covered in depth in $\langle 84CHEC-1(6)177 \rangle$. There have been no studies since 1984 on substituent tautomerism reported in the literature.

3.04.4.4.2 Ring-chain tautomerism

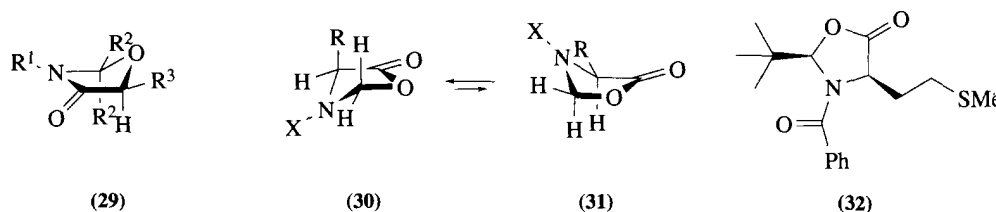
Oxazolidines are subject to ring-chain tautomerism. A variety of substituted oxazolidines in the solid state exist in the chain form, based on ^{13}C NMR experiments $\langle 85T5919, 92T4979 \rangle$. In solution, the two forms are in equilibrium, the position of which depends on the solvent and the substituents. Oxazolidines prepared from *meta*- and *para*-substituted benzaldehydes and 2-amino-2-methylpropanol, norephedrine, norpseudoephedrine, and serine esters all give good linear plots for the equation: $\log K_x = \sigma^+ \rho + \log K_{x=H}$ where σ^+ are the Hammett–Brown values $\langle 93T6701, 93JOC1967 \rangle$. Rho values are small and positive (0.47–0.60), indicating a preference for the ring form with electron-withdrawing groups on the 2-aryl ring. The chain form is favored in solvents with better hydrogen-bonding ability. The percent ring form for the series of 2-phenyloxazolidines is given with their structures in Table 9. The addition of a 2-methyl group to the parent 2-phenyloxazolidine dramatically increases the amount of the ring form. The aldehyde adducts of *trans*-2-aminocyclohexanol existed exclusively in the hydroxy Schiff base form. Although cyclization of the chain to ring form is a formally disallowed 5-endo-trig process, the attainment of equilibrium is fast. For the parent 2-phenyloxazolidine, equilibrium was reached within 18 s.

Table 9 Percent ring form of 2-phenyloxazolidines in chloroform solution.

			
7%	61%	44%	30%
			
69%	4%	61%	

3.04.4.5 Conformational Aspects

Experimental data show that the rings of oxazole and 4,5-dihydrooxazole are planar. Oxazolidines, on the other hand, are not flat, and their conformation depends on the nature and position of substituents. The conformations of 4- and 5-oxazolidinones were studied using circular dichroism $\langle 83T3139, 85T603 \rangle$. 4-Oxazolidinones exist predominantly in the envelope conformer (29). As the size of the C-2 substituents increase, this conformer is destabilized. 4-Substituted-3-alkylsulfonyl-5-oxazolidinones exist mostly in conformer (30), in which the C-4 substituent is in the axial position, but conformer (31) also contributes. The equilibrium shifts towards the diaxial conformer as the size of the C-4 substituent or the alkylsulfonyl group increases. In contrast to these results, an x-ray analysis of crystalline (32) revealed an almost planar structure $\langle 92HCA913 \rangle$.



3.04.4.6 Chromatographic Behavior

The GLC and LC behavior of oxazoles would be expected to be very dependent on the polarity of their substituents, making any attempt at generalizations a futile one. Nevertheless, a comparison of the GLC behavior of oxazole and a set of methyl, ethyl, and propyl oxazole derivatives with the corresponding thiazole compounds on three columns of different polarity showed an interesting dichotomy $\langle 91JC1 \rangle$. Energy contributions of the three alkyl groups to the partial molar free energy of sorption of the compounds were determined. Contributions of the same alkyl group depended on the position of the alkyl group with respect to the heteroatoms in the azole ring. The data was split between compounds with an alkyl group in the 2 position and those without. The difference is a reflection of the relative acidity of the H-2 atom, which makes it capable of donor-acceptor interactions.

3.04.5 REACTIONS OF FULLY CONJUGATED RINGS

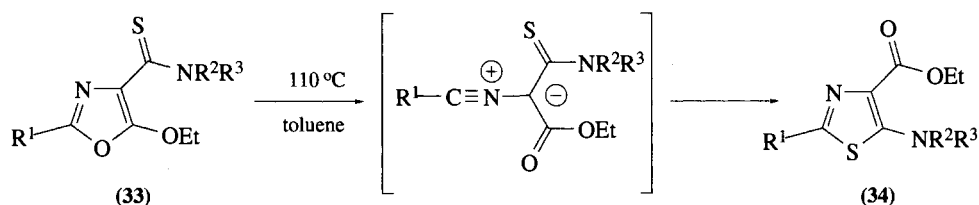
The chemistry of the oxazole ring system is understood from an appreciation of its lack of aromatic character (see Section 3.04.4.3). Thus, it is a reactive diene in Diels-Alder cycloaddition reactions, it undergoes Claisen rearrangements, and is a good substrate for singlet oxygen. The ring nitrogen makes it electron deficient like pyridine: it reacts sluggishly with electrophiles unless the ring is substituted with electron donating groups. It has a high thermal stability, but this can be modified by substituents. It is stable to many nucleophilic reagents unless high temperatures are employed or the ring nitrogen is alkylated to form an oxazolium salt.

Oxazole derivatives have been thoroughly studied and display a wealth of synthetic opportunities. The mesoionic münchnones undergo 1,3-dipolar cycloadditions across the C(2)—C(4) positions. The 5(4H)-oxazolones have excited interest for a long time because they undergo fission of the C(5)—O bond to afford α -amino acids. Appropriately substituted dihydrooxazoles and oxazolidines are effective carriers of asymmetry, and they have only begun to be exploited in this role although numerous possibilities have been demonstrated.

3.04.5.1 Thermal and Photochemical Reactions

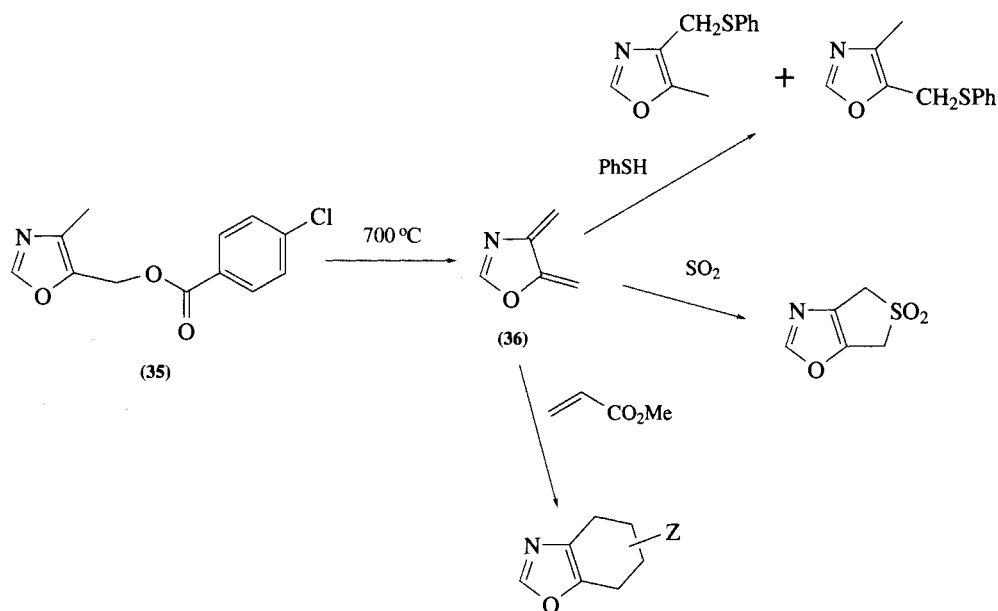
Although oxazole and its alkyl and aryl derivatives are thermally stable to high temperatures, the introduction of functionalized substituents can lead to reaction at lower temperature. The Cornforth rearrangement, discussed in $\langle 84CHEC-I(6)177 \rangle$, is one example. An application of the Cornforth reaction is the conversion of 4-aminothiocarbonyl-5-ethoxyoxazoles (33) to 5-aminothiazoles (34)

<90JOC4484>. The reaction proceeds via a nonisolable nitrile ylide (Scheme 4). Another example is the aza-Claisen rearrangement discussed in Section 3.04.5.6.2.



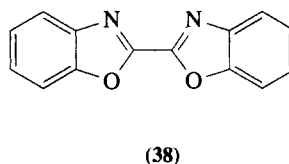
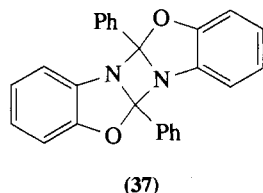
Scheme 4

Flash vacuum pyrolysis of a *p*-chlorobenzoate ester (35) has also led to useful chemistry <90TL1487>. The reaction produced oxazole-4,5-xylylene (36), which could be trapped with thiophenol or SO₂ to give the corresponding adducts in 39% and 25% yield, respectively (Scheme 5). The unstable intermediate also gave a Diels–Alder adduct with methyl acrylate. The *o*-xylylene oxazole derivative and the furan analogue were unique among those of several heterocycles studied in that they underwent Diels–Alder reactions instead of polymerization.



Scheme 5

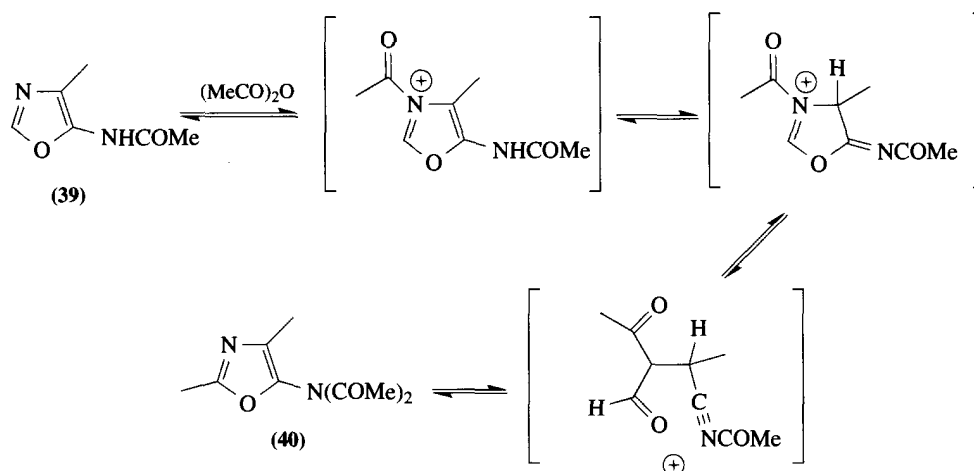
The photochemical reaction of 2-phenylbenzoxazole <84CHEC-I(6)177> forms a head-to-tail dimer, 1,3-diazetidene, (37) <87CC578>. Benzoxazole itself, in the presence of oxygen, gives coupled product, (38) <74TL375>.



3.04.5.2 Electrophilic Attack at Nitrogen

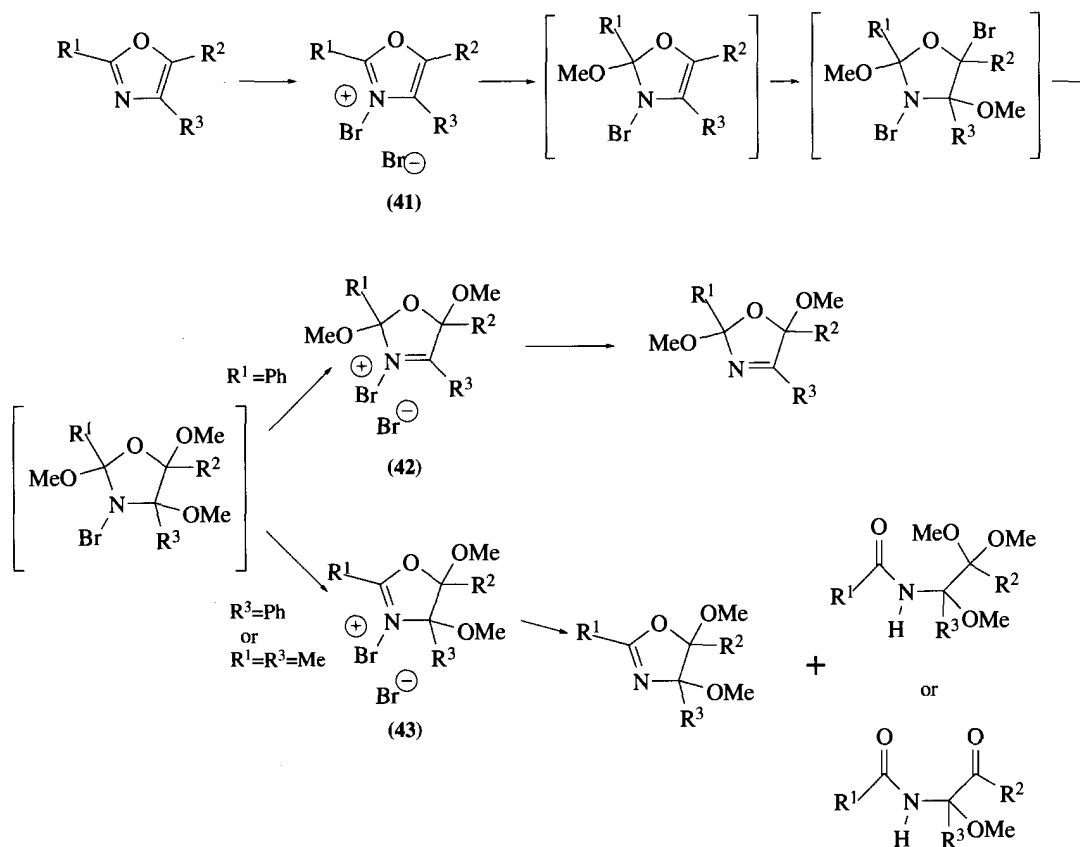
The oxazole nitrogen atom reacts with a variety of alkylating and acylating agents. For example, treatment of 4-methyl-5-acetylaminoxazole (39) with acetic anhydride in the presence of acetic

acid gave a C-2 alkylated product (40) as the primary product via acylation of nitrogen, ring opening, rotation about the C(4)—N bond, and recyclization (Scheme 6) <90CCA215>.



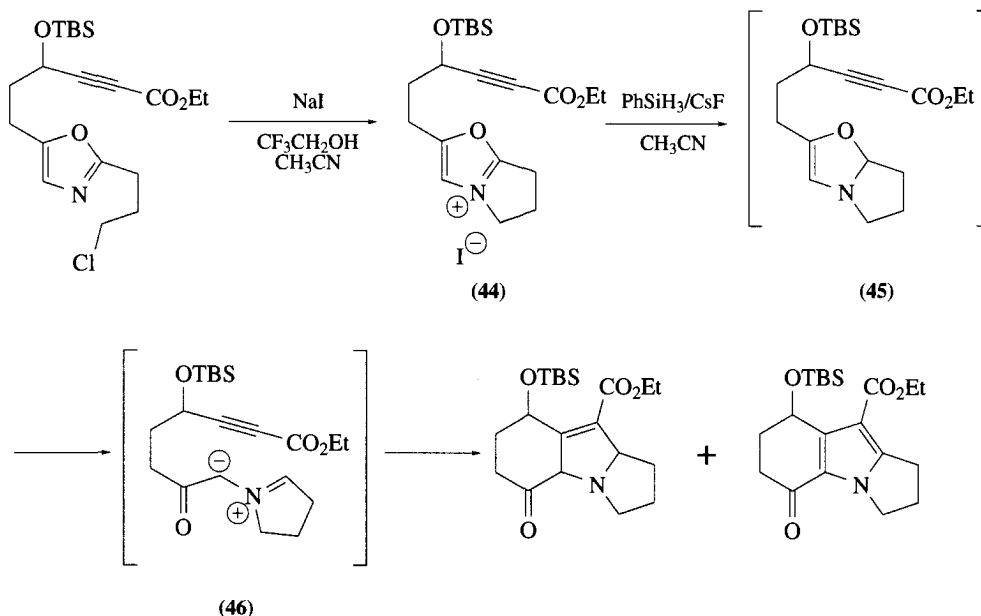
Scheme 6

Oxazole reacts with bromine in methanol to give a mixture of products via initial attack of bromine on nitrogen to form a charged complex, (41) <89T6249>. Subsequent fast reactions with methanol lead to intermediates (42 or (43) depending on the C-2 and C-4 substituents, which may help to stabilize the C=N bond. Thus, a 2-phenyl substituent favors the 2,5-dihydrooxazole structure (42), whereas a 4-phenyl group favors the 4,5-dihydrooxazole structure (43). The intermediates give cyclic or ring-opened products (Scheme 7).



Scheme 7

An intramolecular *N*-alkylation was achieved when 2-(4-bromobutyl)-5-ethoxyoxazole was reacted with KCN in acetone in the presence of NaI <90TL7213>. The intermediate oxazolium salt reacts with the KCN and opens to give a tetrahydropyridine product. A sequence of reactions for the generation of compounds related to the mitosenes also begins with an intramolecular *N*-alkylation of oxazoles <93JOC1341>. The resultant oxazolium salts (44) are reduced to 2,3-dihydro-oxazoles (45), which undergo ring opening to azomethine ylides (46). These react intramolecularly with alkyne dipolarophiles to afford tricyclic products (Scheme 8).

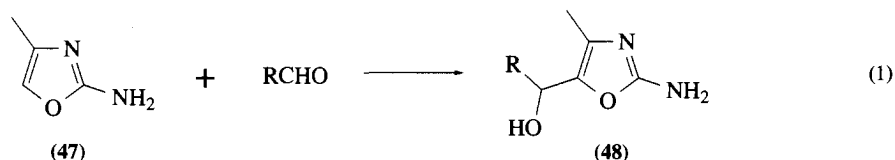


Scheme 8

3.04.5.3 Electrophilic Attack at Carbon

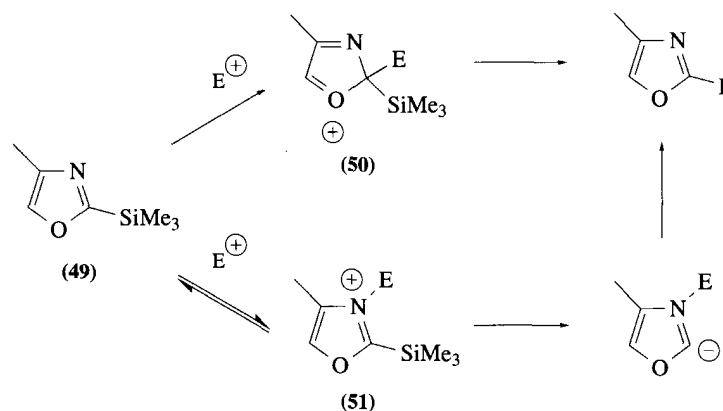
Although oxazoles generally are poor substrates for electrophilic substitution because of their electron-deficient nucleus, both experimental findings and MO calculations indicate that when they do react, the order of preference for reaction site is the 4 > 5 > 2 position. Surprisingly, the deuteration of oxazole using $\text{CF}_3\text{CO}_2\text{D}/\text{D}_2\text{O}$ was reported to occur exclusively at the 2 position <90IJC(B)562>.

The presence of electron-donating substituents on the ring can improve the reactivity of oxazoles with electrophiles. Thus, 2-amino-4-methyloxazole (47) reacts with aldehydes to give oxazole-5-hydroxymethyl derivatives (48) in good yield (Equation (1)) <88JHC815>. This substitution pattern is just sufficient to impart reactivity with these substrates. Without the 4-methyl group, or with a 4-phenyl group or 2-acetamido group, no addition products are formed. Also, less reactive electrophiles, such as acetophenone, do not react. The 4 position of oxazole is acylated under Friedel-Crafts conditions when the ring is activated by a 2-arylthio and a 5-alkoxy group <91OPP670>.



Substitution by carbon and sulfur electrophiles at the 2-position may be achieved by activation of oxazole with a 2-trimethylsilyl group. For example, 4-methyl-2-trimethylsilyloxazole (49) reacts with aldehydes to give silyl ethers, it reacts with acyl chlorides to give acyl derivatives, and it reacts with phenylsulfenyl chlorides to give a mixture of 2-phenylthio and 2,5-di(phenylthio)oxazole <87JOC3413>. Reactions with two α -chiral aldehydes, (*R*)-2,3-*O*-isopropylidene-glyceraldehyde and

(*R,S*)-2-phenylpropanal, showed about 4:1 diastereoselection with the *anti* and *syn* isomers predominating, respectively. The products may arise by a direct ipso substitution process (**50**) or via an oxazolium ylide intermediate (**51**) (Scheme 9).

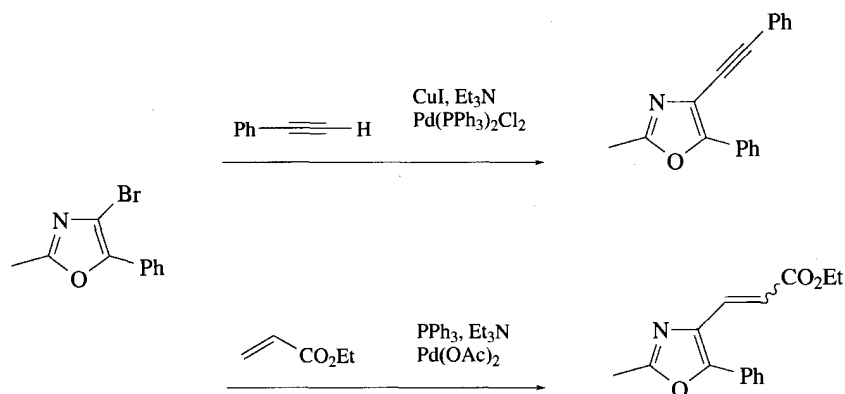


Scheme 9

3.04.5.4 Nucleophilic Attack on Carbon

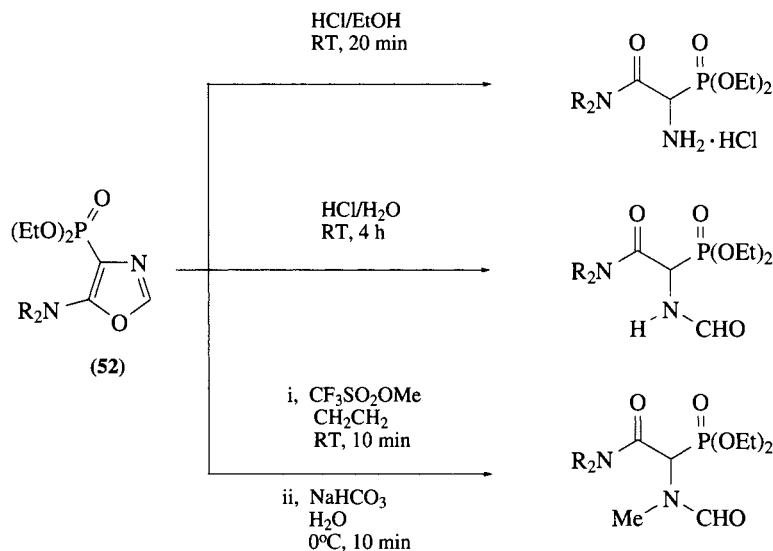
Oxazoles react with amines to form imidazoles. As more examples have been documented, the critical role that the oxazole substitution pattern plays in the reaction outcome has become apparent. For example, 5-acetyl-2-aminooxazole reacts with amines to give imidazoles as the predominant products $\langle 84\text{TL}2957 \rangle$. With the addition of a 4-methyl group, as in 5-acetyl-4-methyloxazole or 5-acetyl-2,4-dimethyloxazole, pyrimidines are formed instead $\langle 60\text{CB}1998, 85\text{JC}(\text{B})535 \rangle$. The reaction of 5-acetyl-2-*N,N*-dimethylaminooxazole with ammonia requires a temperature of 140 °C, whereas the reaction of 5-acetyl-2-aminooxazole with dimethylamine proceeds at room temperature.

Transition metal catalyzed coupling reactions to form carbon–carbon bonds have been applied to oxazoles. Terminal alkynes and alkenes react with 4-bromo and 5-bromooxazoles in the presence of a palladium catalyst to give coupled products in fair to good yields (Scheme 10) $\langle 87\text{CPB}823 \rangle$. 4-Methyl-2-trimethylstannyloxazole reacts with a variety of aryl and heteroaryl halides and tetrakis(triphenylphosphine)palladium to give the 2-substituted products in high yield $\langle 87\text{S}693 \rangle$. 2-Substituted products are also obtained from the reaction of Grignard reagents with 2-methylthio-4,5-diphenyloxazole in the presence of the catalyst, 1,2-bis(diphenylphosphino)ethane nickel(II) chloride $\langle 84\text{S}1047 \rangle$. Coupled products may be obtained by lithium halogen exchange of appropriate derivatives followed by alkylation with electrophiles $\langle 89\text{S}873 \rangle$. Thus, 5-bromo-2-(4-methoxyphenyl)oxazole was converted into 5-benzyl-2-(4-methoxyphenyl)oxazole in 72% yield using butyllithium and benzyl bromide.



Scheme 10

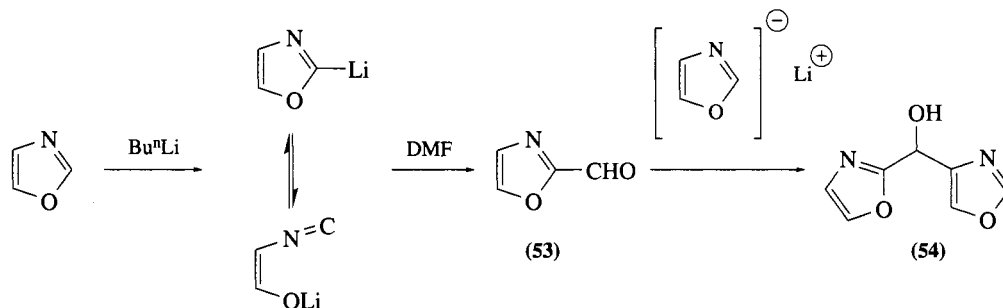
Oxazolium salts, formed by protonation of the oxazole ring nitrogen under acidic conditions, undergo hydrolysis. Mild conditions that have been used to effect this transformation on sensitive systems include TFA/CH₂Cl₂ <90JA7032> and 1 equiv. AcCl/EtOH <88JOC5107>. The solvolysis conditions can sometimes have a dramatic effect on the reaction outcome, as shown in Scheme 11 for 5-amino-4-phosphonooxazoles (**52**) <92S1031>.



Scheme 11

3.04.5.5 Nucleophilic Attack on Hydrogen

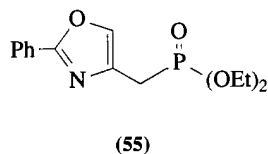
Proton acidity in oxazole follows the order C-2 > C-5 > C-4. The use of 2-lithiooxazoles in synthesis is problematic, however, because they are in tautomeric equilibrium with their open chain form. When 2-lithiooxazole was reacted with DMF at -75°C and the mixture was warmed to RT, oxazole-2-carbaldehyde (**53**) was formed quantitatively. Reaction of this product with a second equivalent of lithiooxazole did not give the expected product, but rather an unsymmetrical bis(oxazolyl)methanol (**54**) <91JOC449> (Scheme 12). Reaction at the 4 position of lithiooxazole was found to be general for aldehydes. Less reactive electrophiles, such as, DMF, benzophenone, and ethyl formate, gave 2-substituted products, and iodobutane, benzyl bromide and ethyl carbonate did not react at all after an extended age at RT. Acylation of 2-lithio-5-phenyloxazole may be accomplished using *N*-methyl-*N*-(2-pyridinyl)-carboxamides <84S1048>.



Scheme 12

The presence of a 4-carboxy substituent enhances the acidity of the 5 position to the exclusion of the 2 position under kinetic and thermodynamic conditions <86JOC5111>. Deprotonation at a C-2

methyl group is likewise not competitive with a C-5 hydrogen (see Section 3.04.7.1). The anion of phosphonate (**55**) upon quenching with D₂O incorporates deuterium at the C-5 hydrogen as well as the methylene hydrogens <91TL1609>

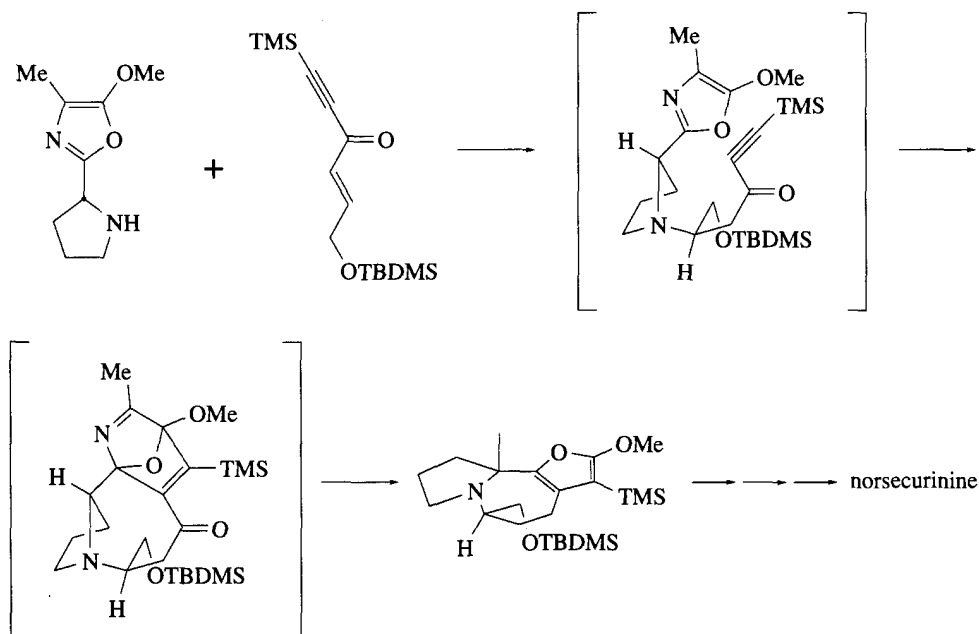


3.04.5.6 Reactions with Cyclic Transition States

3.04.5.6.1 Diels–Alder reactions

Since their discovery in 1957, Diels–Alder reactions of oxazoles have proven useful for the synthesis of a variety of compounds and consequently have been a constant focus of attention <57MI 304-01>. Reaction fundamentals and generalities were discussed in <84CHEC-I(6)177>. Alkynes and alkenes are the usual dienophiles.

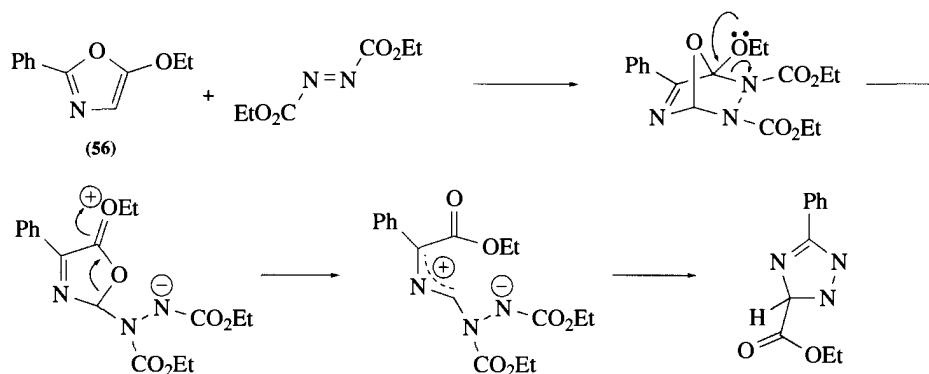
Reactions of alkynes with oxazoles give unstable adducts that lose a nitrile molecule to generate a furan. Advantage was taken of the intramolecular version of this reaction in the development of a strategy that has been employed for the synthesis of several sesquiterpenes, including norsecurinine (Scheme 13) <91JA5384>. Appropriately substituted oxazoles, tethered at either the 2 or 5 position of the oxazole ring, provide for the necessary regio and stereo control to prepare such complex natural products. Although Diels–Alder adducts of most oxazoles with alkynes are unstable, those of 2-aminooxazoles are stable enough to be isolated in low to moderate yield <85JHC1281>. Oxazolo[3,2-*a*]pyrimidines are side products.



Scheme 13

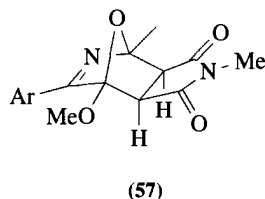
There have been reports on the reaction of oxazoles with heterodienophiles, including N=N, C=N, C=O, and C=S types, to give new heterocycles <89T3535, 88JOC4663>. In most cases, the products may be envisioned to arise from ring opening and rearrangement of Diels–Alder adducts followed by reclosure, but so far no proof of this mechanism has appeared. A reaction of 5-ethoxy-2-phenyloxazole (**56**) with dead is given in Scheme 14. The heterodienophiles vary in reactivity, with dead and 4-phenyl-1,2,4-triazole-3,5-dione the most reactive and some C=N and C=O types such

as the C=N analogue of dead and chloral unreactive. Oxazoles require activation by electron-donating alkoxy or siloxy groups. Intramolecular versions of these reactions have also been explored <91JOC3419>.

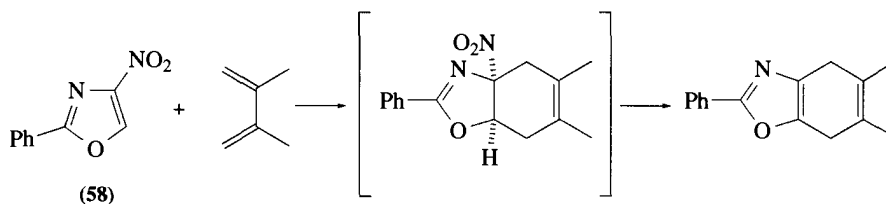


Scheme 14

Alkenes react with oxazoles to give pyridine derivatives after cleavage of the initially formed bicyclic intermediates. A few stable adducts are known, and the first x-ray structural analysis was achieved on the *N*-methylmaleimide exo adduct (57) of 5-methoxy-2-methyl-4-(*p*-nitrophenyl)-oxazole <87BCJ432>.



Diels–Alder reactions in which the oxazole is the dienophile have been discovered. Thus, 4-nitro-2-phenyloxazole (58) reacts with 2,3-dimethylbuta-1,3-diene or cyclohexa-1,3-diene across the C(4)—C(5) bond (Scheme 15) <93CC978>.

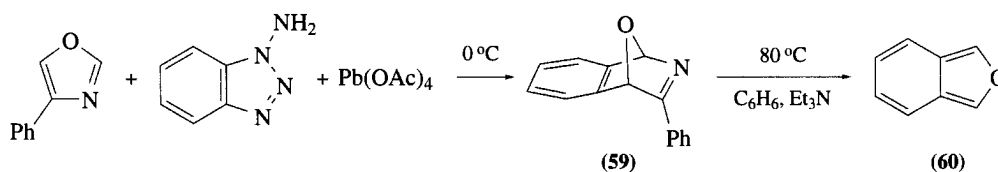


Scheme 15

In the first reported reaction of benzyne with oxazoles, the isolated products were 2 : 1 benzyne : oxazole adducts. In that reaction, the benzyne was generated *in situ* in a thermal process carried out at 101°C. The initially formed adduct loses a nitrile to give an isobenzofuran, which adds a second molecule of benzyne. When benzyne is generated at 0°C from 1-aminobenzotriazole and lead tetraacetate under dilute conditions, the initial cycloadducts (59) are formed in essentially quantitative yield <90JOC929>. They can be handled at room temperature and can be decomposed at elevated temperatures to isobenzofuran (60), which in the presence of other dienophiles leads to a variety of useful products (Scheme 16).

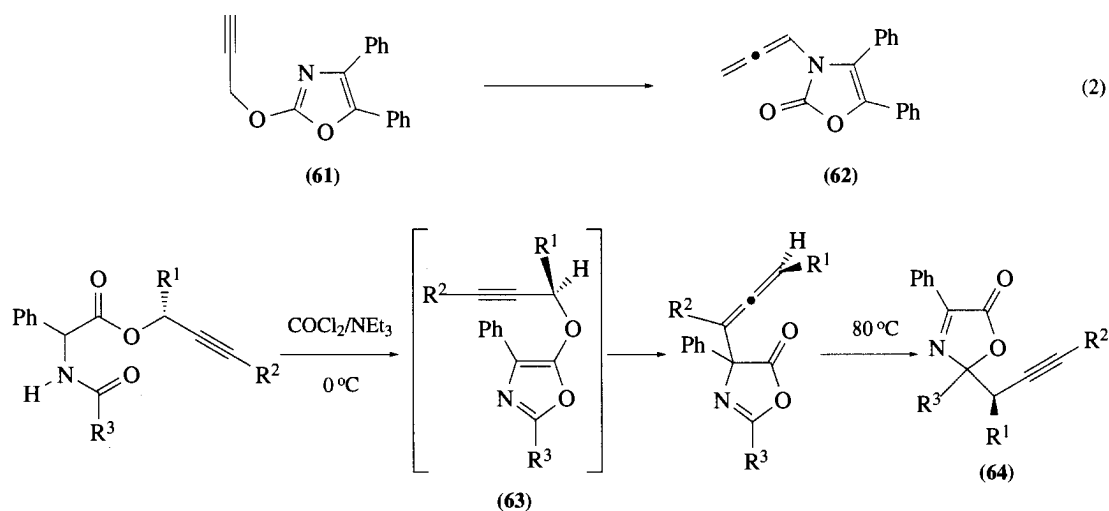
3.04.5.6.2 Claisen rearrangement

2-Allyloxy-substituted 4,5-diphenyloxazoles undergo [3,3]-sigmatropic aza-Claisen rearrangements to 3-allyl-2(3*H*)oxazolones <84JOC399>. The 2-propynyloxy-oxazole (61) affords an allene



Scheme 16

derivative (62) (Equation (2)). In a tandem Claisen aza-Cope rearrangement of 5-propynyloxy-oxazoles (63) to 5(2*H*)-oxazolones (64), transfer of stereochemistry was achieved ^[86T2063]. The nonisolable oxazoles are formed from propargyl *N*-acyl-*C*-phenylglycinates (Scheme 17).

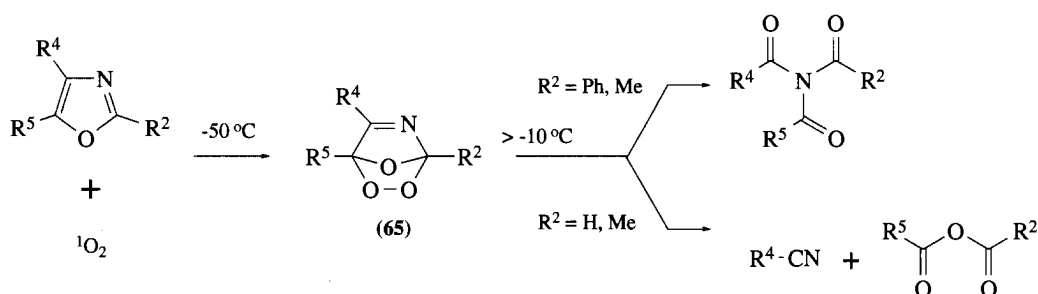


Scheme 17

3.04.5.6.3 Reactions of singlet oxygen

Reactions of oxazoles with singlet oxygen have been studied since their discovery in the 1960s. Labeling studies showed that the reactions proceeded by a [4 + 2] cycloaddition to give an unstable endoperoxide (65) ^[72JA7180]. The first direct evidence (¹H and ¹³C NMR) for these adducts was obtained by running the reactions at temperatures below -50°C ^[88TL1007]. Between -10°C and RT, the peroxide products began to rearrange or fragment (Scheme 18). The reaction pathway depended on the nature of the substituent at the 2 position of the oxazole. For $\text{R}^2 = \text{phenyl}$, triacylamides were formed quantitatively, for $\text{R}^2 = \text{H}$, a 1 : 1 mixture of R^4CN and anhydrides was obtained, and for $\text{R}^3 = \text{methyl}$, both pathways were observed with the ratio of the former to the latter increasing with the number and nature of R^4 and R^5 substituents.

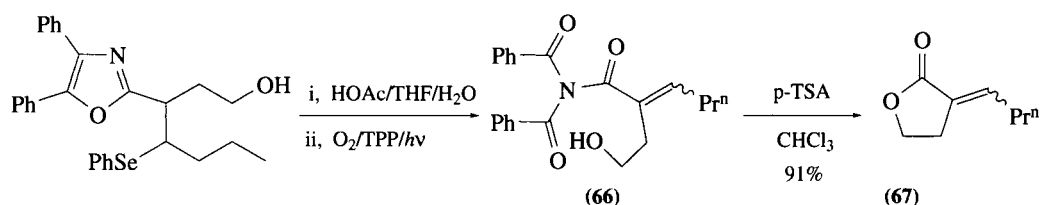
Several interesting applications of the reaction of singlet oxygen with oxazoles to form triamides



Scheme 18

have been reported. In a synthesis of the macrolide, antimycin A₃ the triamide derived from a 4,5-diphenyloxazole was cleaved by a terminal hydroxyl group to form the macrocyclic ring <92TL7059>.

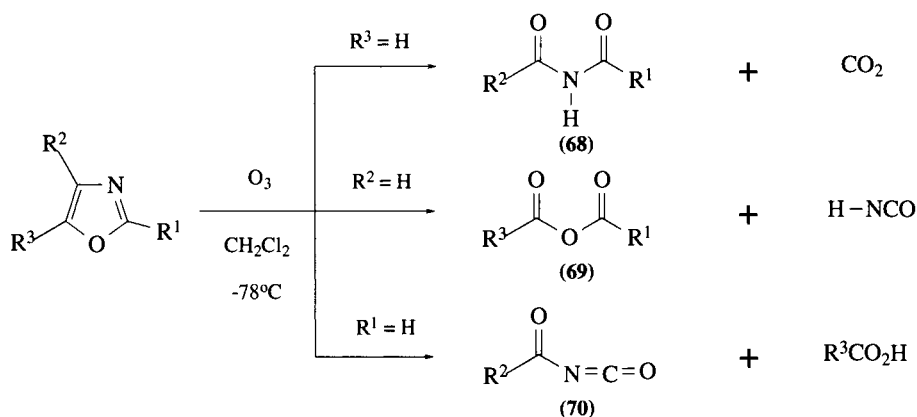
An efficient dual photooxidation of compounds comprised of both oxazole and selenide units was demonstrated <86RTC345>. In a single step, the dye-sensitized reaction yields α,β -unsaturated triamides (**66**), which may be further transformed into α -alkylidene lactones (**67**) on heating in the presence of catalytic acid (Scheme 19).



Scheme 19

3.04.5.7 Miscellaneous Reactions

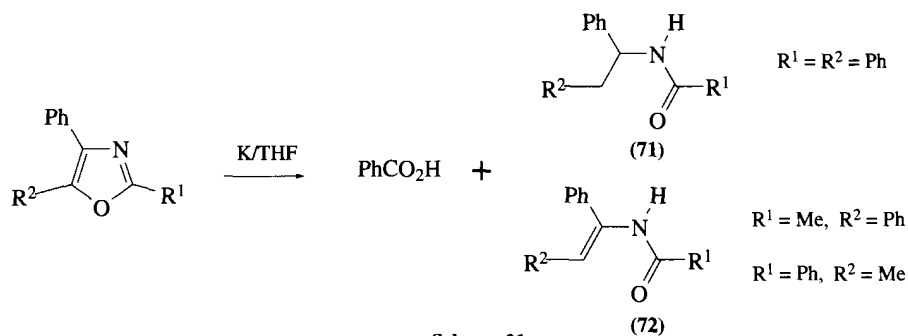
The ozonolysis of oxazoles provides another illustration of the influence the oxazole substitution pattern has on the course of a reaction. Three classes of products may be formed (Scheme 20). If the 5 position is unsubstituted, as in 4-phenyloxazole, *N*-acylamides (**68**) are the major products; if the 5 position is substituted but not the 4 position, as in 5-phenyloxazole, acid anhydrides (**69**) predominate; and if the 4 and 5 positions are both substituted, as in 4,5-diphenyloxazole, *N*-acylisocyanates (**70**) are obtained <91JCR(S)34>. The ozonolysis of oxazoles with a good leaving group at the 5 position, such as 5-bromo- or 5-ethoxy-2-phenyloxazole, also give mainly *N*-benzoylisocyanate as a product or intermediate, depending on the nucleophilicity of the leaving group <91JHC805>. Oxazole itself gives *N*-formylformamide, which formylates a variety of amines and alcohols <89TL1561>.



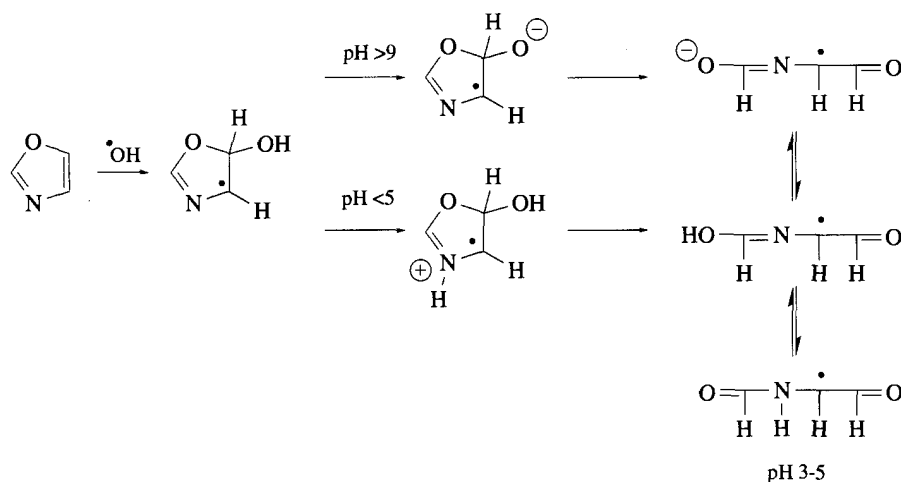
Scheme 20

The reduction of three phenyl-substituted oxazoles with potassium in THF led to ring-cleaved products <90CJC969>. 2,4,5-Triphenyloxazole gave a mixture of *N*-(1,2-diphenylethyl)benzamide (**71**) and benzoic acid, whereas 4,5-diphenyl-2-methyloxazole and 2,4-diphenyl-5-methyloxazole gave *N*-vinylamides (**72**) and benzoic acid (Scheme 21). The reduction of oxazole with nickel-aluminum alloy in potassium hydroxide solution gave 2-(methylamino)ethanol <87JOC1043>. The reagent did not reduce highly substituted oxazoles, such as 2,4,5-trimethyloxazole.

Hydroxyl radical, phosphate radical anion, and sulfate radical anion add to the 5 position of oxazole <90JPC1887>. The hydroxyl radical adduct is stable at pH 5–9, but reacts further above or below that range to give a ring-opened product (Scheme 22).



Scheme 21



Scheme 22

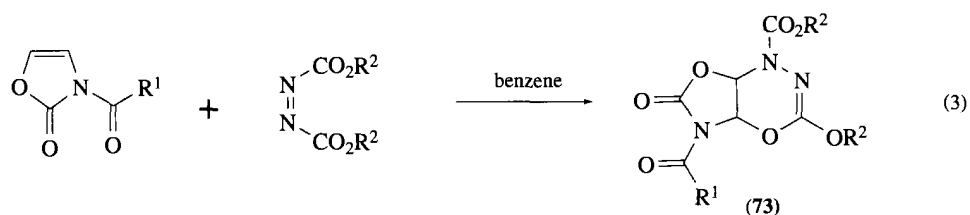
3.04.6 REACTIONS OF NONCONJUGATED RINGS

3.04.6.1 Isomers of Aromatic Compounds not in Equilibrium with Oxazoles: Oxazolones

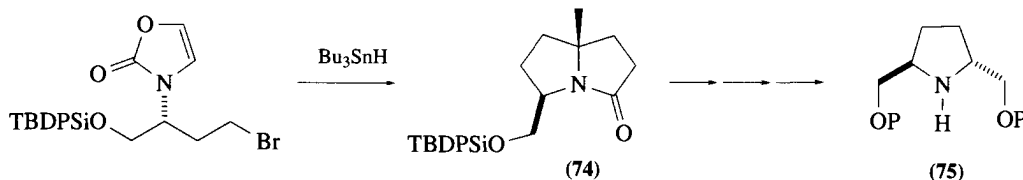
Although there are five possible oxazolones, most of the chemistry reported since the 1980s concerns the 5(4*H*) isomers, the azlactones. There has been nothing new on 2(5*H*) or 5(2*H*)-oxazolones.

3.04.6.1.1 2(3*H*)-Oxazolones

The 2(3*H*)-oxazolones react with electrophiles and nucleophiles as detailed in <84CHEC-I(6)177>. The 4,5 double bond participates in thermal [4 + 2] cycloaddition reactions. With dialkyl azodicarboxylates the addition occurs at 80°C to give the cycloadducts (73) regioselectively and in 83–93% yields (Equation (3)) <92CPB1077>. With a chiral substituent attached to N-3, diastereoselectivities as high as 72% have been obtained. Cycloadditions with cyclopentadiene or benzofuran require higher temperatures and longer reaction times, but can yield highly efficient chiral oxazolidin-2-one auxiliaries <94TL721>.



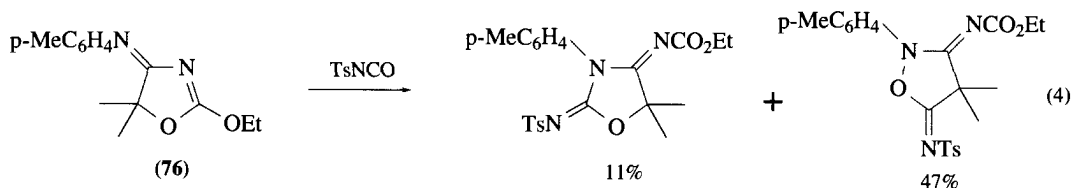
The 4,5 double bond of 2(3*H*)-oxazolones also serves as the radical acceptor in an enantioselective intramolecular radical cyclization reaction $\langle 94CC455 \rangle$. The initially formed pyrrolooxazolidinones (**74**) may be further transformed into 2,5-disubstituted pyrrolidines (**75**) (Scheme 23).



Scheme 23

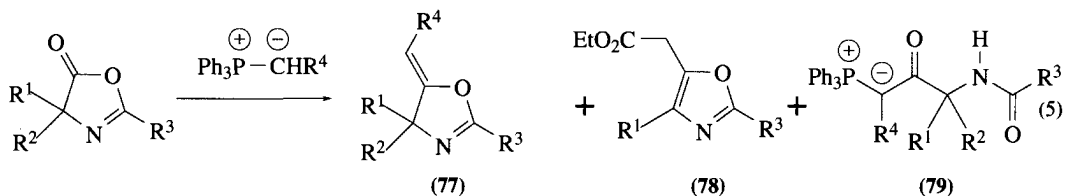
3.04.6.1.2 4(5*H*)-Oxazolones

The imine of a 4(5*H*)-oxazolone (**76**) reacts with electrophilic heterocumulenes to give rearranged products similar to that obtained in the Boulton–Katritzky interconversion (Equation (4)) $\langle 85CC1614 \rangle$.



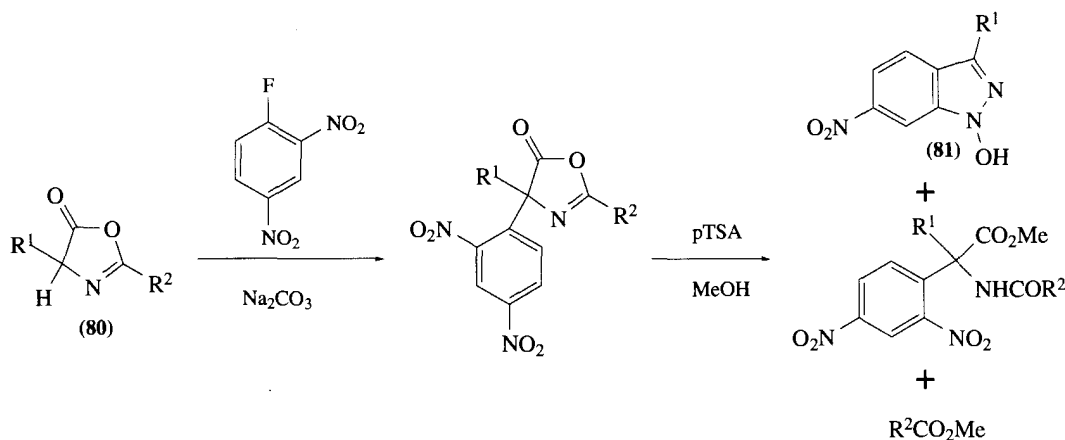
3.04.6.1.3 5(4*H*)-Oxazolones

The 5(4*H*)-oxazolones undergo a variety of reactions, including those with nucleophiles at positions 2 and 5. Triphenylphosphonium methylides react to give 5-alkylidene derivatives (**77**) in addition to oxazoles (**78**), when isomerization is possible, and ring-opened products (**79**) (Equation (5)) $\langle 88CB1519 \rangle$. The reaction of *o*-phenylenediamine with 5(4*H*)-oxazolones in benzene gives ring-opened amides that cyclize to the corresponding benzamidazoles when treated with acetic acid $\langle 87IJC(B)73 \rangle$.

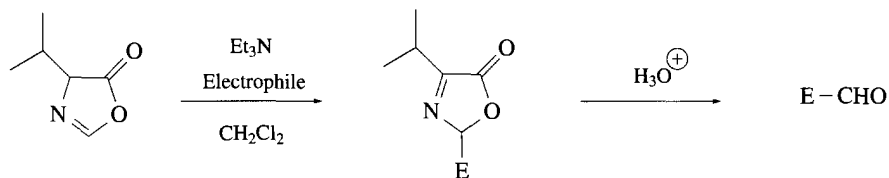


The primary site of electrophilic attack on 5(4*H*)-oxazolones is at position C-4. The oxazolones are activated by deprotonation. For example, a variety of 2,4-disubstituted-5(4*H*)-oxazolones (**80**) react with 1-fluoro-2,4-dinitrobenzene and sodium carbonate to give 2,4,4-trisubstituted products $\langle 88CB67 \rangle$. When the products are refluxed in methanol containing a catalytic amount of *p*-toluenesulfonic acid, they rearrange to 1-hydroxyindazoles (**81**) (Scheme 24). Apparently, under certain conditions the site of electrophilic attack may be diverted to the 2 position $\langle 93TL3907 \rangle$. Methylene chloride solutions of α,β -unsaturated aldehydes, ketones, and esters containing a catalytic amount

of triethylamine react by Michael addition to the double bond (Scheme 25). Simple aldehydes react at the carbonyl carbon and, upon hydrolysis, give substituted aldehydes.



Scheme 24



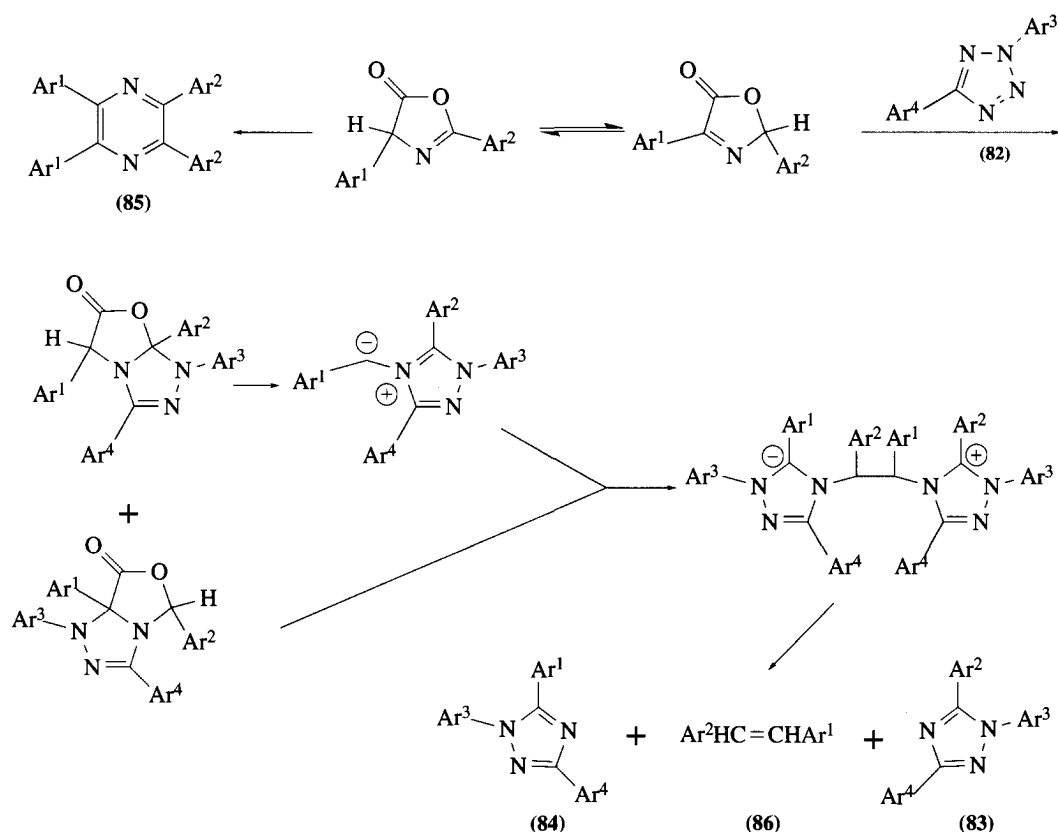
Scheme 25

Although in most cyclization reactions the 5(4*H*)-oxazolones react as 1,3-dipolar reactants (azomethine ylides) through the mesoionic tautomers, they serve as dipolarophiles with nitrile imines <92H(34)315>. The nitrile imines, generated by the thermal decomposition of tetrazoles (82), add across the 2,3 double bond to generate triazoles (83) after further reaction (Scheme 26). Since the 5(4*H*)-oxazolones with a hydrogen at position 4 are in equilibrium with the 5(2*H*)-oxazolones under the reaction conditions, the addition of the nitrile imine also occurs across the 3,4-double bond of these compounds to afford an isomeric triazole (84). Pyrazines (85), which are products of the thermal decomposition of 5(4*H*)-oxazolones <76HCA2149>, as well as diarylethylenes (86), are also formed.

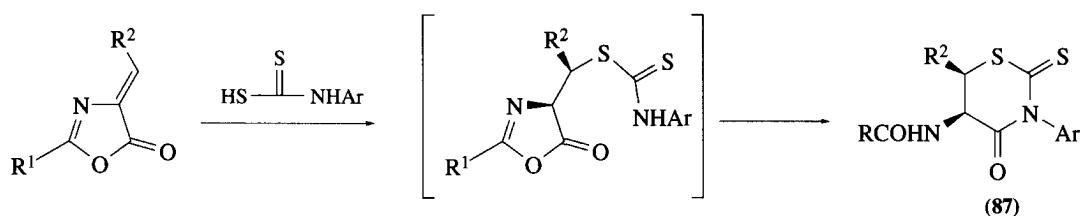
5(4*H*)-oxazolones serve as useful intermediates for the resolution of *N*-acyl- α,α -disubstituted amino acids <92HCA1666>. 4,4-Disubstituted-oxazolones, formed from the racemic amino acids, are reacted with nonracemic amino acids or peptides by nucleophilic attack on the C-5 carbonyl, followed by ring opening. The diastereomers are easily separated. The amino acids are recovered by reforming the oxazolones using HCl(g) in toluene and hydrolyzing these intermediates with HCl(aq) in dioxane. 4-Monosubstituted-oxazolones are easily racemized, but can be obtained pure by synthesis from amino acids and a water soluble carbodiimide using methylene chloride as solvent <88CJC2540>.

4-Alkylidene- and 4-arylidene-5(4*H*)-oxazolones, which are versatile intermediates for the synthesis of didehydroamino acids, offer another site, $\text{C}\alpha$, for reaction. The propensity for nucleophiles to attack at this position has been exploited in the synthesis of other heterocycles. *N*-Acyldithiocarbamic acids add in Michael fashion, and the intermediates undergo cyclization with concomitant oxazolone ring opening to furnish 2-thioxo-1,3-thiazin-4-ones (87) (Scheme 27) <92S919>.

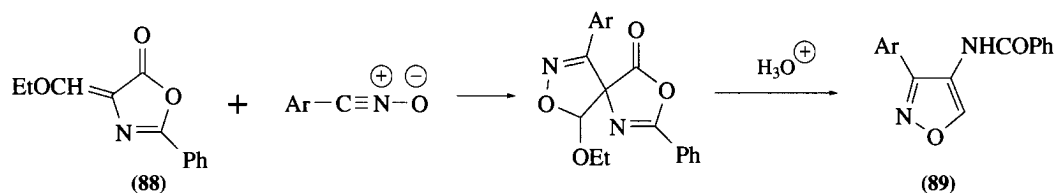
The *exo* double bond of 4-alkylidene and 4-arylidene-5(4*H*)-oxazolones undergoes cycloaddition reactions with 1,3-dipolar reagents. For example, nitrile oxides add to 2-phenyl-4-ethoxymethylene-5(4*H*)-oxazolone (88) to give spirocyclic products that may be hydrolyzed to 4-aminoisoxazoles (89) (Scheme 28) <92JHC251>. Unsaturated 5(4*H*)-oxazolones also serve as dienophiles. The (*Z*) isomer of 2-phenyl-4-benzylidene-5(4*H*)-oxazolone reacts with cyclopentadiene in the presence of aluminum chloride or titanium tetrachloride to afford a mixture of *exo* and *endo* cycloadducts <90S1114>.



Scheme 26



Scheme 27

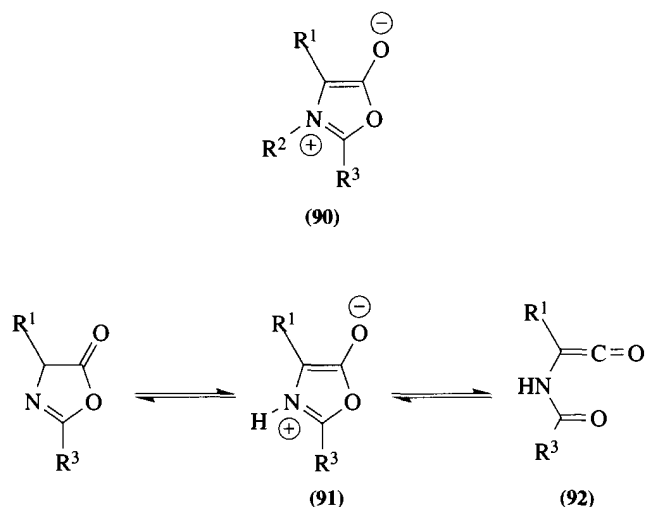


Scheme 28

3.04.6.2 Mesoionic Compounds

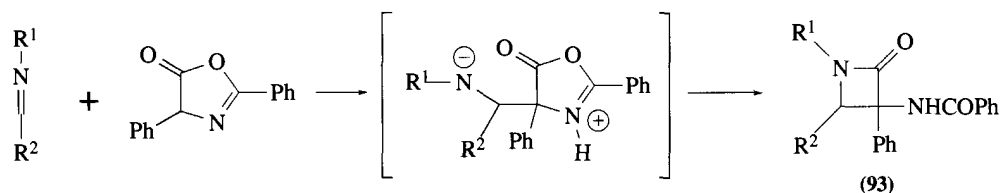
The most studied of the mesoionic compounds are the münchnones (**90**), which are 3-substituted-5(4*H*)-oxazolones with at most one substituent on the 4 position. They react in such a 1,3-dipolar form or in a ring-opened ketene form. Reactions of 3-unsubstituted-5(4*H*)-oxazolones may also proceed through their mesoionic (**91**) or ketene (**92**) tautomers (Scheme 29).

As the body of data has grown it has become evident that the course of the reaction of these compounds depends on the substitution pattern of the reacting species and on the presence or



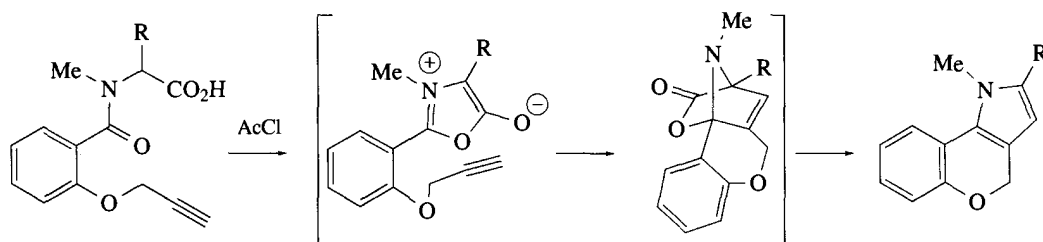
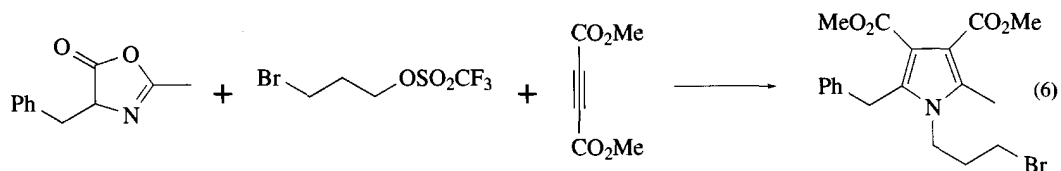
Scheme 29

absence of the N-3 substituent on the oxazolone. The reaction of the münchnones with imines proceeds through the ketene tautomer to give β -lactam products $\langle 80AG(E)966 \rangle$. The 3-unsubstituted 5(4*H*)-oxazolones also react with *N*-alkyl imines to afford β -lactam products (93), but *N*-aryl imines do not react $\langle 85H(23)1611 \rangle$. To account for the results, a stepwise mechanism was suggested (Scheme 30).



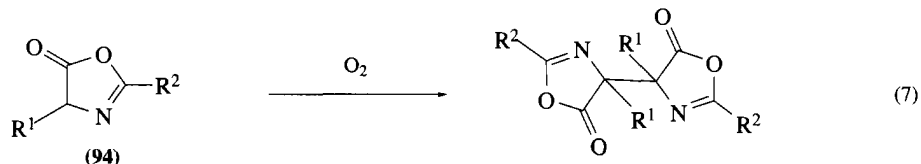
Scheme 30

The reaction of the mesoionic münchnones with alkynes affords pyrroles. The azlactones afford *N*-unsubstituted pyrroles. If the azlactones are treated with a strong alkylating agent such as methyl trifluoromethylsulfonate or triethyloxonium tetrafluoroborate in the presence of 2,6-di-*t*-butylpyridine and the alkyne, *N*-substituted pyrroles are obtained $\langle 88S999 \rangle$. Pyrroles with an *N*-alkyl substituent that contains a reactive group, such as a bromine atom, may be prepared by this method (Equation (6)). An intramolecular 1,3-dipolar cycloaddition of an alkyne with a münchnone affords a fused pyrrole (Scheme 31) $\langle 89JCS(P1)361 \rangle$.



Scheme 31

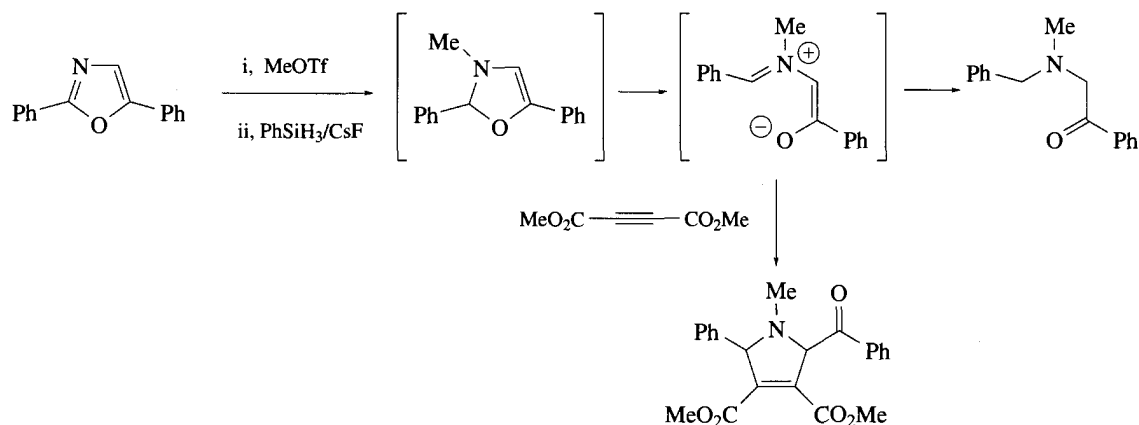
Oxidation of 2,4-diaryl-5(4*H*)-oxazolones (**94**) with molecular oxygen gives dimeric products (Equation (7)) <91T5681>. The reaction rate is dependent on the solvent and oxygen concentration. The oxidation is faster in highly polar solvents, such as DMSO and DMF, that favor the mesoionic form. The dimers are also formed by nickel peroxide oxidation <85T2341>.



3.04.6.3 Dihydrooxazoles

3.04.6.3.1 2,3-Dihydrooxazoles

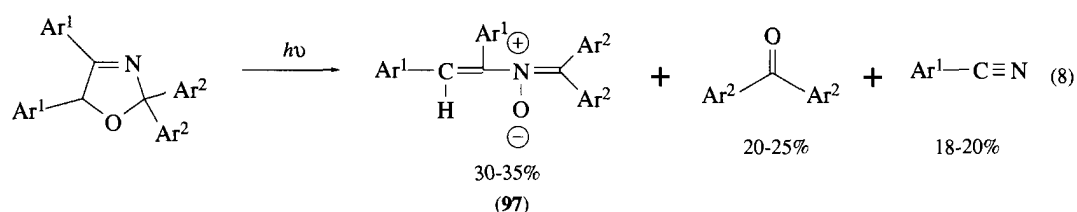
There has been little chemistry reported on 2,3-dihydrooxazoles because usually only those highly substituted with electron-withdrawing groups are stable. 2,3-Dihydrooxazoles substituted in the 4 position with hydrogen or an alkoxy group are unstable and ring open to give azomethine ylides <88JA3238>. These react with excess reducing agent to give amino ketones or, in the presence of reactive dipolarophiles, undergo synthetically useful [3 + 2] cycloadditions (Scheme 32).



Scheme 32

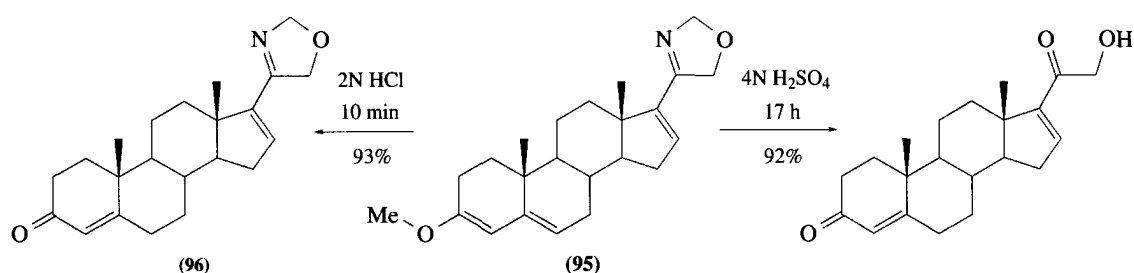
3.04.6.3.2 2,5-Dihydrooxazoles

2,5-Dihydrooxazoles are also uncommon. They have been used as protecting groups for α -hydroxy ketones <94JOC5650>. The dienol ether steroid derivative (**95**) can be selectively hydrolyzed to the enone (**96**) in 93% yield without affecting the 2,5-dihydrooxazole ring. The latter is cleaved in high yield under more forcing conditions (Scheme 33). The photofragmentation of tetraaryl-2,5-dihydrooxazoles affords *N*-oxides of 2-azabutadienes (**97**) in low yield along with diaryl ketones and aryl nitriles (Equation (8)) <91IJC(B)527>.



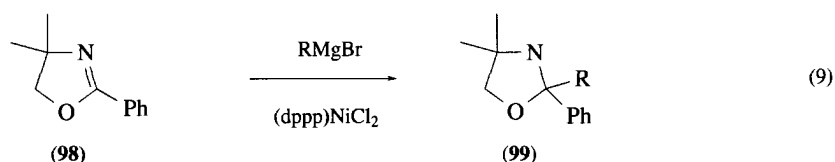
3.04.6.3.3 4,5-Dihydrooxazoles

Because they undergo a variety of reactions, the 4,5-dihydrooxazoles have been proven to be very useful in organic synthesis. They are inert to a variety of reagents, including Grignard reagents,

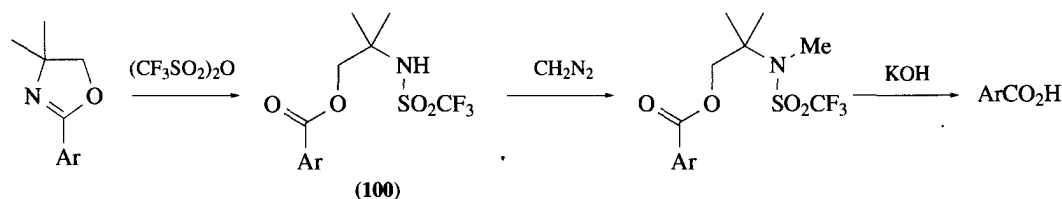


Scheme 33

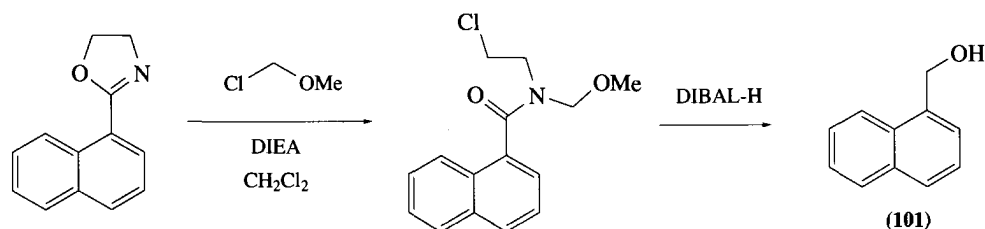
$NaBH_4$, and $LiAlH_4$, and are useful protecting groups for carboxylic acids. When conditions are modified, however, they may become reactive. Thus, in the presence of 1,3-bis(diphenylphosphino)propanenickel dichloride, Grignard reagents add to 4,5-dihydrooxazole (**98**) to give oxazolidines (**99**) in good yield (Equation (9)). Oxazoles do not react. Oxazolium salts, obtained by alkylation of the ring nitrogen, are reduced by $NaBH_4$ [66JHC531].



There are many methods for the cleavage of 4,5-dihydrooxazoles once they have served their purpose. An effective method for hydrolyzing them back to carboxylic acids employs trifluoromethanesulfonic anhydride [92SC13]. Intermediate ring-opened esters (**100**) are *N*-methylated, then saponified to the acids (Scheme 34). The oxazoles may also be converted into aldehydes or nitriles. In a one-pot, two-step procedure, 4,5-dihydrooxazoles are transformed into alcohols (**101**) [93TL4893]. Chloromethyl methyl ether converts the dihydrooxazoles into ring-opened amides in the first step, and these are reduced with diisobutylaluminum hydride (Scheme 35).



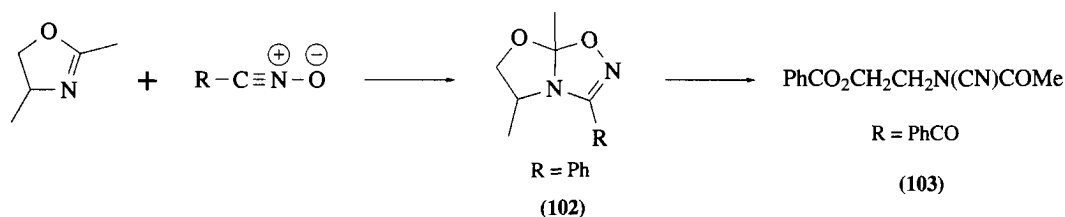
Scheme 34



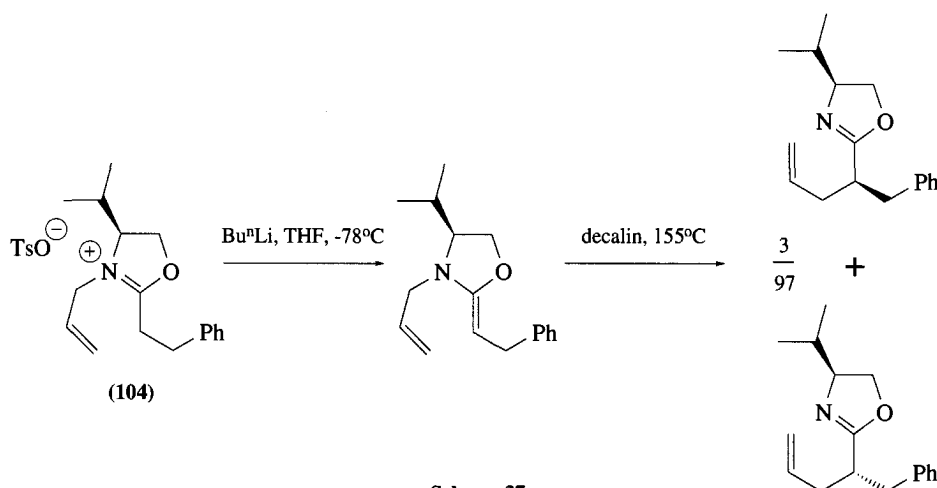
Scheme 35

4,5-Dihydrooxazoles undergo 1,3-dipolar cycloaddition reactions with nitrile oxides to afford oxazolooxadiazoles (**102**) [92T7703]. The products from the corresponding reaction with benzoyl cyanide *N*-oxide are open chain esters (**103**), which apparently arise by rearrangement of the initially formed oxazolooxadiazoles (Scheme 36). 3-Allyl-4,5-dihydrooxazoles (**104**) undergo an aza-Claisen rearrangement to afford 2-homoallyloxazoles upon treatment with *n*-butyllithium, followed by

heating in decalin to high temperature. When chiral dihydrooxazoles are employed, the products are obtained with high diastereoselectivity (Scheme 37) <88S362>.

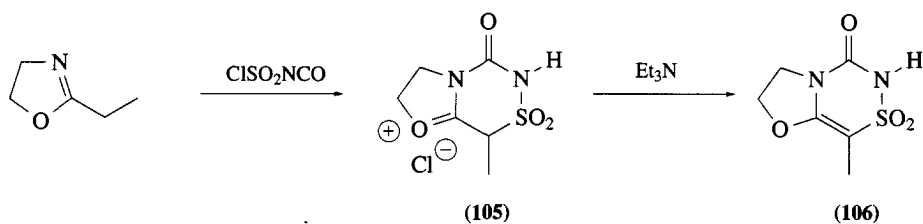


Scheme 36

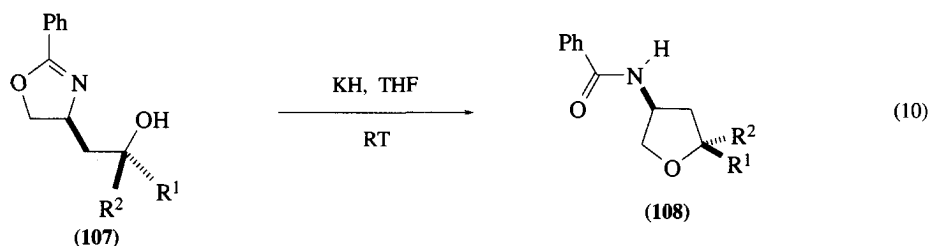


Scheme 37

Other heterocyclic ring systems may be obtained from 4,5-dihydrooxazoles. Chlorosulfonyl isocyanate reacts with 2-ethyl-4,5-dihydrooxazole to give an oxazolium-thiadiazinone (105) <93SC121>. Treatment of the product with mild base generates (106) (Scheme 38). The less reactive aryl isocyanates do not add to 4,5-dihydrooxazoles. 4-β-Hydroxyalkyl-4,5-dihydrooxazoles (107) rearrange via nucleophilic displacement at C-5 to afford tetrahydrofuran derivatives (108) <93JOC1680>. An equilibrium is established between starting material and product with the more stable of the two predominating (Equation (10)).

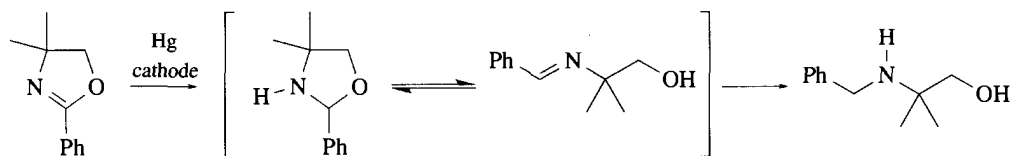


Scheme 38



Amino alcohols may be obtained from 4,5-dihydrooxazoles by a number of reductive methods, including electrochemical reduction <88T6807>. Presumably, oxazolidines are intermediates, but they

are reduced at a faster rate than the dihydrooxazoles because they are in equilibrium with their ring-opened imine tautomers (Scheme 39).

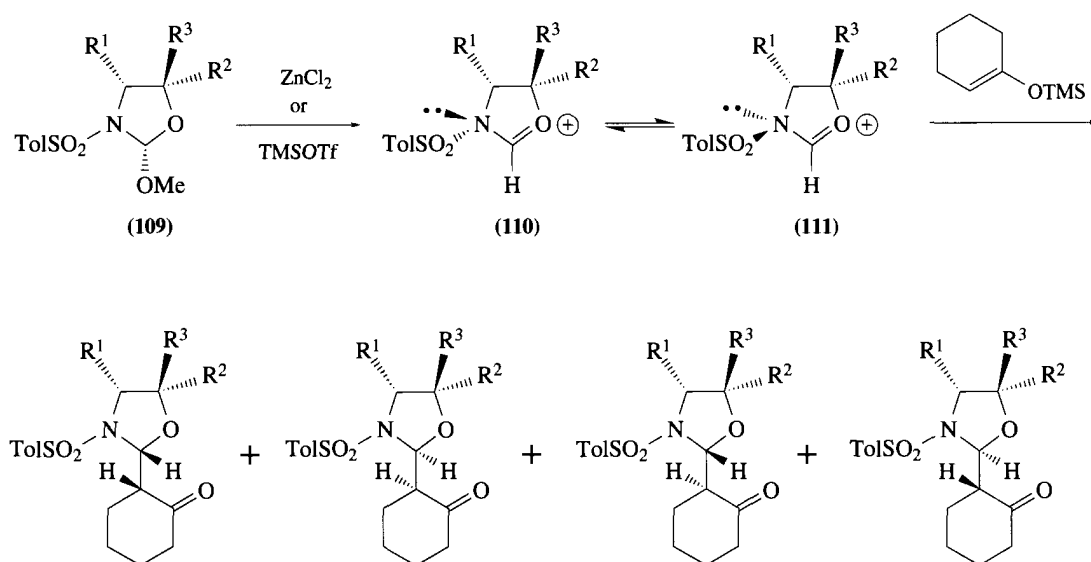


Scheme 39

3.04.6.4 Oxazolidines

The chemistry of the oxazolidines, like the dihydrooxazoles, is characterized by reactions that take advantage of the opportunity for stereoselectivity. The chiral environment is often provided by the same amino alcohols, such as phenylglycinol or norephedrine, used to prepare dihydrooxazoles.

2-Methoxyoxazolidines (**109**) are useful for the asymmetric formylation of various nucleophilic reagents including silyl enol ethers <92T6011>, trimethylsilyl cyanide <93SL921>, enamines <90TL4223>, and allyl silanes. The oxazolidines require an electron-withdrawing group, which is usually *p*-toluenesulfonyl or carbobenzyloxy, attached to the ring nitrogen. A Lewis acid is needed to assist in the ionization of the 2-methoxy group to afford cationic oxazolium species, which have been studied by NMR <92T1343>. The intermediate oxazolium cations can exist as a mixture of rapidly equilibrating conformational isomers (**110**)–(**111**) that can react with the TMS enol ether of cyclohexanone, for example, to give four isomeric products (Scheme 40). The substituents R^1 – R^3 determine the position of the equilibrium. With large R^1 the equilibrium is shifted towards (**111**), but both faces are blocked affording no selectivity. With a small R^1 (Me) and large R^3 (Ph) (**111**) again is favored, but the facial selectivity can be excellent. Various cyclic TMS enol ethers give the adducts in 46–91% yield and from 50 : 50 to >95 : 5 diastereoselectivity about the new bond.

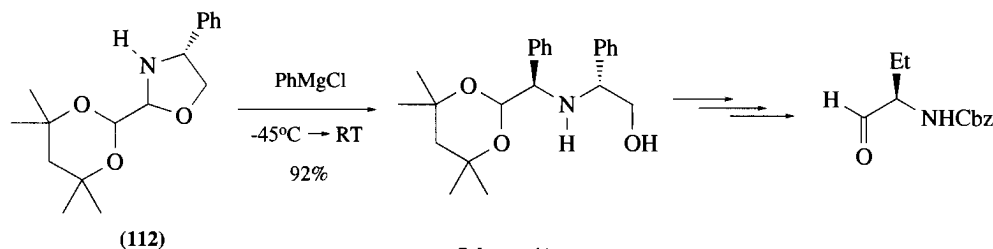


Scheme 40

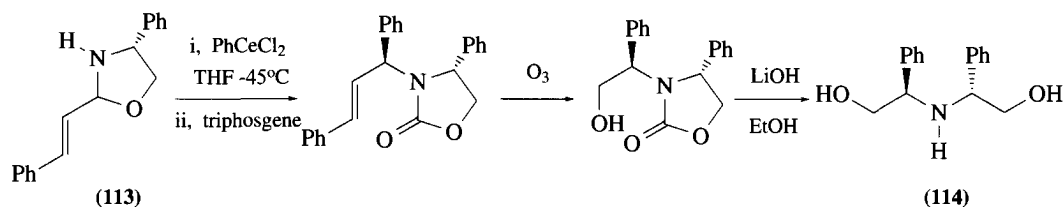
The reaction of nucleophiles with 2-alkyl-2-methoxyoxazolidines offers a general method for asymmetric acylation <91T7925>. The 2-methyl derivative reacts with allyl tin reagents in the presence of BF_3 to afford the adducts in good yields. Because of the limited stability of the intermediate oxazolium species, the less reactive allyl silane reagents give products in only low yield.

Oxazolidines lacking an ionizable group in the 2 position also react with a variety of nucleophiles, albeit stronger ones, such as Grignard and zinc reagents. The reactions proceed with high diastereo-

selectivity, most likely through the imine tautomers, to furnish ring-opened amino alcohols. Phenyl glycinol and its *N*-substituted analogues are generally used to prepare the oxazolidines because the amino alcohol products may be cleaved to amines by simple hydrogenolysis or oxidation with lead tetraacetate. In the addition of methyl Grignard to a series of *N*-alkyl-substituted-2,4-diphenyl-oxazolidines, the selectivity improved with increased steric bulkiness of the alkyl group <90CPB2429>. 2-Acetal-substituted oxazolidines, particularly the cyclic one derived from 2,4-dimethyl-2,4-pentanediol (**112**), are useful substrates for the preparation of α -amino aldehydes <94TL7489>. Grignard reagents add to them in 90% to >98% diastereoselectivity (Scheme 41). The addition of phenylcerium dichloride to oxazolidine (**113**) affords tridentate chiral ligand (**114**) after ozonolysis and ring opening (Scheme 42) <94TL7533>.

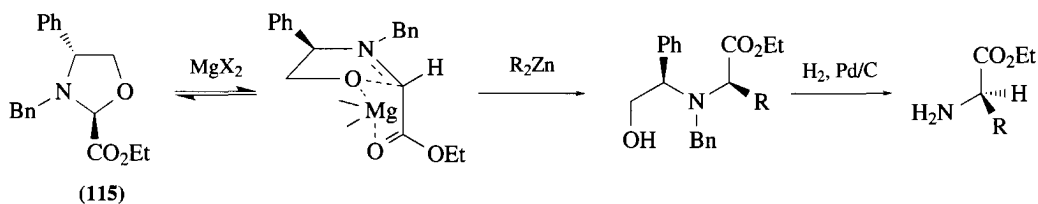


Scheme 41

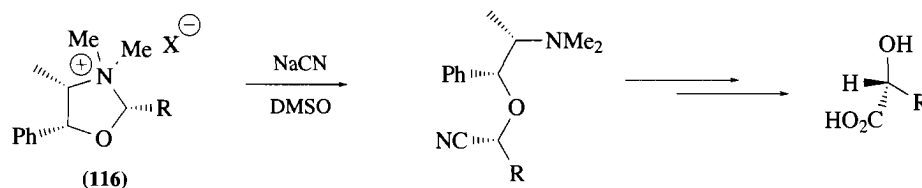


Scheme 42

Addition of zinc reagents to 2-ethoxycarbonyl-oxazolidines (**115**), followed by hydrogenolysis, affords amino acid esters in 42–56% overall yield (Scheme 43) <92TL4743>. Diastereoselectivities in the initial addition are 72–94%. Dialkyl zinc alone does not react, but addition occurs when the reagent is accompanied by magnesium halide or is prepared from an equimolar mixture of zinc halide and alkyl magnesium halide. Amino acid esters are also obtained by ring-opening of *N*-benzyl-oxazolidines with diethylaluminum cyanide, followed by hydrolysis and hydrogenolysis <92SL45>. Oxazolidinium salts (**116**) are ring-opened by sodium cyanide by cleavage of the C(2)—N bond <93TL8325>. α -Hydroxycarboxylic acids are obtained upon hydrolysis (Scheme 44).



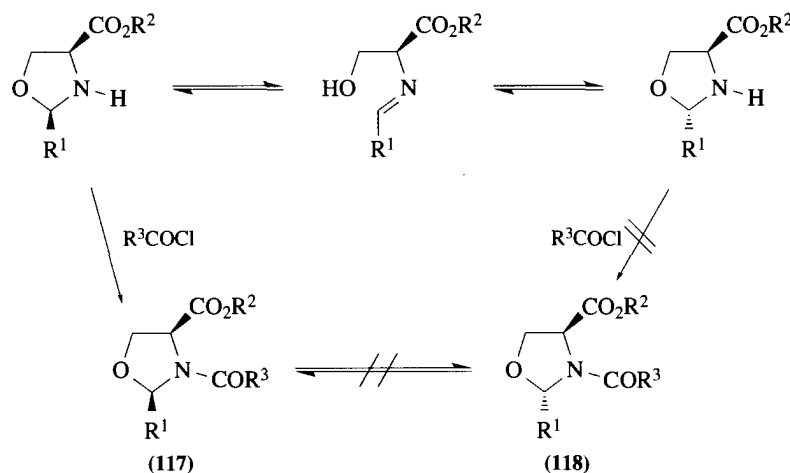
Scheme 43



Scheme 44

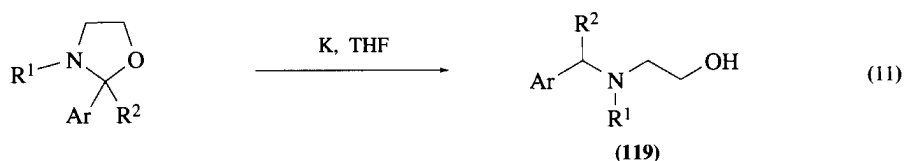
As a consequence of the tautomeric equilibrium of oxazolidines, acylation of 2,4-disubstituted oxazolidines that are a 1:1 mixture of C-2 stereoisomers affords predominately the *cis* product

(117) <83CL1361>. The bulkier the acylating agent, the greater the *cis:trans* ratio of the products. Apparently, attack by acid chlorides on the *trans* isomer (118) is sterically hindered on both faces, whereas one face is open on the *cis* isomer (Scheme 45).



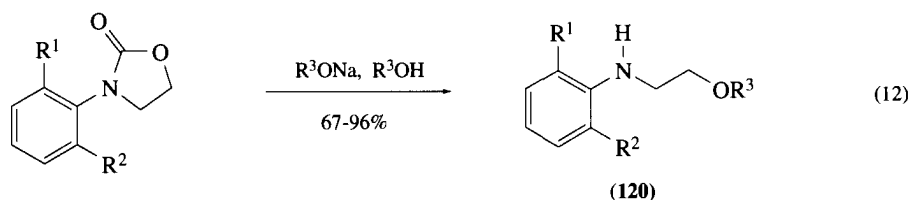
Scheme 45

N-Substituted 2-aryloxazolidinones are reductively cleaved by potassium metal in THF to give amino alcohols (119) in 60–97% yields (Equation (11)) <93JOC6707>. 2-Alkyl analogues are unreactive, suggesting that electron transfer to an aromatic π^* orbital is the first step in the mechanism.

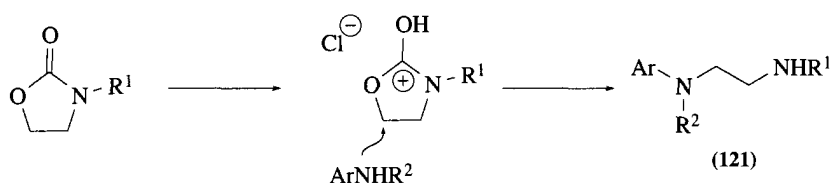


3.04.6.5 Oxazolidinones

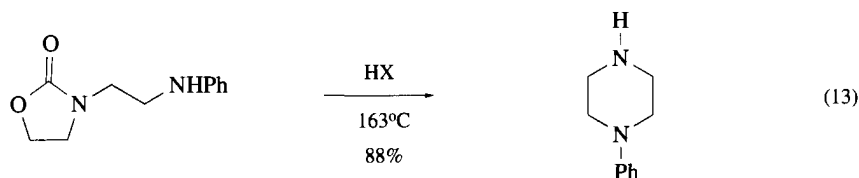
Most of the chemistry associated with 2-oxazolidinones employs the heterocycles as chiral auxiliaries and takes place on a nitrogen substituent (see Section 3.04.8). 2-Oxazolidinones unsubstituted in the 4 and 5 position give ring-cleaved products by attack of nucleophiles at C-5, followed by loss of CO_2 . 3-Aryl-2-oxazolidinones react with sodium alkoxides to afford *N*-(2-alkoxyethyl)anilines (120) (Equation (12)) <88TL5095>.



The hydrochloride salts of anilines cleave N —H or *N*-substituted 2-oxazolidinones at $>130^\circ C$ to give diamines (121) <92JOC6257>. The anilines themselves do not react, and anilines substituted on the aromatic ring with electron-withdrawing groups give higher yields than those with electron-donating groups. This suggests that initial protonation of the oxazolidinone is required for reaction (Scheme 46). In accord with this, thiophenols also react, but phenols and alkyl thiols, which are less acidic, do not. Even alkyl amines react, however, when the reaction is intramolecular and HCl or HBr is present (Equation (13)) <94TL7331>.

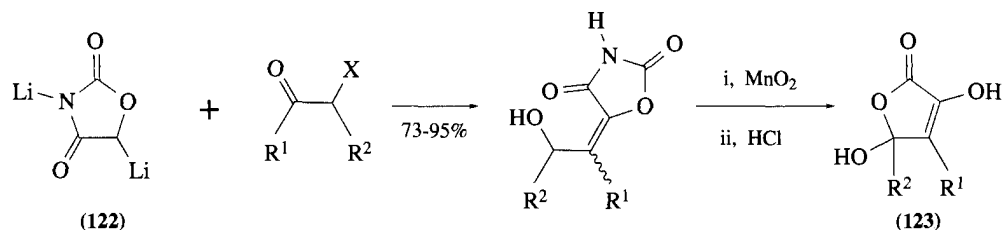


Scheme 46



3.04.6.6 Oxazolidinediones

The lithium dianion of 2,4-oxazolidinedione (**122**) reacts with α -halo ketones to give alkylidene compounds that can be transformed into 3,5-dihydroxy-2(5*H*)-furanones (**123**) by oxidation, followed by hydrolysis (Scheme 47) <92JOC4558>.



Scheme 47

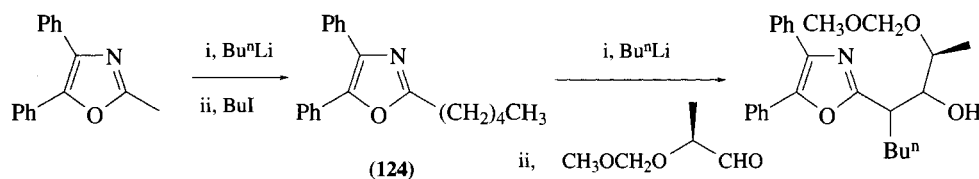
3.04.7 REACTIVITY OF SUBSTITUENTS ATTACHED TO RING CARBON ATOMS

In general, the reactions of substituents attached to oxazole are unaffected by the oxazole nucleus. When anionic chemistry is to be employed, however, the acidity of oxazole bound hydrogens, if any, must be considered as deprotonation at these sites is likely to be competitive with deprotonation at the substituents.

3.04.7.1 Reactions of 2-Alkyl Groups

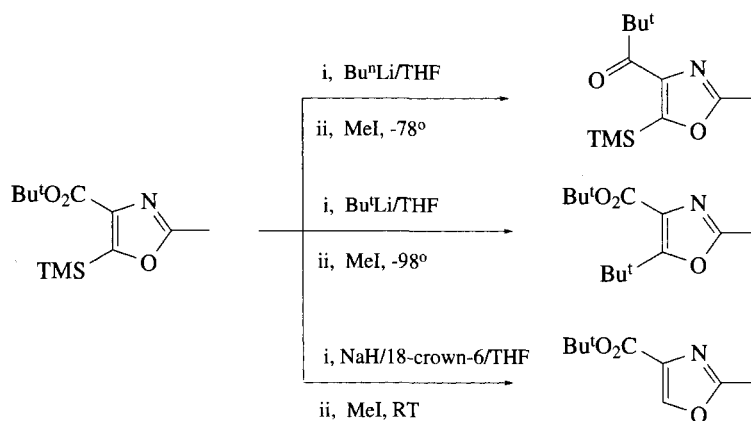
An important reaction of oxazole substituents is alkylation of the methyl group of 2-methyl-oxazole derivatives. Such a reaction provides a convergent approach to the construction of structurally complex molecules that possess an oxazole ring, such as, virginiamycin M, griseoviridin, and madumycin II. Although oxazole, like similar electron-deficient heterocycles, activates a 2-methyl substituent towards deprotonation by its electron-withdrawing effect, the deprotonation and subsequent reaction with electrophiles is not always a straightforward process. For example, chain extension of 2-methyl-5-phenyloxazole does not work at all with BuⁿLi and requires a careful attention to conditions to achieve moderate yields at best when lithiated with LDA and treated with methyl iodide or other alkylating agents <90H(30)487>. The process is dependent on the oxazole ring substituents: 2-methyl-4,5-diphenyloxazole is deprotonated with BuⁿLi at -78°C and reacts with BuⁿI to give the 2-pentyl derivative (**124**) in 93% yield <85JA1423>. The product (**124**) may be further

reacted with Bu^nLi followed by an aldehyde to give a mixture of diastereomers in 58% yield (Scheme 48).

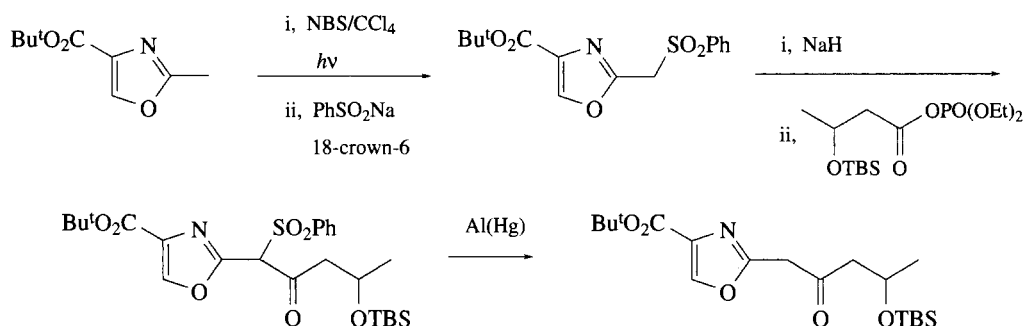


Scheme 48

Synthesis of the natural products mentioned above requires 4-alkoxycarbonyl-2-methyloxazoles as starting materials. However, deprotonation of such compounds under both kinetic and thermodynamic conditions occurs at the unsubstituted 5 position. Several solutions to this synthetic problem have been devised. It is possible to block the acidic hydrogen with a trimethylsilyl group, but deprotonation is still problematic (Scheme 49). A benzenesulfonyl group increases the acidity of the 2-methyl substituent, and the resulting anion reacts with a variety of acylating agents (Scheme 50). Modification of the 2-methyl group may be avoided if an oxazole-4-carboxylic acid rather than ester is employed (83TL4391). With the 5 position blocked with a TMS group, treatment of the oxazole with Bu^tLi gives the dianion, which reacts with iodomethane, isobutyraldehyde, and acetone to form adducts in 86%, 88%, and 90% yields, respectively.



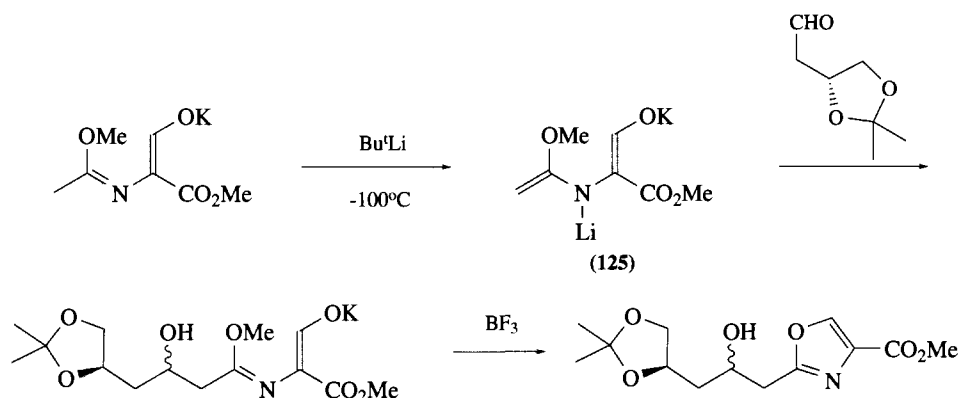
Scheme 49



Scheme 50

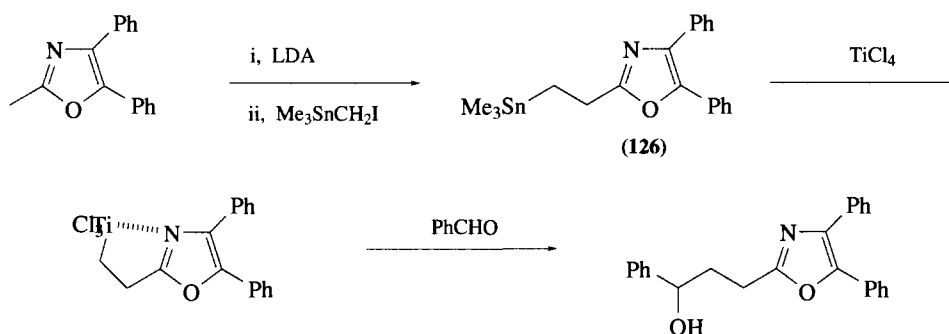
In an alternative solution to the problem, the acyclic precursor of the 4-carboxy-2-methyloxazole is metallated to furnish an amide enolate (125), which reacts with electrophiles and cyclizes to the

oxazole <86JOC5111>. While direct, this route affords products in fair to poor overall yields (Scheme 51).



Scheme 51

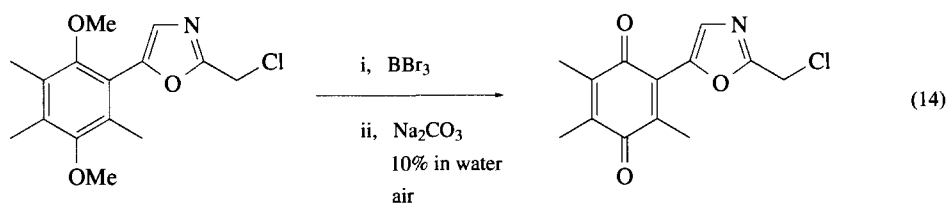
2-Methyl-4,5-diphenyloxazole may be transformed into 2-(2-(trimethylstannyl)ethyl)oxazole (126) by the deprotonation alkylation route. Treatment of (126) with titanium tetrachloride gives a propionate homoenolate equivalent that reacts with aldehydes in high yield (Scheme 52) <85JOC3942>. The need for the oxazole nitrogen atom was demonstrated.



Scheme 52

3.04.7.2 Reactions Under Oxidizing Conditions

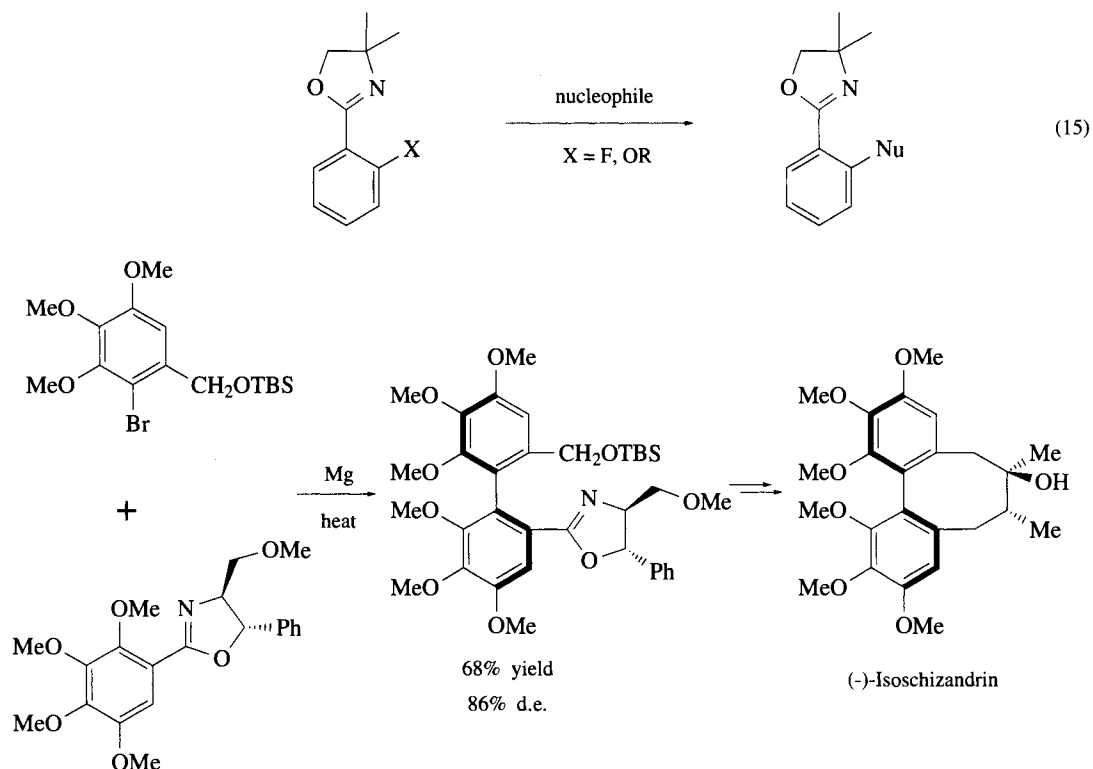
Oxidations of oxazole substituents are not usually possible, because the oxazole ring itself is reactive. An exception is the conversion of hydroquinone to benzoquinone, which was accomplished in high yield by air oxidation <93H(36)45> (Equation (14)). The oxazolyl nucleus is also stable to Sharpless oxidation conditions (Bu'OOH, diethyl tartrate, Ti(OPr')₄) provided it is sufficiently removed from the reaction site <84TL2835>.



3.04.7.3 Reactions of 4,5-Dihydrooxazole Derivatives

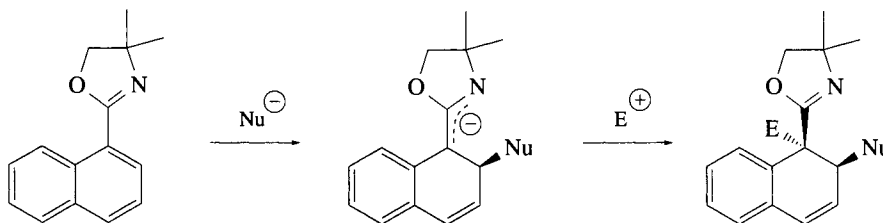
Among the many interesting and useful transformations involving 4,5-dihydrooxazoles are nucleophilic substitutions, additions, and metallations of aromatic compounds mediated by the

dihydrooxazole ring. In these reactions, the energy barrier is lowered by coordination of the incoming reactant with the oxazole nitrogen atom. Unsymmetrical biaryls that are not readily available from traditional Ullman couplings are easily obtained from substitution reactions of *ortho* alkoxy or fluoro groups with strong nucleophiles (Equation (15)). When enantiomerically pure amino alcohols are used to prepare the dihydrooxazoles, the coupling reactions proceed with high diastereoselectivity. This step in a synthesis of (–) isoschizandrin, one of many applications, is shown in Scheme 53.



Scheme 53

4,5-Dihydrooxazoles are also effective *ortho* directors for nucleophilic addition to naphthalene and some heteroaromatic derivatives. Tandem additions result if the reaction mixtures are quenched with electrophiles (Scheme 54). When chiral oxazoles are used, asymmetric syntheses, such as that of scopadulcic acid, are achieved. Although most of the oxazoles employed have chelating groups to enhance stereoselectivity, the steric bias provided by valinol or *t*-leucinol derived oxazoles is often equivalent or superior.

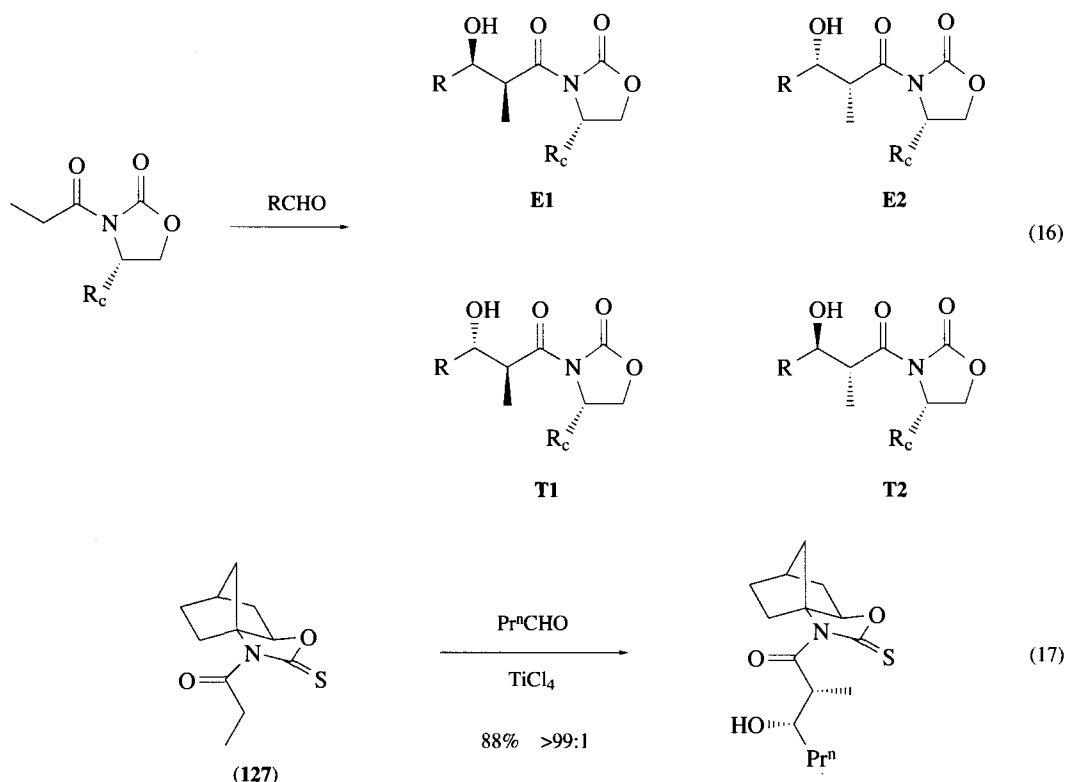


Scheme 54

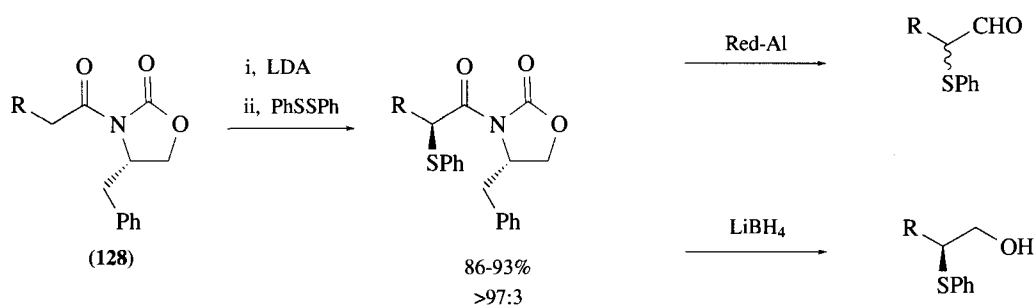
3.04.8 REACTIONS OF SUBSTITUENTS ATTACHED TO RING NITROGEN

There has been only limited development of the chemistry of nitrogen substituents of oxazole and its derivatives that takes advantage of the heterocyclic ring. An exception, however, are reactions

of substituents bound to the nitrogen of 2-oxazolidinones, which have come to play a major role in the asymmetric synthesis of organic compounds. One of the earliest and certainly most studied of these reactions in which an enantiopure oxazolidinone provides a chiral environment is the aldol reaction. The oxazolidinones are usually valine, *t*-leucine, or phenylalanine derived. The reaction of such *N*-propionyl-2-oxazolidinones with an aldehyde can theoretically lead to four isomeric aldol products (Equation (16)). Conditions have been discovered for the selective formation of three of the four diastereomers. Isomer (**E1**) predominates when an aldehyde is reacted with the boron enolate of the oxazolidinone <81JA2127>. If the aldehyde is precomplexed with TiCl_4 , the other *syn* isomer (**E2**) is the major product formed, but if the Lewis acid is SnCl_4 or Et_2AlCl , one of the *anti* isomers (**T2**) is obtained <91JOC5747>. The selectivity for the (**E2**) isomer is enhanced when a chlorotitanium enolate, prepared from a camphor based oxazolidinethione (**127**), is used (Equation (17)) <93JA2613>.



The titanium enolate of phenylalanine-derived oxazolidinone (**128**) reacts with a variety of other electrophiles, including alkyl halides, ortho esters and acetals, with high diastereoselectivity <90JA8215>. The lithium enolate of (**128**) reacts with diphenyldisulfide to give 2-phenylthio aldehydes or alcohols after reduction with Red-Al or LiBH_4 , respectively (Scheme 55) <94TL3991>.



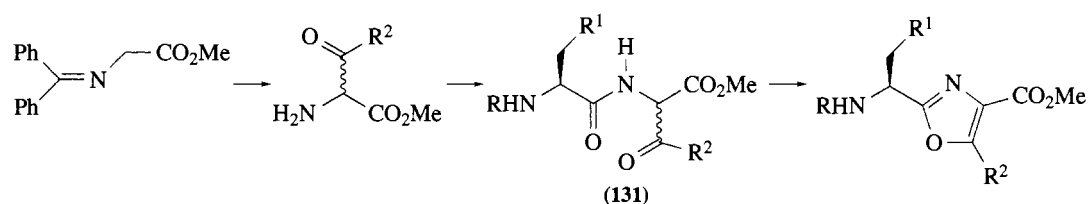
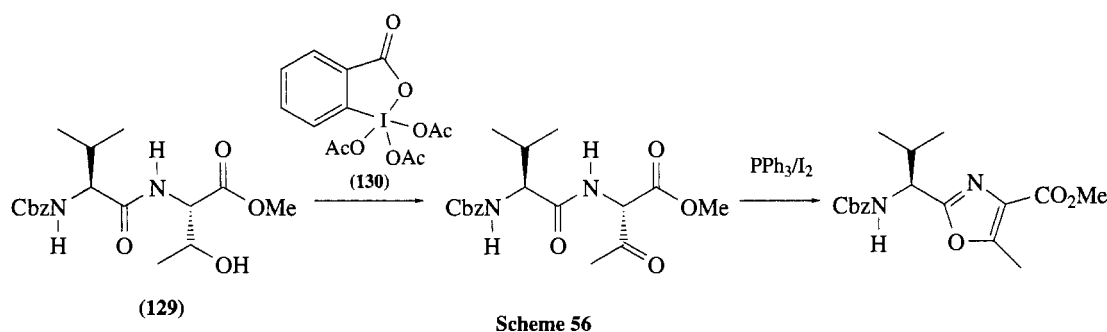
Scheme 55

α,β -Unsaturated-*N*-acyl-2-oxazolidinones are substrates for asymmetric 1,4-conjugate addition reactions <93TL2561>. The oxazolidinones are also useful dienophiles for asymmetric Diels–Alder cycloadditions <88JA1238>, and they undergo Lewis acid catalyzed ene reactions <91JOC4908>.

3.04.9 RING SYNTHESSES OF OXAZOLES CLASSIFIED BY NUMBER OF RING ATOMS IN EACH COMPONENT

3.04.9.1 One Bond

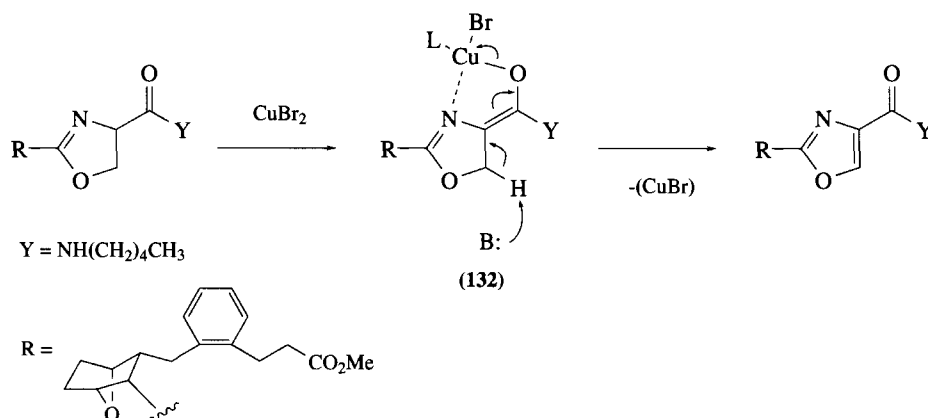
In many of the total syntheses of natural products of which an oxazole ring is part of the molecule, the oxazole ring has been generated by oxidation of an intermediate dihydrooxazole, for which there are numerous synthetic routes (see Section 3.04.11.2). This deceptively simple step is often problematic in practice, and several methodologies have been developed to effect this transformation. Often a nickel peroxide oxidant derived from nickel sulfate and sodium hypochlorite is used for the oxidation, but yields are sometimes variable and low. Manganese dioxide has also been used for the oxidation <93CL1405>. An alternative when an alkoxycarbonyl group is located in position 4 of a 4,5-dihydrooxazole is to form a selenide by reaction of the corresponding enolate with phenylselenenyl chloride, and follow this reaction with an oxidative elimination using hydrogen peroxide <92JA9434>. A 4-alkoxycarbonyloxazole may also be obtained by the well-known Robinson–Gabriel synthesis, although the sensitivity of the β -ketoester group requires mild conditions. Oxidation of the β -hydroxy group of (**129**) with Dess–Martin reagent (**130**) and cyclization using triphenylphosphine/iodine meets these needs (Scheme 56) <93JOC3604>. The latter transformation has also been accomplished with $\text{PPh}_3/\text{dbu}/\text{CCl}_4$, however, in this case the β -ketoester (**131**) was obtained by acylation of the Schiff base of an α -aminoester (Scheme 57) <93TL1901>.



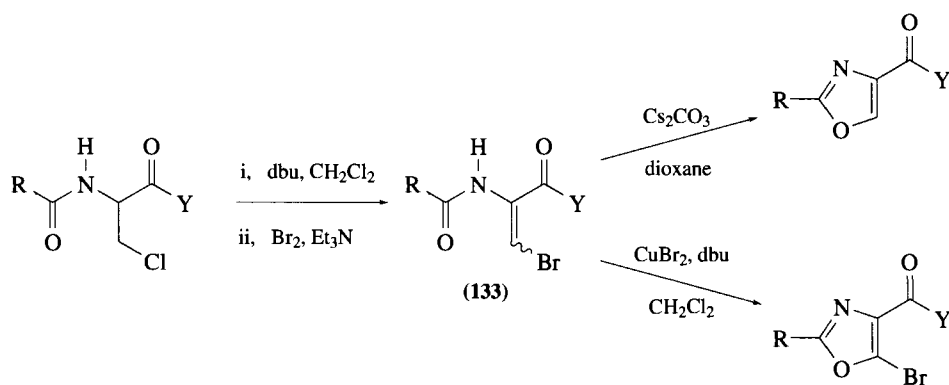
Scheme 57

A mixture of copper(II) bromide, hexamethylenetetramine, and dbu gives superior results to nickel peroxide in the direct oxidation of 4-carboxydihydrooxazoles <93JOC4494>. Since the reaction does not proceed in the absence of a 4-carboxy group and goes equally well with copper(II) triflate, a mechanism involving an intermediate copper enolate (**132**) was proposed (Scheme 58). The same product was also obtained by cyclization of the vinyl bromide (**133**) derived from a common intermediate <92TL7835>. Cyclization of the vinyl bromide under CuBr_2 conditions furnished the 5-bromooxazole (Scheme 59). A related set of conditions was reported to effect the transformation of 4-cyanomethyl-4,5-dihydrooxazole (**134**) <85TH304-01>. In this case, the use of bromine in place of

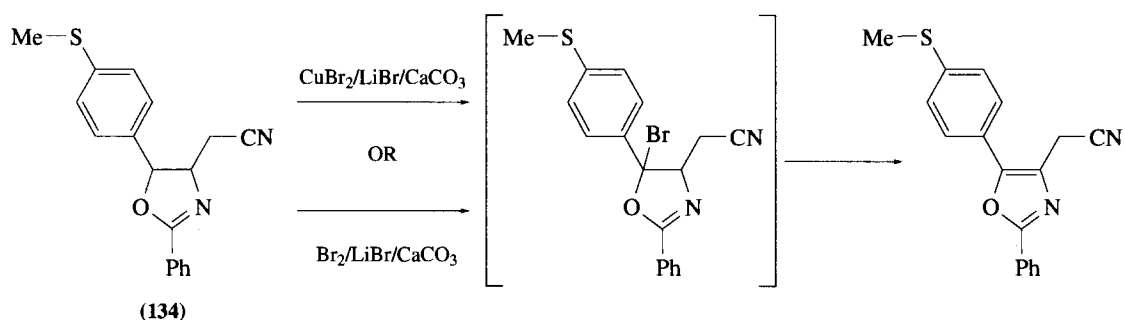
CuBr_2 gave almost the same result, suggesting that a 5-bromo derivative may be an intermediate for both reactions (Scheme 60).



Scheme 58



Scheme 59

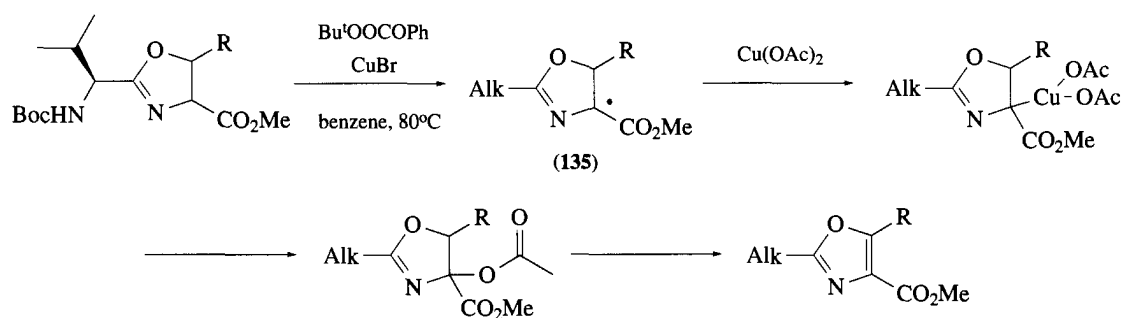


Scheme 60

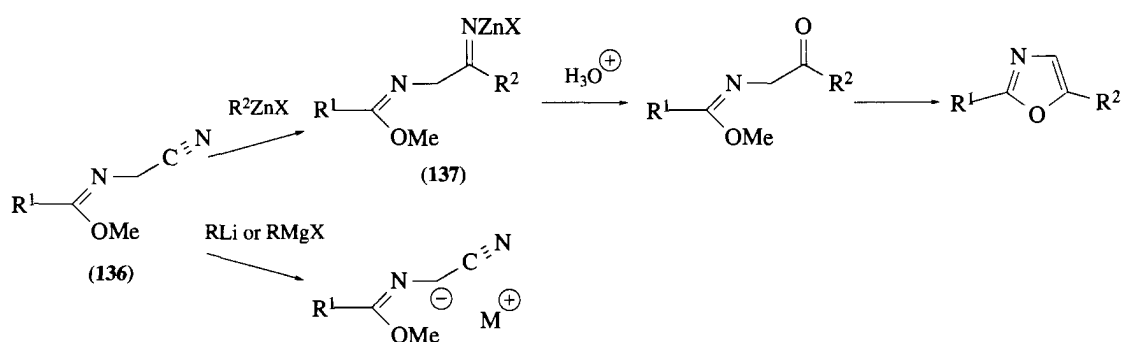
The oxidative transformation of dihydrooxazoles to oxazoles has also been achieved using the Kharasch–Sosnovsky reaction ^[94TL6803]. The first step is a hydrogen atom abstraction by a species generated from a copper-ion catalyzed (CuBr) decomposition of a peroxyester ($\text{Bu}^t\text{OOC}(\text{O})\text{Ph}$). Yields are better when a copper(II) species is added, perhaps because of faster reaction with the radical intermediate **(135)** (Scheme 61).

Several new syntheses of 2,5-disubstituted oxazoles have been reported. The reaction of allyl zinc bromides with *N*-cyanomethylimidates **(136)** leads to 2-alkyl- or aryl-5-allyloxazoles in 50–65% yields after hydrolysis of intermediate imine salts **(137)** ^[91SC1501]. The allyl zinc reagents add to the nitrile, in contrast to organolithium and magnesium reagents, which are too basic (Scheme 62).

2,5-Disubstituted oxazoles are obtained from *N*-propargylamides by acid, base, and metal catalysis ^[89JHC269]. The reaction proceeds through an allene intermediate **(138)** (Scheme 63). The base-

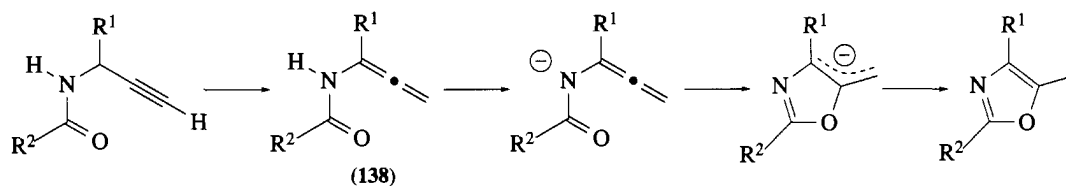


Scheme 61

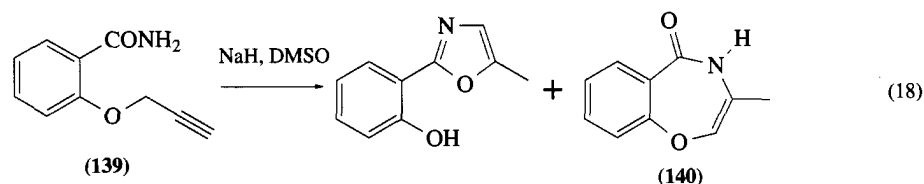


Scheme 62

catalyzed rearrangement of 2-propargyloxybenzamide (**139**) also produces an oxazole, as well as a benzoxazepinone (**140**) (Equation (18)) <90JHC343>. The mechanism is unknown, but does not appear to proceed through a likely intermediate (**141**) as this compound gives only a trace of oxazole under the same base conditions.

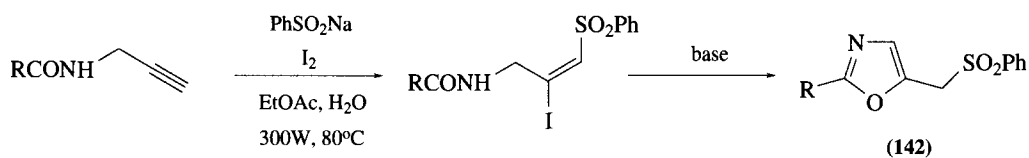
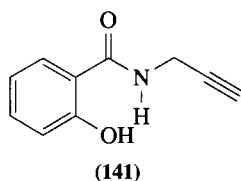


Scheme 63



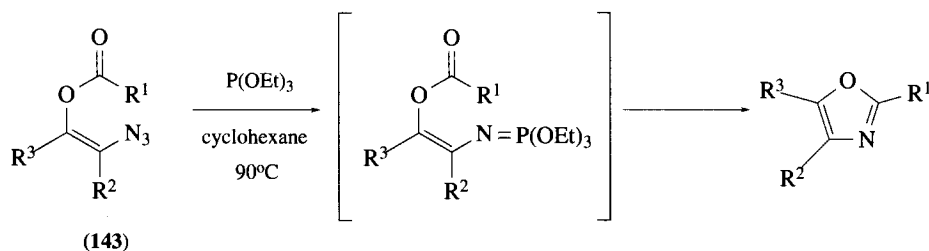
N-propargylamides are the starting material in another synthesis that gives 5-phenyl-sulfonylmethyl substituted oxazoles (**142**) rather than 5-methyloxazoles <93TL71>. The propargylamides are reacted with sodium sulfinate and iodine under photolytic conditions to give iodo(vinyl)sulfones that form oxazoles in high yield upon treatment with base (Scheme 64).

A new synthesis of 2,5-di- and 2,4,5-trisubstituted oxazoles begins with β -(acyloxy)vinyl azides (**143**) <89JOC431>. An intramolecular aza-Wittig reaction ensues upon treatment of the azides with phosphorus(III) reagents (Scheme 65). Yields of oxazoles, including furyl- and pyridyl-substituted



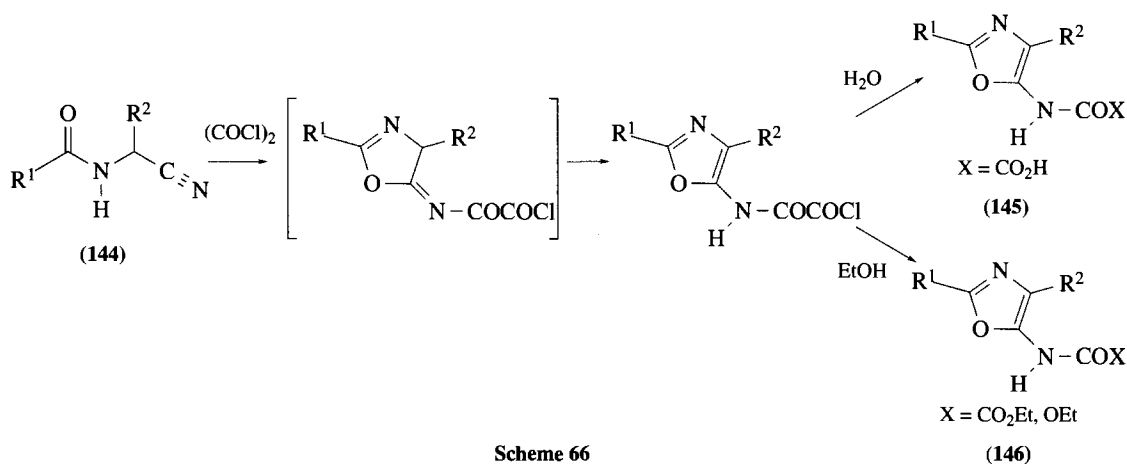
Scheme 64

oxazoles, which are difficult to obtain by routes that use strong dehydrating conditions, range from 48–93% when $\text{P}(\text{OEt})_3$ is used.

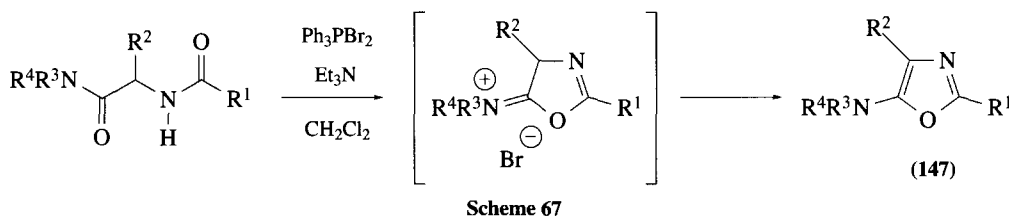


Scheme 65

There are several routes to 5-aminoxazoles. Treatment of *N*-acyl- α -aminoacetonitriles (**144**) with oxalyl chloride produces 5(4*H*)-iminooxazoles that tautomerize and afford (**145**) or (**146**) depending on workup (Scheme 66) <84T2395>. The same starting materials react with acid bromides or chlorides in the presence of BF_3 etherate in chlorinated solvents to give the *N*-acyloxazoles in good yield <83JA7703>. Diamides also react with acid halides and Lewis acids, preferably zinc bromide or chloride, to give 5-acetamidooxazoles. *N,N*-disubstituted-5-aminoxazoles (**147**) are formed when α -acylamino amides are reacted with dibromotriphenylphosphorane and triethylamine in methylene chloride <92S941>. Although this route can give 4-unsubstituted-5-aminoxazoles, 2-unsubstituted-5-aminoxazoles are not obtained from α -formylamino amides (Scheme 67).



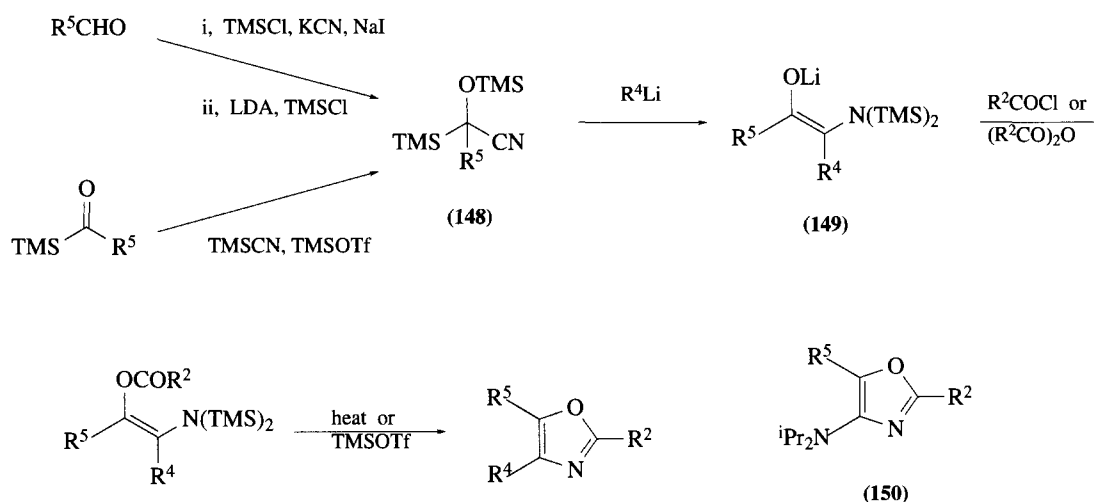
Scheme 66



3.04.9.2 Two Bonds

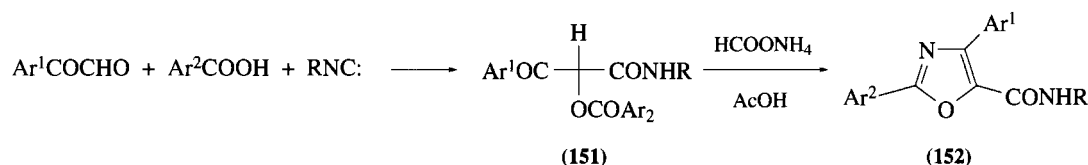
3.04.9.2.1 From [4 + 1] atom fragments: O—C—C—N + C

Control in the selection of ring substituents is an important element of oxazole synthesis. This is a feature of a new route that employs *O*-trimethylsilyl acyltrimethylsilane cyanohydrins (**148**), which are obtained from aldehydes or acyl silanes <92JOC3331>. These intermediates, which provide the C-5 substituent and four of the five ring atoms, are reacted sequentially with organolithium reagents (C-4 substituent) and acyl chlorides or anhydrides (C-2 substituent) to furnish *N,N*-bis(trimethylsilyl) enamines (**149**), which cyclize under thermal conditions or upon treatment with trimethylsilyl trifluoromethanesulfonate (Scheme 68). The range of oxazoles accessible by this method includes those with alkyl, alkenyl, phenyl, and functionalized substituents at C-2, alkyl, alkenyl, and phenyl substituents at C-4, and alkyl and phenyl substituents at C-5. The rare 4-(*N,N*-dialkylamino)oxazoles (**150**) may also be prepared.



3.04.9.2.2 From [4 + 1] atom fragments: C—C—O—C + N

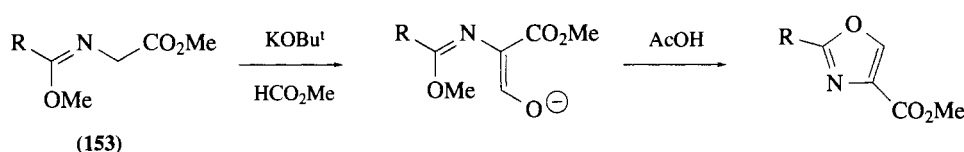
Application of the Davidson oxazole synthesis to products of the Passerini reaction has expanded the usefulness of this well-known route <91LA1107>. The α -acyloxy ketones or α -acyloxy β -keto esters employed in the Davidson synthesis are not readily available. However, the use of arylglyoxals as the carbonyl component of the Passerini reaction, along with cyclohexyl isocyanide and carboxylic acids, gives a wide variety of *N*-cyclohexyl-2-acyloxy-3-aryl-3-oxopropionamides (**151**). Reaction of these intermediates with ammonium formate in acetic acid affords *N*-cyclohexyl-2,4-diaryl-5-oxazolecarboxamides (**152**) in fair yields (Scheme 69).



Scheme 69

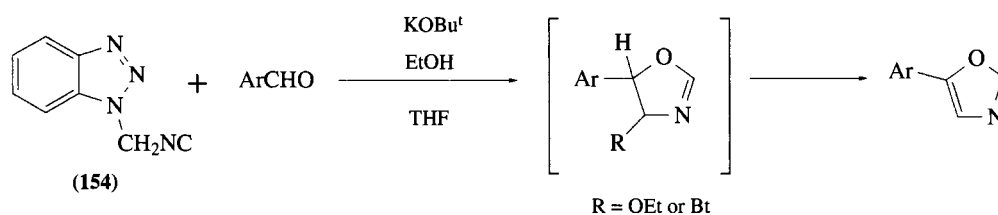
3.04.9.2.3 From [3 + 2] atom fragments: C—N—C + C—O

The Cornforth synthesis of oxazoles is useful for the preparation of 4-methoxycarbonyl derivatives, which are found in many natural products <92CC1240>. In the method, a glycine imidate (153) is reacted with strong base and methyl formate to give an enolate that cyclizes upon treatment with acetic acid (Scheme 70).



Scheme 70

The reaction of aryl aldehydes with benzotriazol-1-ylmethyl isocyanide (154), obtained in two steps from benzotriazole, formaldehyde and formamide, gives 5-aryl-substituted oxazoles in 35–69% yields (Scheme 71) <89TL6657>.



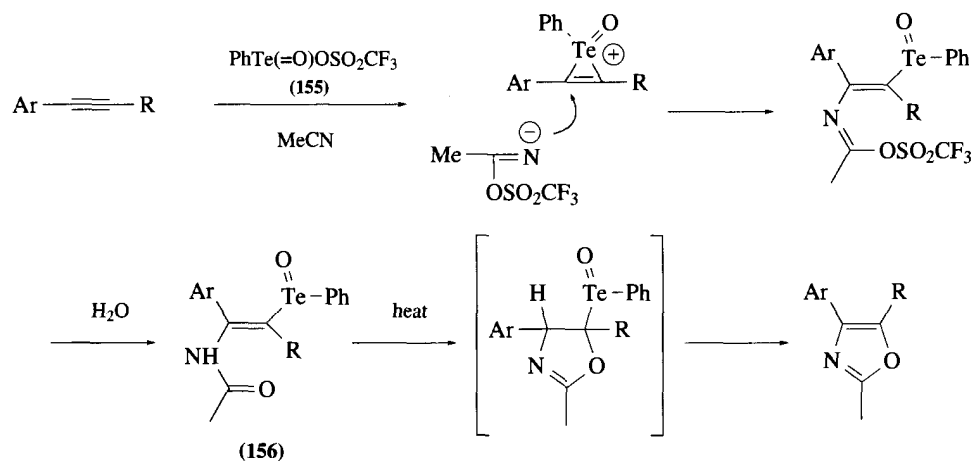
Scheme 71

3.04.9.2.4 From [3 + 2] atom fragments: N—C—O + C—C

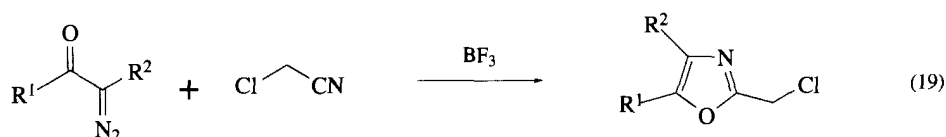
Benzenetelluranyl trifluoromethanesulfonate (155) reacts with internal alkynes in acetonitrile to afford oxazoles via a spontaneous intramolecular cyclization of the initially formed addition products (156) <92CC1070>. The reactions with aryl alkyl alkynes are regioselective. The addition products from terminal alkynes do not cyclize, but isomerize to stable (Z)-alkenes instead. The pathway shown in Scheme 72 accounts for the products.

3.04.9.2.5 From [3 + 2] atom fragments: C—C—O + N—C

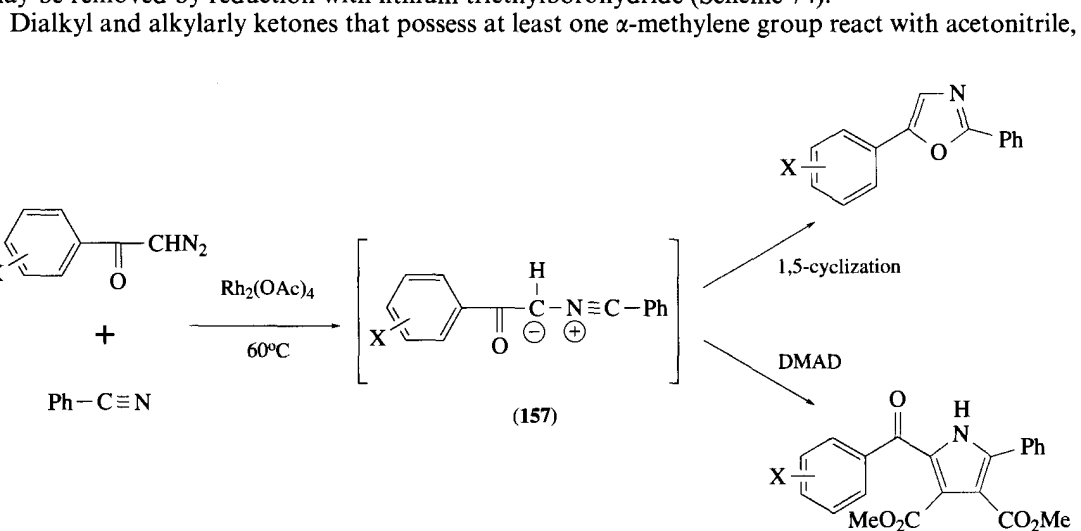
There has been continued interest in the synthesis of oxazoles from α -diazo carbonyl compounds and nitriles catalyzed by Lewis acids. The BF_3 -catalyzed reaction of α -diazoacetophenones or methyl *p*-nitrophenyldiazoacetate with chloroacetonitrile affords 5-aryl-2-chloromethyloxazoles or 2-chloromethyl-5-methoxy-4-(*p*-nitrophenyl)oxazole, respectively (Equation (19)) <89BCJ618>. The former products react with primary, secondary, and tertiary amines by nucleophilic displacement of the chloride group. Methyl or ethyl isocyanate may be used as the nitrile component to prepare 2-alkylthio-5-aryloxazoles in 65–91% yields <84BCJ2450>. Dimethylcyanamide also reacts but the yields are low.



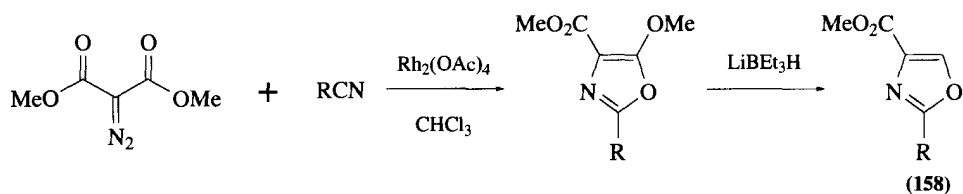
Scheme 72



A rhodium-catalyzed decomposition of α -diazooacetophenones in benzonitrile gives an intermediate acyl-substituted nitrile ylide (**157**) that cyclizes to the oxazole or may be trapped with DMAD to produce a pyrrole (Scheme 73) <92CL2197>. Ethyl cyanoformate and ethyl 3,3,3-trifluoro-2-diazopropionate form ethyl 5-ethoxy-4-(trifluoromethyl)-2-oxazolecarboxylate when heated with rhodium diacetate in chloroform <91JFC(52)149>. 4-Carbomethoxy substituted oxazoles (**158**) are available from dimethyl diazomalonate by this method <86TL5559>. The resulting 5-methoxy group may be removed by reduction with lithium triethylborohydride (Scheme 74).

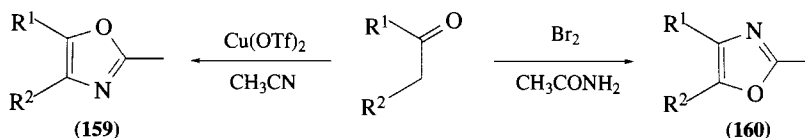


Scheme 73



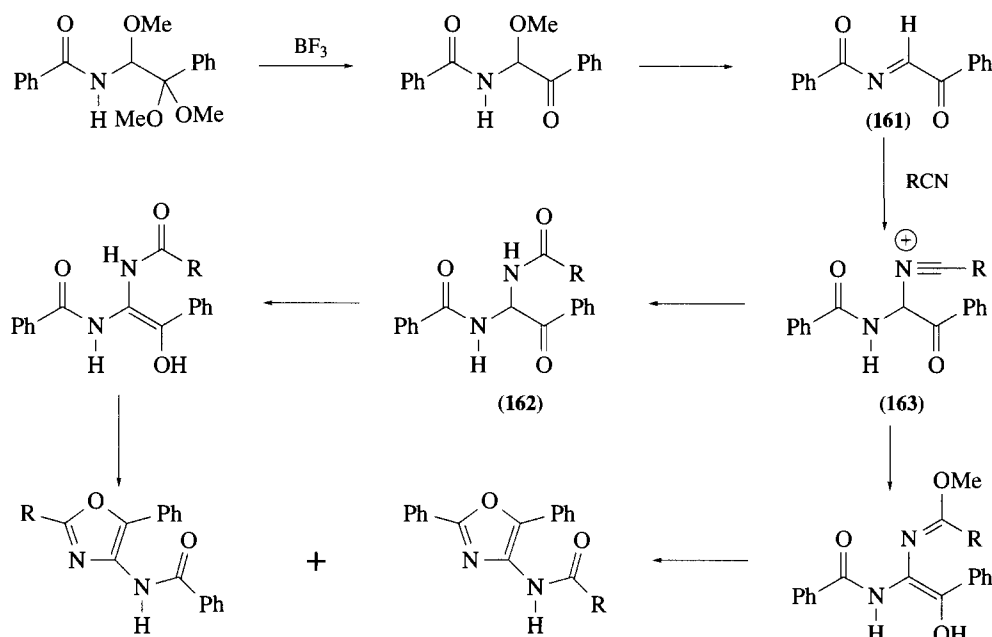
Scheme 74

copper(II) trifluoromethanesulfonate and a catalytic amount of *p*-toluenesulfonic acid to furnish 2,4,5-trisubstituted oxazoles (**159**) <83CL1355>. Methyl ketones react at the position opposite the methyl group, and ketones without an enolizable proton at this position, such as acetophenone, do not react. This reaction complements the conventional ketone plus amide routes to oxazoles (**160**) because it forms regioisomeric products (Scheme 75). The reaction is limited to nitriles that can be used as solvents <92JHC1245>.



Scheme 75

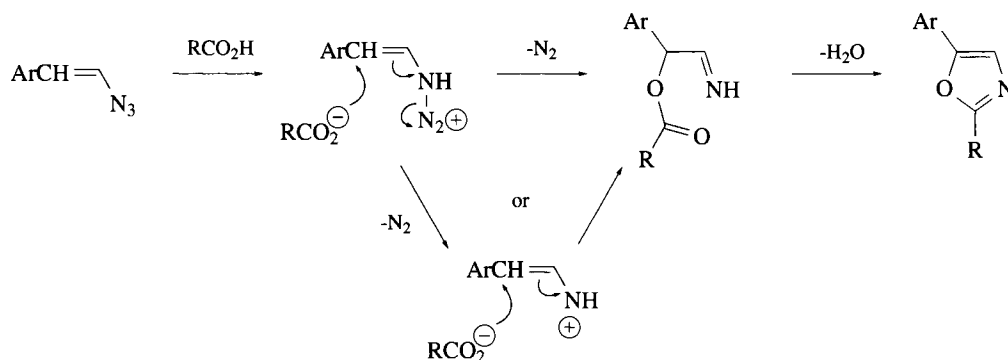
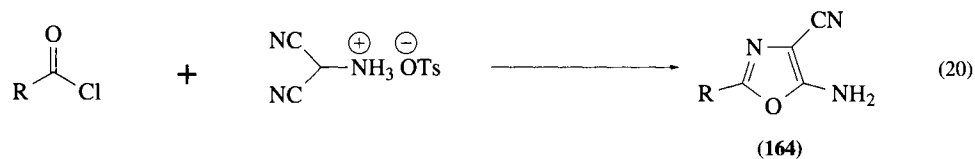
4-Amidooxazoles are produced from nitriles and *C,N*-diacylimines (**161**), which are formed *in situ* by the action of Lewis acids on *N*-(methoxyalkyl)amides <90JOC5225>. The later compounds are available by treatment of 2-aryloxazoles with bromine in methanol. A mixture of oxazole isomers is obtained in quantitative yield from acetonitrile, other nitriles also give diamide products (**162**). The reaction proceeds through a nitrilium ion intermediate (**163**) that may form the oxazoles by one of two pathways, one of which includes the diamides as intermediates (Scheme 76).



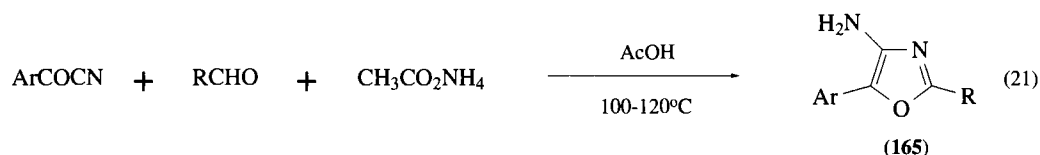
Scheme 76

3.04.9.2.6 From [3 + 2] atom fragments: C—C—N + O—C

2-Alkyl- and 2-aryl-5-amino-4-cyanooxazoles (**164**) are prepared in 51–95% yields from aminomalononitrile tosylate and acid chlorides (Equation (20)) <89TL2631>. 2-Halogenomethyl-5-phenyloxazoles are formed in 40–50% yields in the reaction of β -azidostyrene with halogenoacetic acids <89CC1414>. A possible mechanism is attack of the halogenoacetate anion on the benzylic carbon of the protonated β -azidostyrene followed by cyclization and dehydration (Scheme 77). A synthesis of the unknown 4-aminooxazoles (**165**) from α -oxonitriles (Equation (21)) was reported <89OPP141>, but the results were not reproducible <90JOC5225>.

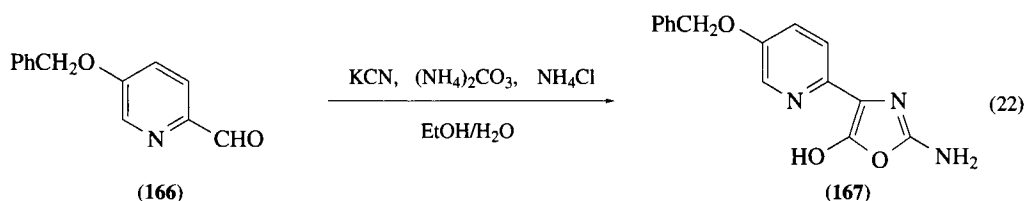


Scheme 77



3.04.9.3 More than Two Bonds

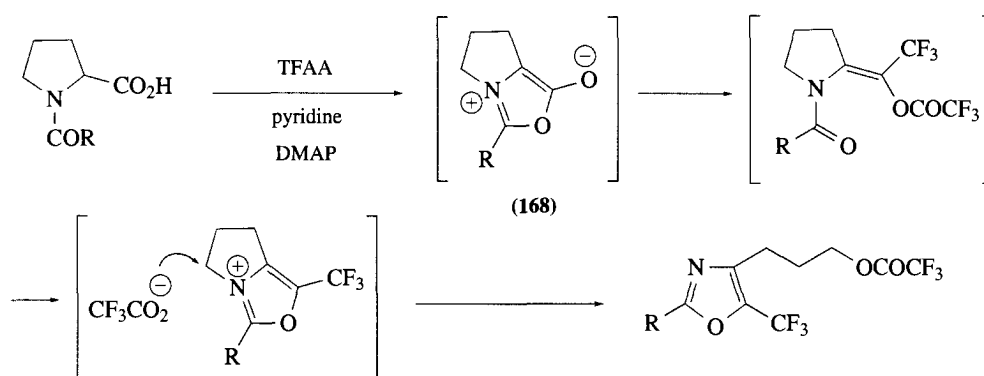
The Bucherer–Bergs reaction of (5-benzyloxy-2-pyridyl)carbaldehyde (**166**) produced a 2-amino-5-hydroxy-4-pyridyloxazole (**167**) instead of the expected hydantoin product (Equation (22)) <86H(24)1019>.



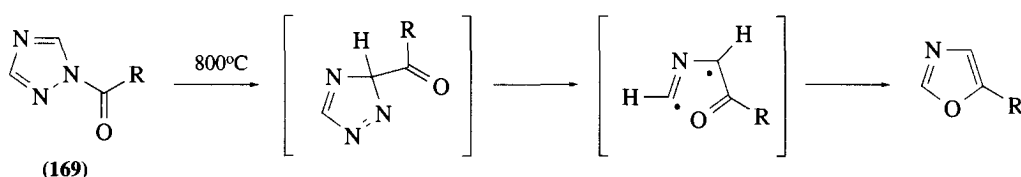
3.04.10 RING SYNTHESIS BY TRANSFORMATION OF ANOTHER RING

N-Acylprolines, in a reaction with trifluoroacetic anhydride and catalytic base, rearrange to oxazoles via mesoionic oxazolium-5-olates (**168**) <93TL859>. The yields are good for *N*-benzoyl, *N*-cinnamoyl, and *N*-pivaloylprolines, but no oxazole is formed with *N*-acyl groups bearing α hydrogens on an sp^3 carbon. A possible mechanism is shown in Scheme 78.

A short route to 5-monosubstituted oxazoles is based on the flash vacuum pyrolysis of azolides of 1,2,4-triazole (**169**) <89H(29)103>. 5-Aryloxazoles are obtained in excellent yield, but the formation of ketene is a major side reaction for alkyl analogues with an α hydrogen. The rearrangement is believed to proceed by [1,5] sigmatropic shift of the acyl substituent followed by loss of nitrogen and cyclization of a diradical intermediate (Scheme 79).



Scheme 78



Scheme 79

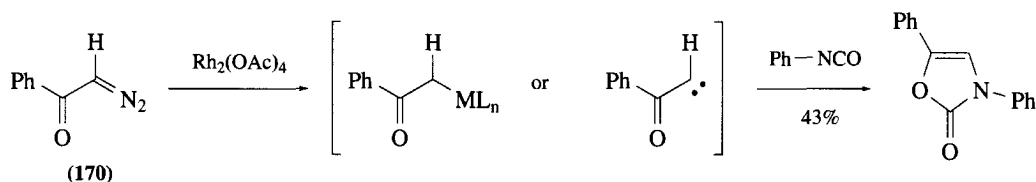
3.04.11 SYNTHESIS OF PARTICULAR CLASSES OF COMPOUNDS AND CRITICAL COMPARISON OF THE VARIOUS ROUTES AVAILABLE

3.04.11.1 Oxazolones

Nearly all of the literature since the 1980s on oxazolone synthesis concerns the 5(4*H*)-oxazolones. No reports were found on the 2(5)- and 4(5*H*)-oxazolones.

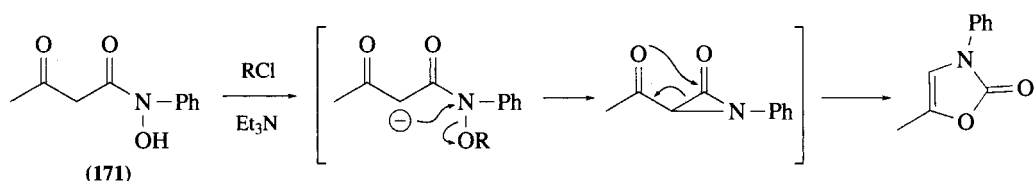
3.04.11.1.1 2(3*H*)-Oxazolones

A common method for 2(3*H*)-oxazolone synthesis involves cyclization of isocyanate intermediates. In a new variation of the route, α -diazocarbonyl compounds (170) are treated with rhodium acetate in phenyl isocyanate <93ACS218>. A regioselective 1,3-cycloaddition of a keto carbene or metalcarbene intermediate ensues to afford the product in fair yield (Scheme 80). 2(3*H*)-Oxazolones were the unexpected product of the reaction of *N*-aryl-*N*-hydroxyacetoacetamides (171) with ethyl chloroformate <86CPB1553>. In the likely mechanism, acylation of the hydroxy group occurs first, followed by intramolecular displacement and rearrangement (Scheme 81). A survey of reagents showed that yields are highest when *p*-nitrobenzenesulfonyl chloride is used for the initial step.



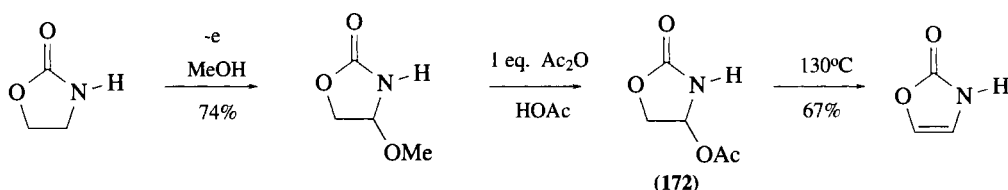
Scheme 80

The electrochemical methoxylation of 2-oxazolidinones affords 4-methoxy derivatives, which, for 3-alkyl compounds, lose methanol upon distillation at 80°C under reduced pressure to give 4,5-unsubstituted-2(3*H*)-oxazolones in 75–80% yield <85H(23)2237>. When the 3 position is unsubstituted *N*-acetyl-2(3*H*)-oxazolone is formed upon heating to 120°C in acetic anhydride. If the 4-methoxy-



Scheme 81

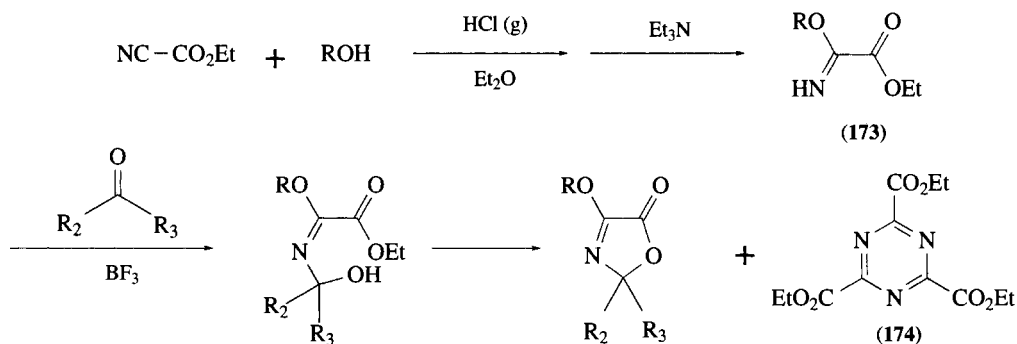
oxazolone is treated with only one equivalent of acetic anhydride in acetic acid, the 4-acetoxy derivative (172) is obtained (88BSB859). Heating this product to 130°C affords the unsubstituted oxazolone in 67% yield (Scheme 82).



Scheme 82

3.04.11.1.2 5(2H)-Oxazolones

4-Alkoxy-5(2H)-oxazolones are available from ethyl cyanofornate via a simple albeit poor yielding route (89HCA825). Imino esters (173), formed from the cyanofornate and an alcohol, are reacted with a ketone or aldehyde in the presence of BF_3 etherate to give the oxazolone and a triazine triester (174) as the main product (Scheme 83). In a related synthesis, tosyloxyminoacetates (175) are reacted with ethanethiol, triethylamine, and a ketone (Scheme 84) (92TL6523).

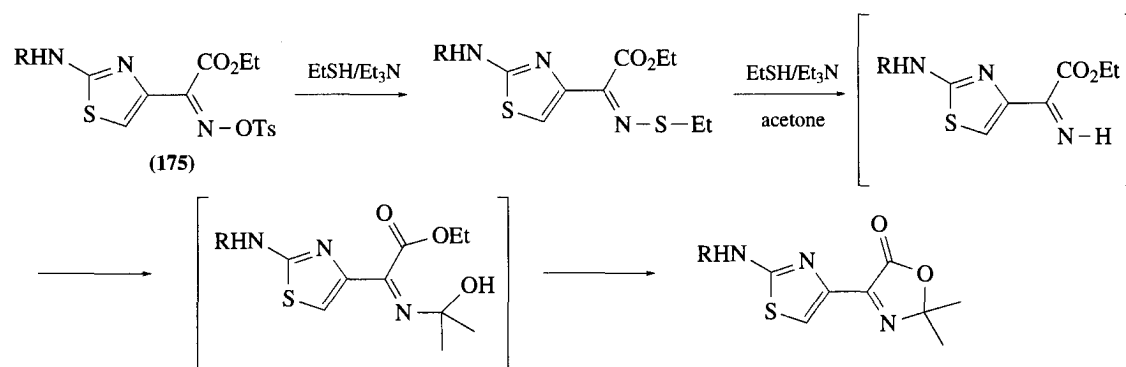


Scheme 83

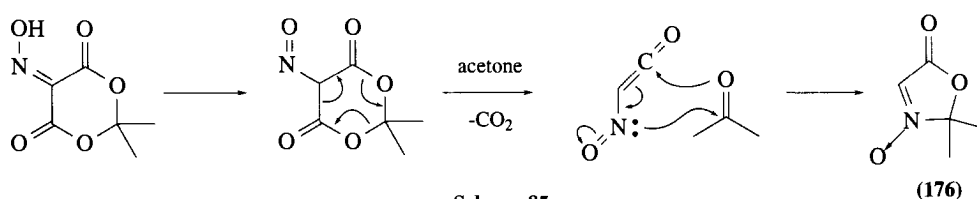
N-Oxides of 5(2H)-oxazolones (176), the cyclic nitrones, are the products of thermolysis of hydroxyimino Meldrum's acid in the presence of ketones (94CC281). Nitrosoketenes are intermediates (Scheme 85).

3.04.11.1.3 5(4H)-Oxazolones

5(4H)-Oxazolones are commonly prepared by cyclodehydration of *N*-acylamino acids, and there are many reagents for effecting this transformation. A newcomer to this list is *N,N*-dimethylchlorosulfite methaniminium chloride (177), which is made from DMF and SOCl_2 . This reagent offers the advantages that it is not needed in large excess and it does not lead to unwanted derivatization (acetylation with acetic anhydride) of the substrate. 4-Arylidene-5(4H)-oxazolones, where the aryl group is a phenol, may be obtained in good yield by this method (Scheme 86)

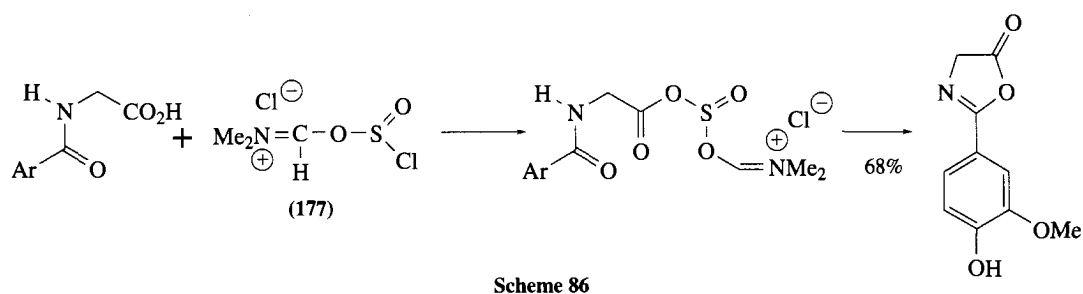


Scheme 84

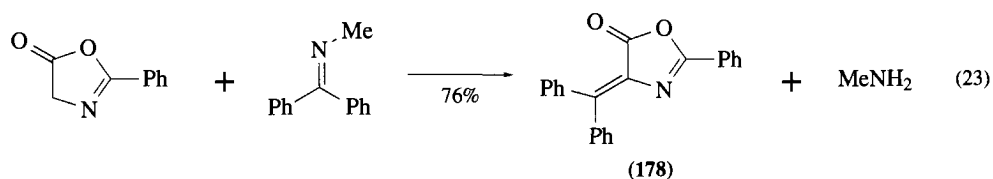


Scheme 85

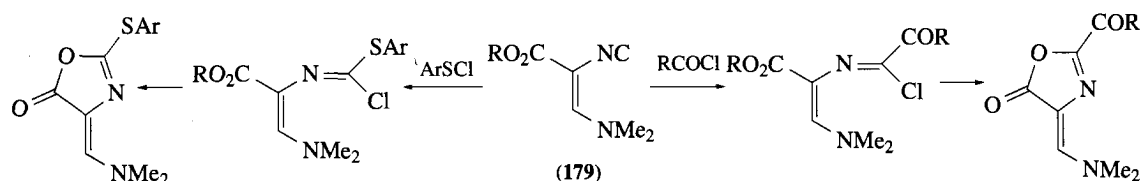
<90CI(L)499>. A 4-diphenylmethylidene-5(4*H*)-oxazolone (**178**) was prepared by reaction of the unsubstituted oxazolone with the *N*-methylketimine of benzophenone (Equation (23)) <92T177>.



Scheme 86



3-Dimethylamino-2-isocyanoacrylates (**179**) react with arenesulfonyl chlorides or acyl chlorides to furnish 4-dimethylaminomethylene-5(4*H*)-oxazolones (Scheme 87) <93JCR(S)1, 93JHC575>. The structure of the acyl chloride product was secured through x-ray analysis.

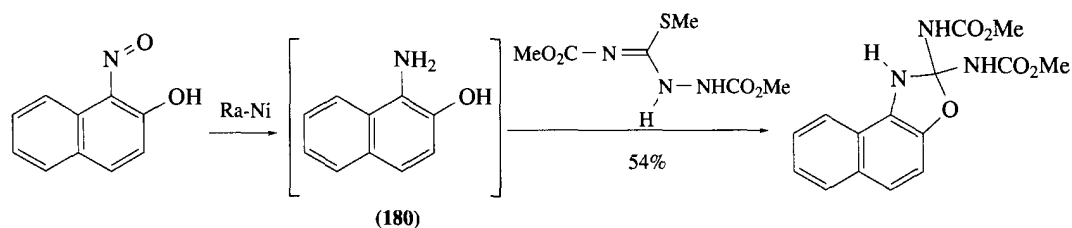


Scheme 87

3.04.11.2 Dihydrooxazoles

3.04.11.2.1 2,3-Dihydrooxazoles

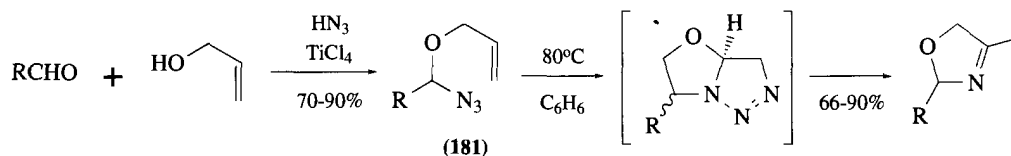
2,3-Dihydrooxazoles are accessible via reduction of oxazolium salts with $\text{PhSiH}_3/\text{CsF}$ [88JA3238]. The compounds are not stable, but ring open to give azomethine ylides, which can be trapped with dipolarophiles (see Section 3.04.6.3.1). Treatment of 1-amino-2-hydroxynaphthalene (**180**), obtained from the corresponding nitroso compound by Raney nickel reduction, with 1,3-bis(methoxycarbonyl)-*S*-methylisothiurea affords a 1,2-dihydronaphthoxazole [90S151]. The product is unusual in that it contains a carbon atom linked to one oxygen and three nitrogen atoms (Scheme 88).



Scheme 88

3.04.11.2.2 2,5-Dihydrooxazoles

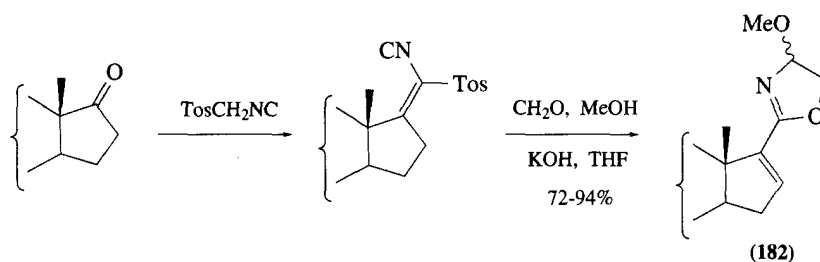
Several routes to 4-alkyl-2,5-dihydrooxazoles, which were not available by previous methods, have been discovered. Thermolysis of allyl α -azidoalkyl ethers (**181**) gives 2,5-dihydrooxazoles via triazoline intermediates [88JOC27]. The starting materials are obtained from aldehydes, allyl alcohol, and hydrazoic acid (Scheme 89). *N*-chlorination of oxazolidines with *t*-butyl hypochlorite, followed by dehydrochlorination using potassium superoxide, also provides 4-alkyl-2,5-dihydrooxazoles in 40–93% yield [92TL7751].



Scheme 89

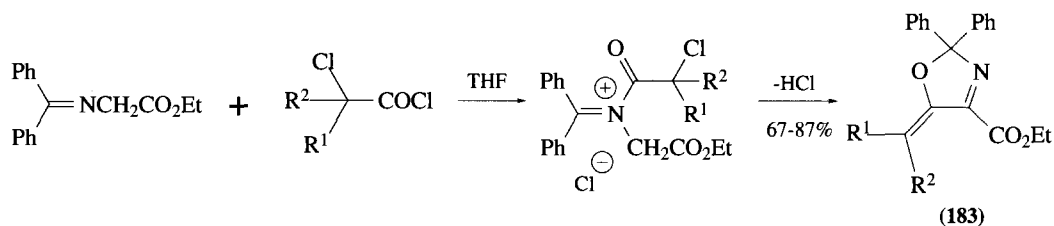
4-Methoxy-2-alkenyl-2,5-dihydrooxazoles (**182**) are the products of a sequence of reactions that begins with the addition of tosylmethyl isocyanide to steroidal ketones [94JOC5650]. The isocyanato-tosylmethylene intermediates react with formaldehyde, methanol and base to afford the products in good to excellent yields (Scheme 90).

5-Alkylidene-2,5-dihydrooxazoles (**183**) are obtained by reaction of glycine Schiff bases with α -



Scheme 90

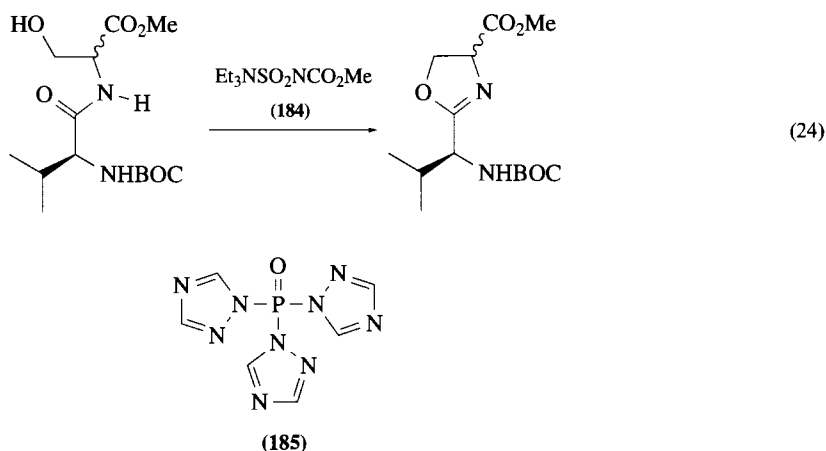
chloroacyl chlorides (Scheme 91) <90TL3343>. Thermolysis of 4-alkoxy-2-phenyl-5(2*H*)-oxazolones, which form alkoxy substituted nitrile ylides, in the presence of trifluoroacetophenone affords 2,5-dihydrooxazoles in low yield <89HCA825>.



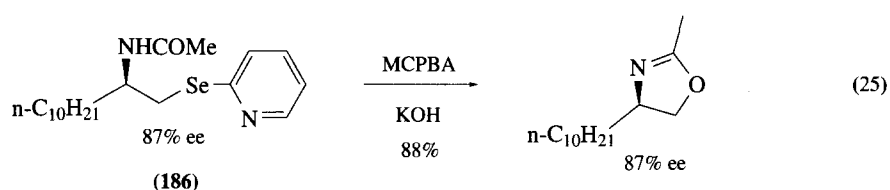
Scheme 91

3.04.11.2.3 4,5-Dihydrooxazoles

The usefulness of 4,5-dihydrooxazoles in organic synthesis has stimulated continued interest in their construction. The cyclization of β -hydroxyamides has been a common approach, and since the 1980s the focus has been on milder conditions. 4,5-Dihydrooxazoles are obtained in generally good yields using triphenylphosphine and diethylazodicarboxylate <85SC675>. These Mitsunobu conditions have been used to introduce dihydrooxazoles into peptide backbones <92TL2807> and to prepare 2-alkoxy derivatives from β -hydroxyurethanes <94TL4585>. Other reagents that have been employed for the conversion of β -hydroxyamides into 4,5-dihydrooxazoles include Burgess reagent (184) (Equation (24)) <94TL2477>, phosphoro-tris(1,2,4-triazolide) (185) or *o*-chlorophenylphosphoro-bis(1,2,4-triazolide) <87S853>, and diphenyl sulfoxide/trifluoroacetic anhydride <92SL153>. Yields using these reagents generally range from 55 to 85%, but 4-methoxycarbonyl derivatives are obtained in 95% yields using the last set of conditions.

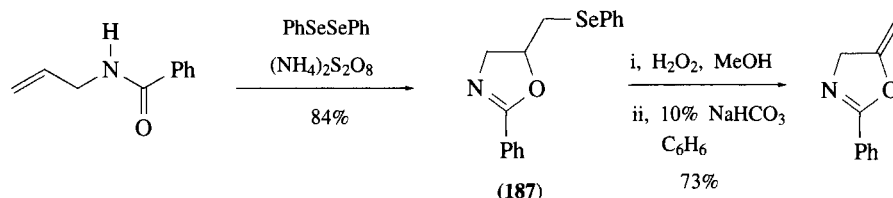


The selenoxide produced by oxidation of *N*-(2-phenylselenylethyl)benzamide with MCPBA undergoes cyclization to furnish 4,5-dihydrooxazoles in high yield <92TL4017>. An optically active amide bearing a 2-pyridylseleno group on the β carbon (186) is cyclized without racemization (Equation (25)).



4,5-Dihydrooxazoles are also accessible by phenylselenenyl bromide <91JOC3425> or phenylselenenyl sulfate <93JOC1349> induced cyclization of *N*-allylamides. Oxidation of the 5-phenylselenenylmethyl

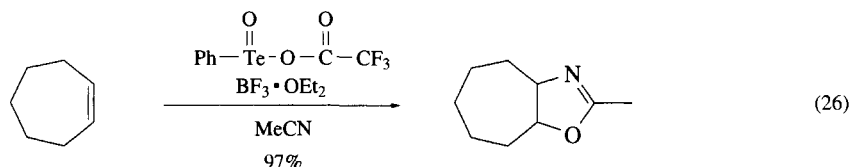
product (**187**), followed by elimination affords 5-methylidene-4,5-dihydrooxazoles (Scheme 92). A sulfenyl cyclization occurs upon treatment of the same substrates with manganese(III) acetate and diphenyl disulfide in $\text{CH}_2\text{Cl}_2/\text{TFA}$ <88JCS(P1)2517>. Allylic ureas react with phenylselenenyl chloride in the presence of silica gel to give 2-amino-4,5-dihydrooxazoles <89CC450>.



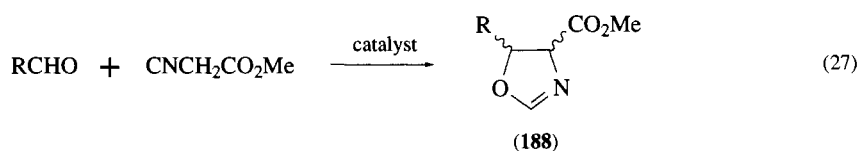
Scheme 92

The direct conversion of carboxylic acids and amino alcohols to 4,5-dihydrooxazoles has been achieved in yields of up to 80% using triphenylphosphine, hexachloroethane and triethylamine <93T9353> and in yields up to 97% with boric acid <85JCS(P1)1865>. Amino alcohols react with dimethylformamide dimethylacetal in the presence of Amberlite resin to give the oxazoles in 65–90% yield <91JOC1961>.

Alkenes are converted into 4,5-dihydrooxazoles by reaction with benzenetelluranyl trifluoroacetate, boron trifluoride etherate, and acetonitrile (Equation (26)) <88TL1049>.



Transition-metal complexes bearing chiral ligands catalyze an asymmetric aldol condensation of isocyanoacetates with aldehydes to afford a mixture of *cis*- and *trans*-4,5-disubstituted-4,5-dihydrooxazoles (**188**) in high optical purity (Equation (27)). Both gold and silver ferrocenylphosphine complexes are effective <94TL2713>.



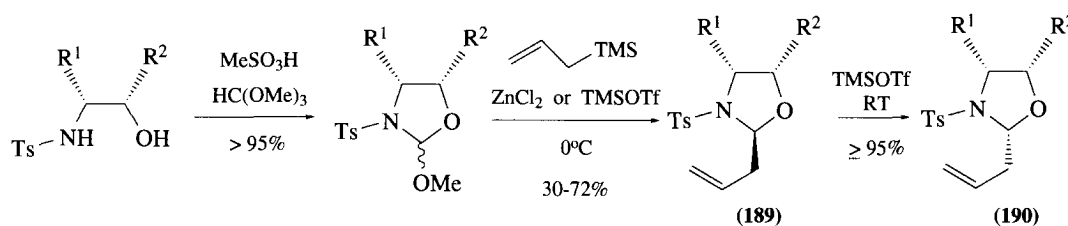
Optically active bis(4,5-dihydrooxazoles), which are effective ligands for asymmetric synthesis (Section 3.04.12.5), have been prepared by zinc chloride-catalyzed coupling of amino alcohols and dinitriles <91CB1173> and by sodium hydroxide induced cyclization of bis(*N*-(2-chloroethyl)amides) <91JA728>.

3.04.11.3 Oxazolidines

The traditional method for preparing oxazolidines is to heat a mixture of amino alcohol and aldehyde in a solvent such as benzene with removal of water. A milder procedure that affords some products in high yield when they would otherwise be obtained in only trace amounts is to dehydrate the same mixture with molecular sieves in methylene chloride at room temperature <89JHC1687>. A method that has been effective with amino sugar derivatives is to cyclize with dibromomethane under phase transfer conditions <93MI 304-02>.

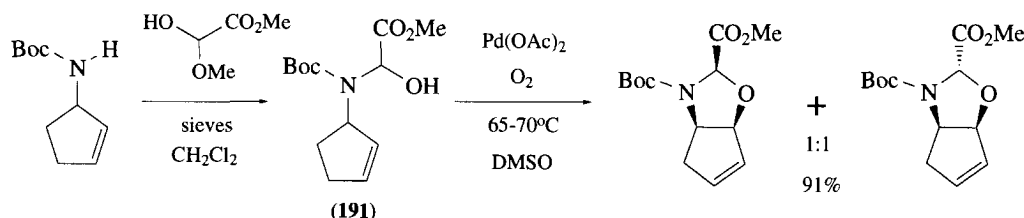
With optically active amino alcohols and aldehydes, a mixture of diastereomers generally results. For *N*—H oxazolidines, the ratio of isomers is about 2 : 1, and for *N*—Me or *N*—Prⁱ analogues the ratio is about 9 : 1. For *N*-tosyl derivatives, however, diastereomerically pure 2,4-*cis*-oxazolidines are isolated <92H(33)281>. *Trans* isomers (**189**) are obtained in ratios > 10 : 1 from the zinc chloride or trimethylsilyl triflate-catalyzed reaction of 2-methoxy-oxazolidines with allyltrimethylsilane or

trimethylsilyl enol ethers at 0°C <90SL99>. At room temperature, trimethylsilyl triflate isomerizes the *trans* isomers to *cis* (**190**) in >95% conversion (Scheme 93).



Scheme 93

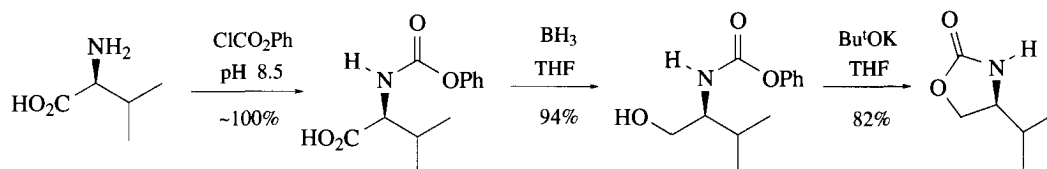
Oxazolidines are obtained in good to excellent yields by the palladium(II)-catalyzed cyclization of *N*-Boc protected *N*-allyl-*N*-hydroxymethylamines (**191**) <94CC357>. The palladium species is regenerated by molecular oxygen in DMSO (Scheme 94). Allyl carbamoylmethyl ethers cyclize to oxazolidines by reaction with mercuric acetate <89H(28)663>. Silver triflate catalyzes the cyclization of *O*-propargyl isoureas to 4-alkylidene-oxazolidines with high diastereoselectivity <88CC1175>.



Scheme 94

3.04.11.4 Oxazolidinones

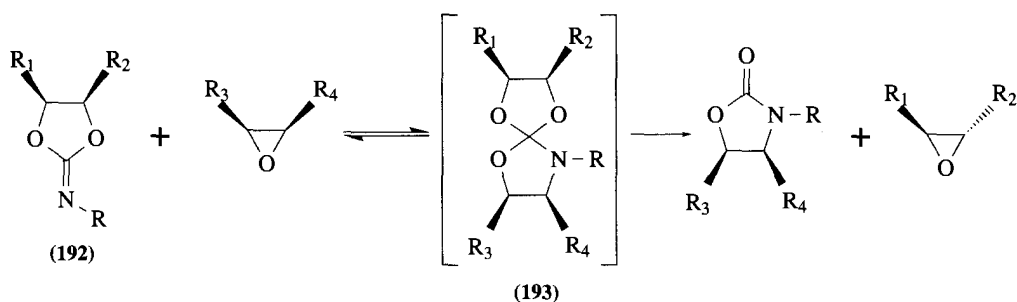
2-Oxazolidinones are commonly prepared from amino alcohols by incorporation of a carbonyl unit. Additions to the list of reagents that effect the transformation are bis(trichloromethyl)carbonate <89S875> and trichloromethyl chloroformate <89JOC3231>, which offer the advantages of easier handling and reduced risk of exposure compared to phosgene. As a further step in that direction, 2-oxazolidinones have been prepared by cyclization with CS₂, followed by H₂O₂ oxidation <93JHC1235>. The amino alcohols can be costly to purchase and difficult to isolate because of water solubility. A route that begins with the introduction of the carbonyl unit to an amino acid, the usual precursor of the amino alcohol, avoids these problems (Scheme 95) <89S622>.



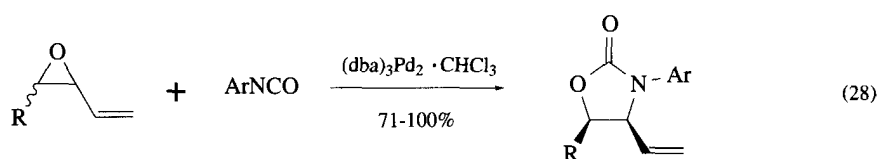
Scheme 95

Another standard method for the synthesis of 2-oxazolidinones is by reaction of epoxides with isocyanates. Although 4,5-disubstituted derivatives are not readily accessible by this route, it has been shown that iminodioxolanes (**192**) add to epoxides in the presence of AlCl₃ to afford these oxazolidinones in high yield <91JOC2684>. The reaction proceeds through a spirocyclic intermediate (**193**) (Scheme 96). The reaction of vinyl epoxides with aryl isocyanates is facilitated by palladium catalysis (Equation (28)) <89TL3893>. The products are obtained by a double inversion process, but

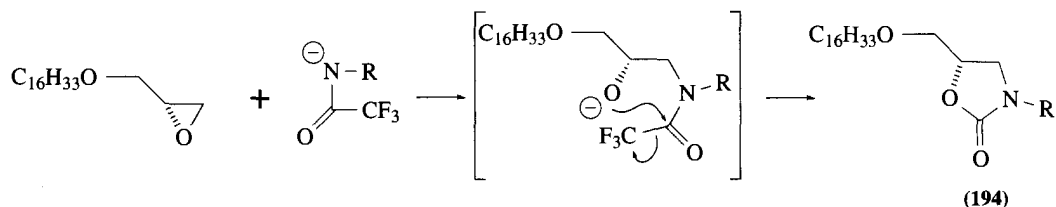
the π -allyl intermediates interconvert. Thus the (*Z*)-isomer is obtained stereoselectively from either isomer of the epoxide.



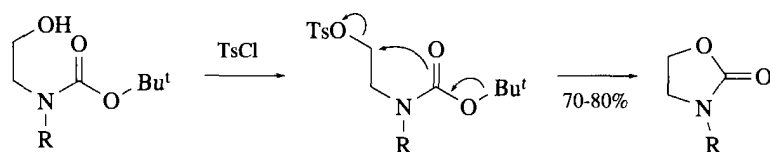
Scheme 96



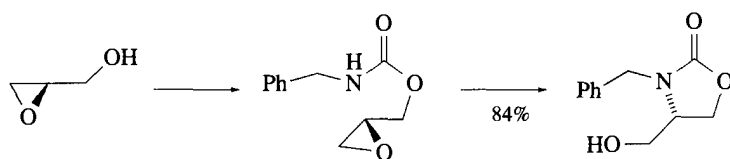
N-substituted 2-oxazolidinones (**194**) are the products of reaction of trifluoroacetamide sodium salts with terminal epoxides or α -hydroxy tosylates (Scheme 97) <92TL377>. When the nitrogen is unsubstituted, the reaction stops before cyclization, presumably because the acetamide N—H is more acidic than the hydroxy group. Tosylation of *N*-Boc derivatives of β -amino alcohols furnishes 2-oxazolidinones by an intramolecular displacement (Scheme 98) <93TL4509>. Optically active glycidol reacts with benzyl- or benzoylisocyanate to afford 2-oxazolidinones with no loss of optical purity (Scheme 99) <91CL1245>.



Scheme 97



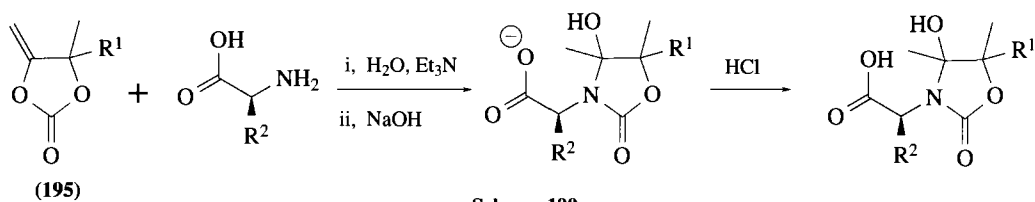
Scheme 98



Scheme 99

Several methods involve an electrophilic cyclization of a carbamoyl group onto a double bond. The iodocyclization of carbamates of secondary α -allenic alcohols afford 4-vinyl-2-oxazolidinones in fair to good yield <91JOC4888>. Palladium catalyzes a similar reaction <93TL7611>. *O*-propargyl carbamates cyclize to 4-alkylidene derivatives <90TL4887>. The nature of the substituents determines whether or not a metal catalyst is needed. Carbamates of *N*-propargyl amines undergo an iodocyclization to afford 5-iodoalkylidene 2-oxazolidinones <87TL1127>.

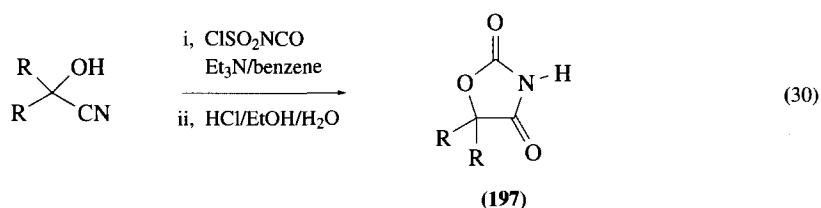
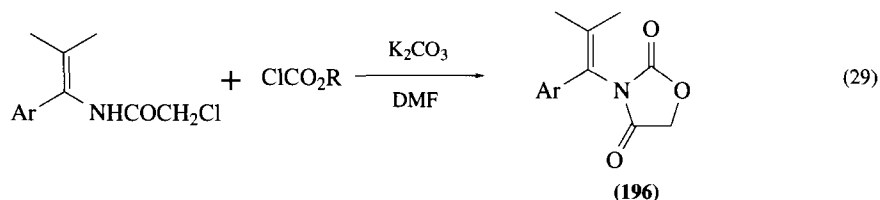
Amino acids react with cyclic α -methylene carbonates (**195**) to give 4-hydroxyoxazolidinones <93SL423>. Sodium salts of the carboxylic acids are obtained in 93–97% yield, but protonation with HCl afforded the products in only about half that yield (Scheme 100). Reaction of the carbonates with ammonia gives *N*-unsubstituted 4-hydroxyoxazolidinones.



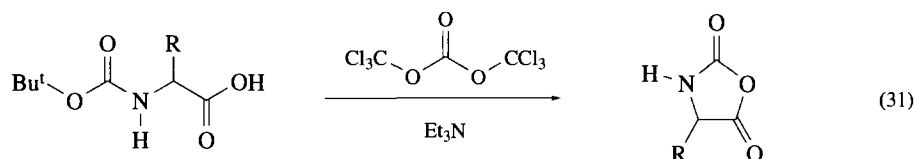
Scheme 100

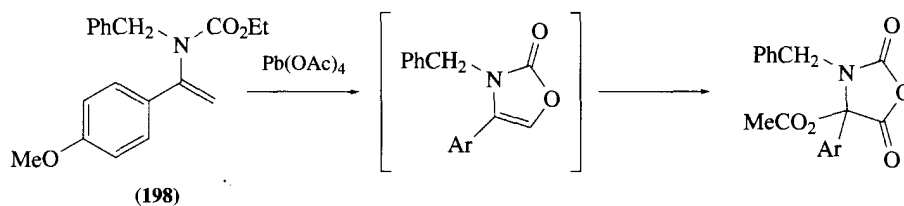
3.04.11.5 Oxazolidinediones

3-Propenyl-2,4-oxazolidinediones (**196**) are obtained from *N*-propenyl-2-chloroacetamides and ester chloroformates in the presence of potassium carbonate (Equation (29)) <91H(32)1697>. Cyano-hydrins react with chlorosulfonyl isocyanate to afford 5,5-disubstituted 2,4-oxazolidinediones (**197**) after acid hydrolysis (Equation (30)) <91S697>.



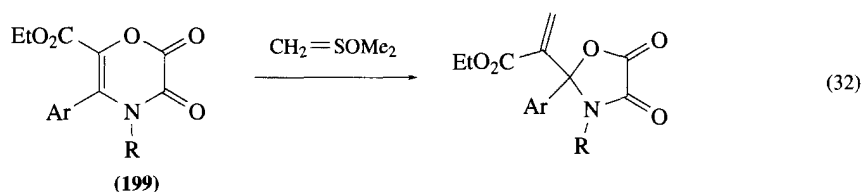
The preparation of 2,5-oxazolidinediones, the *N*-carboxy α -amino acid anhydrides, has received considerable attention, because of their usefulness in peptide chemistry. In a modification of a common route, *N*-Boc amino acids were reacted with triphosgene, followed by triethylamine <92JOC2755>. The products were obtained in 65–83% yield (Equation (31)). Oxidation of 1-arylvinyl carbamates (**198**) with lead tetraacetate proceeds through an oxazolone intermediate to afford 2,5-oxazolidinediones in moderate yield (Scheme 101) <90JOC1753>.





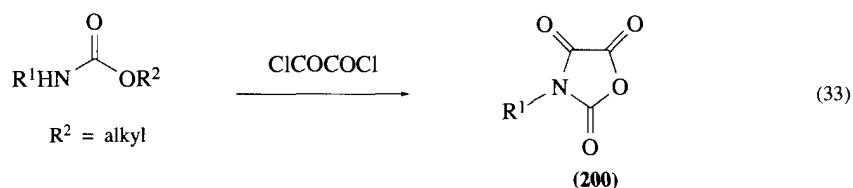
Scheme 101

The reaction of oxazinediones (**199**) with dimethylsulfoxonium methylide furnished 4,5-oxazolidinediones (Equation (32)) <94CPB739>.



3.04.11.6 Oxazolidinetriones

The reaction of alkyl carbamates with oxalyl chloride is the only known route to 3-substituted-2,4,5-oxazolidinetriones (**200**) (Equation (33)) <84JOC3675>.



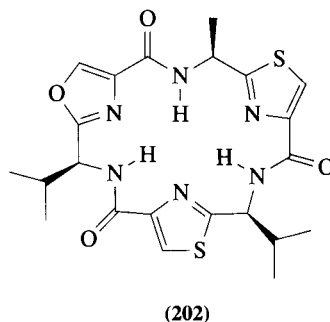
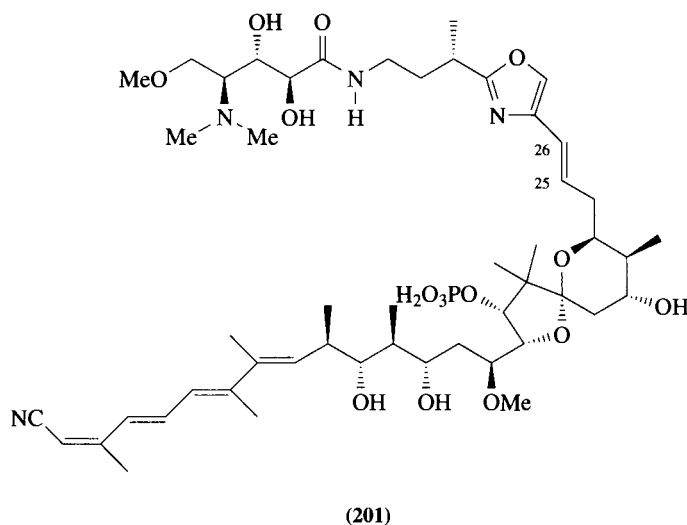
3.04.12 IMPORTANT COMPOUNDS AND APPLICATIONS

3.04.12.1 Natural Products

The biosphere has been a source for a number of biologically active compounds containing the oxazole ring. Metabolites that exhibit anthelmintic, antifungal, cytotoxic, tumor-promoting, antiviral, and peripheral analgesic properties have been isolated from a variety of bacterial, fungal, algal, and higher organisms. Of those from the marine environment, one of the more intensely studied compounds has been (–)-calyculin A (**201**), which was isolated from a marine sponge in 1986. Both the natural <94AG(E)673> and unnatural forms <92JA9434> of the molecule have been the products of successful total synthesis efforts. A key disconnection in both routes was between C-25 and C-26, leaving a 2,4-disubstituted oxazole as one of the fragments.

Cyclic hexapeptides containing the oxazole ring, such as bistratamides A–D (bistratamide C (**202**)), have been isolated from ascidians <92JOC6671>. These metabolites, like several other complex natural products that incorporate the oxazole ring, also contain other heterocyclic rings. A study of the cytotoxic effect of cyclic peptides of marine origin showed that their activity is dependent on the oxazole rings <87BP4181>.

A cytotoxic chlorooxazole (**203**) was also isolated from an ascidian <91JA2303>. The metabolite is one of several, including the hennoxazoles (**204**) <91JA3173> and the ulapualides (**205**), from ascidians and sponges that possesses a bisoxazole or trisoxazole in the structure. A strategy for the synthesis of the trisoxazole unit of ulapualide A involves three sets of dihydrooxazole cyclization–oxidation reactions on serine substrates <90SL36>. Multiple rhodium acetate-catalyzed cycloaddition reactions



of diazomalones with nitriles have also been used to prepare bisoxazole and trisoxazole systems <92TL2159>.

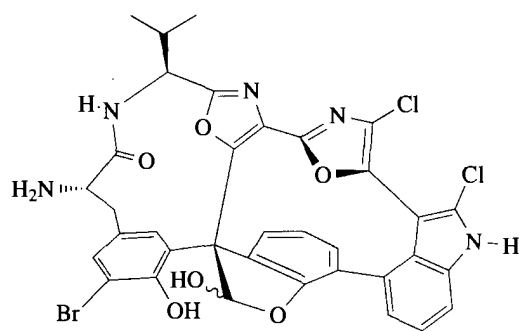
The biosynthetic source for the oxazole ring of plant secondary metabolites of the Gramineae and Rutaceae families is the chorismic acid–phenylalanine pathway. Serine and threonine are probable sources for the oxazole ring of most bacterial and marine natural products. Both triserine peptides or polyketides have been suggested as sources of the trisoxazoles. Labeling studies have shown that the oxazole ring of virginamycin M₁ is formed from the (*S*)-isomer of serine (206) with loss of the 3-(pro-*S*)-hydrogen <87CC302>. Assuming that the ring oxygen atom is from serine, a likely mechanism is that shown in Scheme 102.

3.04.12.2 Medicinal Compounds

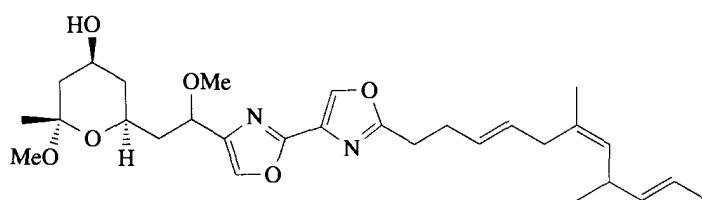
Oxazole and its derivatives have been incorporated into a large number of compounds of potential medicinal value. Aluminum salts of oxaprozin are claimed to have value as antiinflammatory agents <85BRP2148894>. Other 4,5-diphenyl-2-oxazolyl derivatives showed activity as prostacyclin mimetics <93JMC3884>. The most potent compound of the series (207) contained another oxazole ring, which locked an important double bond in the *cis* configuration and served as a hydrogen bond acceptor. Another set of compounds to show inhibition of blood platelet function were the 5-substituted oxazole 4-carboxylic acids and carboxamides <83CPB4417>. Derivative (208) was the most active.

A series of triazolylmethyloxazolidine derivatives (209) were designed as potential inhibitors of the cytochrome P₄₅₀ 14 α -demethylase enzyme <90CPB2476>. The 3-acyl-4-methyloxazolidine with the indicated stereochemistry was expected to mimic the skeleton of the enzyme substrate, lanosterol.

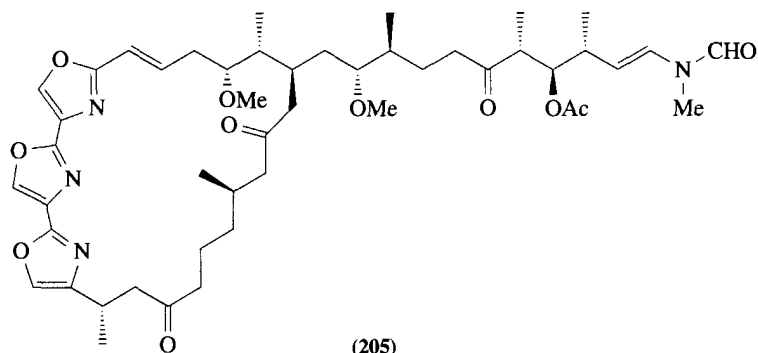
Oxazoles have been claimed as stimulants of cognitive function, adrenergic antagonists, fungicides, anthelmintic agents, antihypertensive agents, and antiulcer agents. They are also reported to show activity as pesticides, agrochemical fungicides, and insecticides.



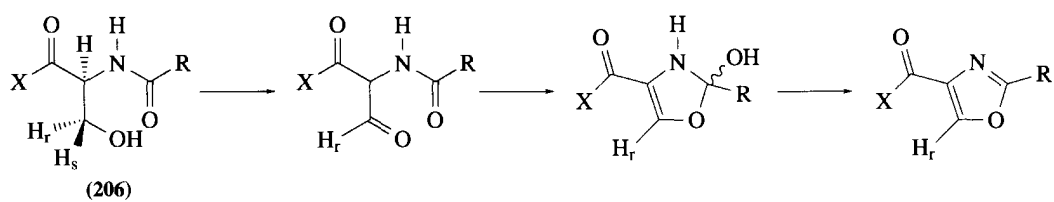
(203)



(204)

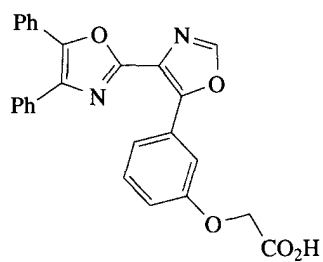


(205)

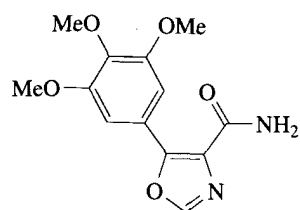


(206)

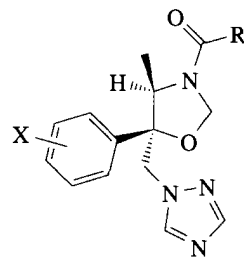
Scheme 102



(207)



(208)



(209)

3.04.12.3 Polymers

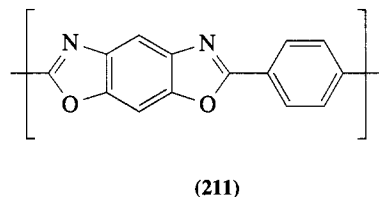
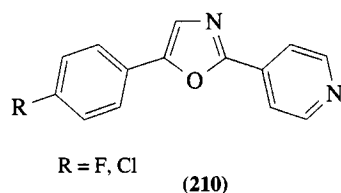
Polymers of 4,5-dihydrooxazole have been studied for some time, and copolymers have been prepared for such uses as adhesives and coatings. A thermo-sensitive polymer, prepared by copolymerization of 2-isopropyl-4,5-dihydrooxazole and ethylene glycol dimethylacrylate, was developed for bioapplications <92CL1643>. The first polymers of 2,3-dihydrooxazoles were reported <85JHC417>.

Polymers of 2-oxazolidinone are also known, but in all but one the heterocyclic ring is attached to the polymer chain through the ring nitrogen. The syntheses of two 3-unsubstituted 2-oxazolidinone polymers has been reported <88BCJ3559>. The polymers are useful as carriers for biocides, as polymer bound ligands for metal catalysts, and as sequestering agents for heavy metals.

Polymers of oxazolidines have been used for moisture scavenging polyurethane coatings <93MI 304-03>.

3.04.12.4 Uses Based on the Fluorescence Properties of Oxazoles

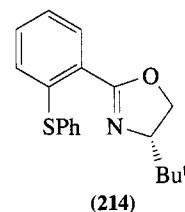
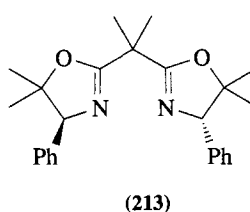
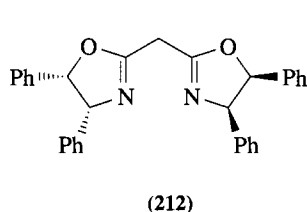
2,5-Diphenyloxazole is a common scintillator and laser dye that is commercially available. Compounds (210) with modified structures have been prepared to provide laser dyes with wavelength maxima in the blue-green region <87MI 304-01>. A bilayer thin film of the conjugated polymer, poly(*p*-phenylene-2,6-benzobis(oxazole)) (211) and the donor molecule, tris(*p*-tolyl)amine, shows blue luminescence <94MM739>. These materials were designed for use in light emitting diodes, photodetectors, solar cells, and electrophotographic photoreceptors.



Fluorescent oxazole derivatives have also been used for labeling small molecules, such as amines and thiols, for analytical detection <93MI 304-04>.

3.04.12.5 Ligands for Asymmetric Synthesis

The usefulness of chiral bis(dihydrooxazole) ligands in metal complexes for asymmetric synthesis has been demonstrated by several research groups, and a review has appeared <91AG556>. A copper(I) complex of bis(dihydrooxazole) (212) catalyzed the cyclopropanation of 2,5-dimethyl-2,4-hexadiene in 90% diastereoselectivity and 94% enantioselectivity <91TL7373>. A magnesium complex of chiral ligand (213) was effective for enantioselective Diels-Alder additions <92TL6807>. Bidentate ligands (214) composed of a 4,5-dihydrooxazole group and a tethered donor atom have been employed in palladium-catalyzed allylic substitution reactions <93TL7793>.



3.05

Isothiazoles

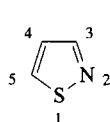
ROBERT F. CHAPMAN and BARRY J. PEART
Rhône-Poulenc Rorer Ltd, Dagenham, UK

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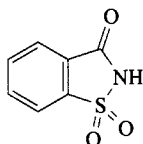
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3.05.1 INTRODUCTION

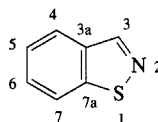
Isothiazole (1) was first described comparatively recently, in 1956, whilst the benzisothiazoles have been known for a long time, the most widely known, saccharin (2) having been originally prepared in 1879. There are two series of benzisothiazoles, 1,2-benzisothiazole (3) and 2,1-benzisothiazole (4).



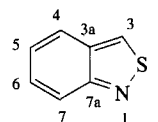
(1)



(2)



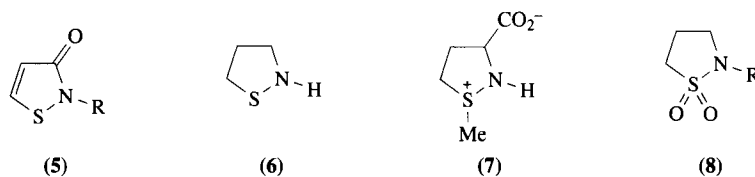
(3)



(4)

Isothiazoles form S-oxides and dioxides (sulfoxides and sulfones); these are referred to as 1-oxides or 1,1-dioxides in this chapter. There are several possible forms of isothiazole having an exocyclic carbonyl group, but the ones which will be considered in most detail in this chapter will be isothiazolin-3-one derivatives (5). Fully saturated isothiazoles (6) are referred to as isothiazolidines. One of the most well-known isothiazolidines is the zwitterion dehydromethionine (7). Saturated 1,1-dioxides are increasingly important compounds in synthetic chemistry, and are referred to as

sultams or propane-sultams (8). Further details of the possible structures for di- and tetrahydroisothiazoles are given in Sections 3.05.6.3.1 and 3.05.6.4.1.



There are a number of more complex isothiazole structures, including naphthyl isothiazoles, steroidal isothiazoles <81JHC1485>, and isothiazoles incorporated into large molecules, such as bleomycin derivatives <87JA938>, but these will not be discussed.

Isothiazoles and benzisothiazoles were described in the first edition of *Comprehensive Heterocyclic Chemistry* (CHEC-I) <84CHEC-I(6)131>. The present work summarizes and augments, where appropriate, information from the first edition, but concentrates very much on literature published since 1982. Wherever possible, information is arranged in a similar format to that used in the first edition to facilitate comparisons. The chemistry of isothiazoles is regularly reviewed in *Progress in Heterocyclic Chemistry*, and specific subjects are discussed occasionally in *Advances in Heterocyclic Chemistry*, for example benzisothiazoles <85AHC(38)105> and aromaticity <93AHC(56)303>.

3.05.2 THEORETICAL METHODS

3.05.2.1 Electron Densities and Bond Orders

Earlier calculations of electron densities of isothiazole indicated, in the ground state, a high net charge density on the nitrogen, a small net positive charge on the sulfur, and a high electron density on the carbon atom at the C-4 position <84CHEC-I(6)131>. The net charge densities for isothiazole and its 1-oxide and 1,1-dioxide, have been calculated using more recent basis sets of atomic orbitals (STO-3G*/6-31G*) and are given in Table 1. These calculations indicate that C-5 has a higher electron density than C-4 in isothiazole, and it can be clearly seen that the net positive charge on the sulfur atom is much increased for the 1-oxide and 1,1-dioxide <92JP074>.

Table 1 Calculated net atomic charges of isothiazole and its 1-oxides <92JP074>.

Compound	Net charge at atom					
	S	N	C-3	C-4	C-5	O
Isothiazole	+0.47	-0.57	+0.03	-0.23	-0.4	-
Isothiazole-1-oxide	+1.12	-0.58	+0.07	-0.18	-0.46	-0.71
Isothiazole-1,1-dioxide	+1.61	-0.57	+0.07	-0.17	-0.46	-0.63

The STO-3G* basis set has also been used to calculate bond lengths for these compounds (Table 2). The values for isothiazole should be compared with the values obtained from electron diffraction (see Table 5); the values are similar except that the theoretical methods in general give too short a bond length for C(4)—C(5) <92JP074, 88JST(176)61>.

Theoretical calculations give dipole moments (2.6–2.9 D) which are slightly higher than the

Table 2 Calculated bond lengths of isothiazole and its 1-oxides <92JP074>.

Compound	Bond length (pm)					
	S—N	N—C	C(3)—C(4)	C(4)—C(5)	C—S	S=O
Isothiazole	164.4	132.4	143.1	135.3	168.4	-
Isothiazole-1-oxide	173.7	129.1	148.8	131.9	178.7	147.7
Isothiazole-1,1-dioxide	176.0	128.4	150.7	131.1	181.1	145.6

experimental value of 2.4 D $\langle 87\text{KGS}544, 88\text{JST}(176)61, 92\text{JPO}74 \rangle$, and ^{13}C NMR and ^{15}N NMR chemical shifts have also been calculated to a first approximation from charge densities using Pariser–Parr–Pople (PPP) calculations $\langle 87\text{KGS}544 \rangle$.

3.05.2.2 Energy Levels

The advent of more sophisticated molecular orbital calculations has led to an improvement in accuracy of calculation of electron energy levels. The semiempirical AM1 method gives the most reliable set of energy levels for the frontier molecular orbitals of isothiazole to date with the HOMO and LUMO (π and π^*) orbital energies calculated to be -9.93 eV and -0.21 eV, respectively $\langle 89\text{JST}325 \rangle$. The calculated energy of the HOMO is in good agreement with measured values for the ionisation energy of $9.5\text{--}9.8$ eV $\langle 84\text{CHEC-I}(6)131 \rangle$. These theoretical calculations also predict fairly well the observed low-energy ultraviolet absorptions of isothiazole at 5.08 eV (calculated: two bands, 4.78 eV and 5.30 eV) and 6.05 eV (calculated: 6.32 eV). The x-ray photoelectron spectrum of isothiazole has also been reported $\langle 82\text{SA}(A)85 \rangle$, and suggests that the low energy “shake-up” satellites arise from charge transfer away from the heteroatoms toward the ring. A study of the lowest energy singlet excited states of 3-, 4-, and 5-phenyl isothiazoles has been used to explain the photoisomerization pathways $\langle 81\text{T}3627 \rangle$. Attempts have been made to calculate $\text{p}K_{\text{a}}$ values for organic bases from first principles relating them to the ionization potential and total ($\sigma + \pi$) atomic charge of the proton-accepting atom calculated from the MOSP approximation. For isothiazole the calculated $\text{p}K_{\text{a}}$, -1.29 , is about one unit more negative than the experimental value of -0.51 , whilst for 2,1-benzisothiazole a closer result was obtained (calculated, $+0.10$; experimental, -0.05) $\langle 92\text{RRC}819 \rangle$. Similarly, a parameter has been proposed for softness of the heteroatoms, based on calculated electron density and polarizability $\langle 92\text{IJC}(4)586 \rangle$. Calculations of heats of formation, using the AM1 method, have been used to indicate preferred tautomeric structures (see Section 3.05.4.5).

3.05.3 EXPERIMENTAL STRUCTURAL METHODS

3.05.3.1 Molecular Dimensions

3.05.3.1.1 X-ray diffraction

In recent years x-ray diffraction has become a much more widely available experimental technique, and it has been applied to a range of isothiazoles and benzisothiazoles. Interesting developments have taken place in the use of x-ray techniques to map electron density distributions to complement theoretical calculations $\langle 91\text{AX}(B)905 \rangle$. Bond lengths should be compared with standard single bond lengths of C—C (153.7 pm), S—N (173.5 pm), C—N (141.3 pm), and C—S (181.2 pm), and double bond lengths of C=C (133.5 pm), S=N (153 pm), C=N (129 pm), C=S (155.4 pm), and C=O (ketone) (122 pm). Table 3 lists bond lengths and angles for a number of isothiazoles, including the 1,1-dioxide 3-oxo compound (**9**) and the cation (**10**). In the neutral molecules the heterocyclic rings are planar, and bond lengths are intermediate between those of single and double bonds. The bond lengths in the 1,1-dioxide are closer to standard single and double bonds (cf. Table 2). Exocyclic substituents are normally more or less coplanar with the heterocyclic ring so that conjugation can occur. In compound (**9**) the sum of the internal bond angles is 540° , confirming a planar ring system, and the relatively short C(4)—C(5) bond length suggests much more double bond character than in the parent isothiazoles. Compound (**9**) exists in the solid state as a network structure linked by $\text{NH}\cdots\text{O}=\text{C}$ hydrogen bonds. The cationic species (**10a**) has longer N—S and C(4)—C(5) bonds than the neutral species, and the C(3)—C(4) and exocyclic C(5)—N bond lengths (133.5 pm) are shortened, because of the possibility of resonance forms (**10b**). The x-ray structure is consistent with protonation of the ring nitrogen, and although the sum of internal angles is 539.95° , the exocyclic nitrogen is slightly (10 pm) out of the plane of the ring.

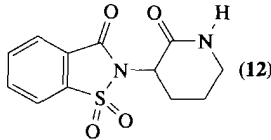
Bond distances and angles for a number of 1,2- and 2,1-benzisothiazoles are given in CHEC-I $\langle 84\text{CHEC}(6)131 \rangle$. A further example (**11**) illustrates a number of relevant features common to 1,2-benzisothiazoles; the C=N bond is shorter than in isothiazoles and the length is much more typical of a double bond, the S—N bond is more single bond in character, and the benzene ring is distorted, with the internal bond angles at positions 4 and 7 significantly less than 120° $\langle 90\text{AX}(C)510 \rangle$.

There is a considerable body of literature on saccharin, its salts and metal complexes, and

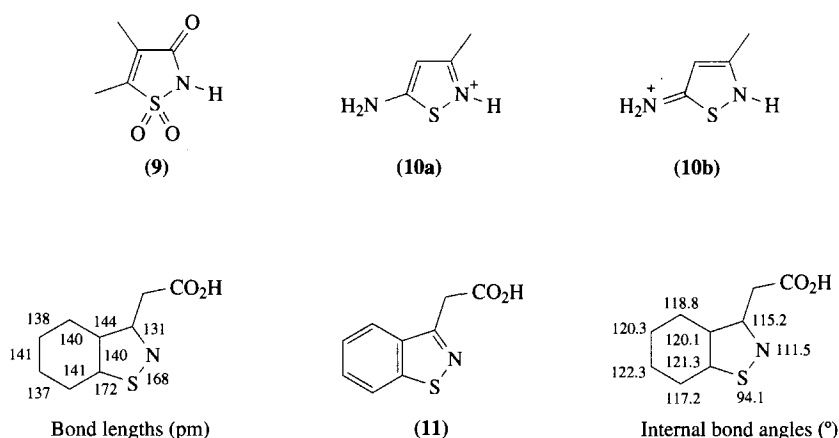
Table 3 Internuclear distances and bond angles of isothiazoles.

Substituent				Bond lengths (pm)					Heterocyclic ring angles (°)					Ref.
<i>I</i>	<i>3</i>	<i>4</i>	<i>5</i>	<i>S—N</i>	<i>N—C</i>	<i>C(3)—C(4)</i>	<i>C(4)—C(5)</i>	<i>C(5)—S</i>	<i>CSN</i>	<i>SNC</i>	<i>NCC</i>	<i>CCC</i>	<i>CCS</i>	
—	CO ₂ H	Cl	Cl	164.6	132.4	142.4	137.0	169.7	93.7	110.9	115.4	109.0	111.0	92KGS399
—	CH=CMe ₂	H	NMe ₂	166.7	134.5	141.7	137.6	174.2	95.8	108.6	116.3	112.0	107.4	92M133
O ₂	OE _t	NH ₂	CO ₂ Et		128.0	150.7	136.0							83JOC763
O ₂	=O(2H) Compound (9)	Me	Me	164.2	136.3	148.7	132.7	175.7	93.2	113.7	110.4	112.5	110.3	93MI30501
—	Me(2H ⁺) Cation (10a)	H	NH ₂	168.3	134.5	139.2	140.3	173.5	91.36	113.5	113.3	111.8	110.0	83ACS(B)121

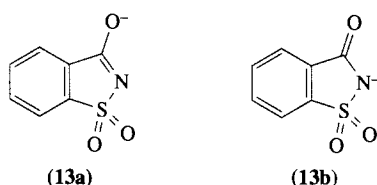
Table 4 Internuclear distances and bond angles of saccharin and related compounds.

Compound	Bond lengths (pm)							Heterocyclic bond angles (°)					Ref.
	<i>S—N</i>	<i>N—C</i>	<i>C(3)—C(3a)</i>	<i>C(3a)—C(7a)</i>	<i>C(7a)—S</i>	<i>C=O</i>		<i>CSN</i>	<i>SNC</i>	<i>NCC</i>	<i>CCC</i>	<i>CCS</i>	
Saccharin	166.3	136.9	147.4	136.9	175.8	121.4		92.2	115.1	109.6	112.9	110.1	69AX(B)2257
Saccharin Na salt	160.3	135.7	149.4	138.9	176.4	123.7		97.8	111.0	113.5	111.3	106.3	82CSC247
4-OH saccharin Na salt	160.6	135.6	149.4	139.0	175.6	124.5		97.8	110.9	113.8	110.8	106.7	91AX(B)905
Thiosaccharin Na salt	163.9	133.2	150.1	139.7	175.7	167.5		97.6	109.9	115.4	110.1	106.9	90AX(C)2341
Saccharin Co complex	163.4	136.4	149.9	138.5	175.3	124.4	(C=S)	97.1	110.6	113.4	111.1	107.6	83ICA21
 (12)	168.4	136.7	148.5	139.5	174.2	121.3		92.7	114.8	109.5	112.5	110.4	83LA2021
Saccharin N—CH ₂ CN ^a	165.7 168.9	138.6 138.1			174.3 175.5	121.4 120.9		92.3 91.8	115.0 114.3	109.5 109.8	112.5 112.8	110.7 111.2	89MI 305-02

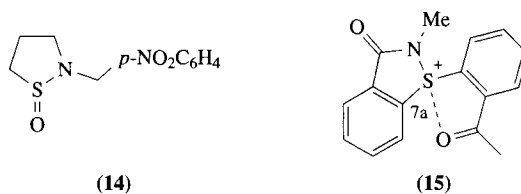
^aTwo molecules per unit cell with differing geometries.



thiosaccharin salts. Some of the published data relate to studies on sweetness (see Section 3.05.12.2). Representative data (by no means exhaustive) for the heterocyclic rings are gathered in Table 4. In the 1,1-dioxides the S=O bond length is typically 144 pm. In all cases the molecules are effectively planar apart from the sulfur oxygen atoms, but as can be seen there are some significant differences in geometry on going from the neutral molecule to the salt or metal complex. Anion formation widens the CSN and narrows the SNC angles, with significant shortening of the S—N bond. Theoretical calculations and experimental measurements (from x-ray diffraction) of electron density in the sodium salt of 4-hydroxysaccharin are consistent with these changes in bond length and angle <91AX(B)905>. The C=O distances are greater in the anions than expected for the formal double bond structure, consistent with the presence of resonance structures such as (13a) and (13b). Saccharin also forms salts with organic bases, and x-ray studies confirm that proton transfer occurs, resulting in a saccharinate anion <83AX(C)502, 91AX(C)100>. *N*-Substituted saccharin molecules retain the overall geometry and planarity of saccharin, with similar CSN and SNC angles. Many of the complexes with divalent metals (M) (e.g., Fe, Co, Ni, Cu, Zn, Cd, and Mn) exist as distorted octahedral structures with the general formula $[M(\text{saccharinate})_2(\text{H}_2\text{O})_4](\text{H}_2\text{O})_2$. The two saccharin molecules are coordinated in a *trans* configuration, through the nitrogen atom. The saccharin molecules remain planar, and bond angles and distances are generally similar to those of the saccharin anion. Metal–nitrogen bond distances are consistent with changes in ionic size except for the copper complex, which displays significant Jahn–Teller distortion (see, for example, Haider et al. <83ICA21, 84AX(C)1147>). The mercury complex is unusual in having a covalent Hg—N bond, but the saccharin bond lengths and angles are similar to those of the sodium or magnesium salts <82CSC263>.



Only a few fully saturated isothiazoles have been studied by x-ray techniques. The 1-oxide (14) has a non-planar ring, as expected. The sum of bond angles around sulfur is 307.5°, consistent with trigonal geometry at this atom, and the sum of angles around the heterocyclic nitrogen atom, 346°, is intermediate between sp^3 (328.5°) and sp^2 (360°) hybridization. The inference is that there is little p_π – d_π bonding between sulfur and nitrogen <93JOC696>. X-ray diffraction techniques have been used to support a proposed structure (15) for a cyclic sulfonium salt based on a three-centre four-electron bond involving sulfur <90MI 305-01>. The sulfur atom has a trigonal bipyramidal configuration, with the N—S—O bond axial, and the anion (e.g., Cl^-) filling the third equatorial position. The isothiazole NSC(7a) angle is 90.5°, the S—N bond distance is 168.5 pm, similar to (12) (Table 4), and the S—C(7a) bond length of 179 pm is significantly longer than in benzisothiazoles or saccharin derivatives.



3.05.3.1.2 Other techniques

Neutron diffraction has been used to determine the molecular geometry of sodium salts of derivatives of saccharin (88AX(C)1083, 89AX(C)1013). The results are very similar to those from x-ray diffraction. Gas phase electron diffraction studies give accurate molecular dimensions for isothiazole itself; these are compared with those calculated from microwave spectroscopy in Table 5 (88JST(176)61). The mean C—H bond length is 110.2 pm. Pulsed FT microwave spectroscopy of 4-methylisothiazole in the gas phase (1–2% in argon) indicates a principal axis almost along the C—Me bond (at an angle of 5.4° from this bond). The measured barrier to internal rotation about the C—Me bond is 105.8 cm⁻¹, much less than that of the corresponding isoxazole derivative (91ZN(A)635). The relationship between the principal inertial axes and rotational axes of isothiazole, together with measurements of viscosity, have been calculated from measurement of ¹³C and ¹⁴N nuclear relaxation rates and nuclear Overhauser measurements (84MP1411).

Table 5 Geometry of isothiazole from electron diffraction and microwave measurements (88JST61).

	Bond lengths (pm)					Heterocyclic bond angles (°)				
	S—N	N—C	C(3)—C(4)	C(4)—C(5)	C—S	CSN	SNC	NCC	CCC	CCS
Electron diffraction	164.2	131.9	143.6	138.8	170.2	96.1	112.2	111.8	113.8	106.2
Microwave (calculated)	165.1	132.8	137.7	136.7	173.7	95.8	106.4	120.0	110.0	107.7

3.05.3.2 NMR Spectroscopy

3.05.3.2.1 Proton NMR spectra

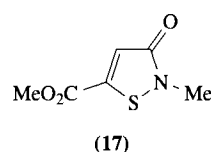
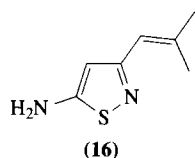
Information on chemical shifts and coupling constants for a range of typical compounds is given in CHEC-I (84CHEC-I(6)131). For isothiazole itself the chemical shifts and coupling constants in CCl₄ solution are H-3 8.54 ppm, H-4 7.26 ppm, and H-5 8.72 ppm, with ³J_{3,4} 1.66 Hz, ³J_{4,5} 4.66 Hz, and ⁴J_{3,5} 0.15 Hz. For aromatic isothiazoles the signal for H-4 is normally to highest field; there is a downfield shift, typically of 0.5 ppm, of H-5 on going from CDCl₃ to DMSO as the solvent; the signal from H-3 may be broadened because of the adjacent quadrupolar nitrogen atom; and coupling constants (³J_{4,5}) can be used to distinguish between isothiazole and 3(2*H*) isothiazoline structures, where ³J_{4,5} increases to approximately 6 Hz in isothiazolin-3-ones. In the present work, information on further aromatic isothiazole systems is briefly summarized, and coverage is extended to some saturated systems.

The signal at H-4 is shifted upfield with a 5-amino substituent; for example in (16) this signal resonates at 5.90 ppm in CDCl₃ solution (92M133). As noted in CHEC-I (84CHEC-I(6)131), chemical shift information should be used with care when attempting to distinguish between possible tautomeric structures. Table 6 lists chemical shifts for a series of 3-substituted isothiazoles and isothiazol-3-ones (17) in CDCl₃ solution (85EJM447). The chemical shifts are insufficiently different to differentiate unequivocally between possible tautomeric forms of the 3-hydroxy compound, and IR spectroscopy is more helpful.

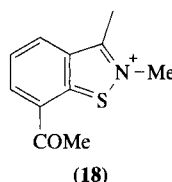
In 1,2-benzisothiazole H-3 has a signal at 8.73 ppm in CCl₄ solution. Chemical shifts for some substituted 1,2-benzisothiazoles are given in Table 7. In the cation (18) the coupling constants in the benzene ring of 7.9 Hz are marginally greater than in the comparator neutral molecule (7.6 Hz). The aromatic CH signals are all moved significantly downfield in the salt, consistent with deshielding caused by protonation of the nitrogen atom, but the change of solvent should be noted. The ¹H NMR spectra of some aromatic and reduced 1,2-benzisothiazole-1,1-dioxides (19) are given in Table

Table 6 Proton NMR chemical shifts of 3-substituted isothiazoles and isothiazole-3-ones in CDCl₃ <85EJM447>.

Substituent				δ (ppm)		
2	3	4	5	H-4	3-OMe	OH
–	OMe	H	CH ₂ OH	6.43	3.95	3.7
–	OMe	H	CO ₂ Me	7.08	3.93 or 4.03	–
–	OH	H	CO ₂ Me	7.10	–	10.2
Me ^a	=O ^a	H ^a	CO ₂ Me ^a	6.87	(NMe 3.40)	–

^aCompound (17).

8. The 3-oxo compounds have an aromatic multiplet shifted slightly to lower field than in 1,2-benzisothiazole itself (7.12–8.00 ppm) and the reduced compounds (X = CH₂, CHMe; Table 8).



The chemical shifts of a series of reduced isothiazole 1-oxides and 1,1-dioxides (**20**) are given in Table 9. The 1-oxides clearly show the presence of the two S=O configurations. It has been confirmed by deuteration experiments (**20**; X = SO, R¹ = H, D, R² = H, R³ = D) that the lower-field signal at C-5 (2.95 ppm) arises from the hydrogen atom *syn* to the S=O bond. In the case of the 1,1-dioxides, rapid inversion at the nitrogen atom at normal temperatures results in averaging of the conformations on the NMR timescale. Some applications of ¹H NMR spectroscopy in the conformational analysis of reduced isothiazoles are given in Section 3.05.4.4.

3.05.3.2.2 Carbon-13 NMR spectra

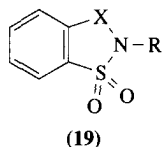
The use of ¹³C NMR spectroscopy is now routine, and there is a vast amount of information in the literature. Table 10 lists some ¹³C chemical shifts of isothiazoles which are complementary to those given in CHEC-I <84CHEC-I(6)131>. As expected, CN causes an upfield shift of the adjacent carbon atom. The shift of this signal has been related to chemical reactivity of nitriles to give enamino ketones <82H(19)221>. It is worth noting also the substantial upfield shift at C-4 caused by a 5-amino substituent; this must arise from resonance forms involving Me₂N=, which cause an increase in electron density at the adjacent 4 position. Coupling constants (¹J_{c,c}) have been related to the double or single bond nature of the C—C bond <94MRC62>. The values for ¹J_{3,4} and ¹J_{4,5} for isothiazole are 52.5 Hz and 62.3 Hz. Attempts have been made to calculate carbon chemical shifts for isothiazole and 1,2-benzisothiazole on the basis of the π electron density on the relevant carbon atom <83JOC763, 87KGS544>. Such calculations are more relevant for ¹³C than ¹H chemical shifts because the effect of the ring current is much less with ¹³C. The calculated shifts are within 3 ppm of the experimental values for C-3 and C-4, but the perturbations introduced by the adjacent sulfur atom give a poorer result for C-5.

The signals from the carbons of the benzene ring of 1,2-benzisothiazole absorb in the region of 120–135 ppm. Their assignments can be made on the basis of prediction from substituent effects, but should be made with more certainty from multiplicity and from two-dimensional NMR experiments which give unequivocal information from spin couplings. The heterocyclic part of the molecule can be considered to a first approximation as a 4,5-dialkyl-substituted isothiazole. Some typical ¹³C

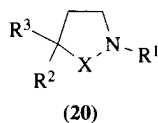
Table 7 Proton NMR spectra of 1,2-benzisothiazoles and a quaternary salt.

Substituent						Chemical shift (ppm)					Solvent	Ref.
2	3	4	5	6	7	H-3	H-4	H-5	H-6	H-7		
1,2-Benzisothiazoles												
–	Me	H	H	H	COMe	(Me 2.76)	8.12	7.55	8.12	–	CDCl ₃	91JHC749
–	H	H	OMe	OMe	H	8.71	7.30	–	–	7.37	CDCl ₃	89T2731
–	Me	H	COMe	H	H	(Me 2.83)	8.60	–	8.07	8.09	CDCl ₃	91JHC749
–	Me	H	COMe	SMe	H	(Me 2.80)	8.83		(SMe 2.51)	7.72	CDCl ₃	91JHC749
Quaternary N—Me salt (18) ^a												
Me	Me	H	H	H	COMe	(Me 3.24)	9.10	8.13	9.10	–	CD ₃ COCD ₃	91JHC749

^a +N—Me 446 ppm.

Table 8 Proton NMR data on 1,2-benzisothiazole 1,1-dioxides (19).

Substituent		Chemical shift (ppm)			Solvent	Ref.
R	X	R	X	Aromatic		
H	CH ₂	6.45	4.55	7.3–7.55	CD ₃ COCD ₃	83JOC537
Cl	CH ₂	–	4.58	7.18–7.9	CDCl ₃	83JOC537
H	CHMe	5.25	(1.55 (Me)) (4.73 (CH))	7.2–7.8	CDCl ₃	83JOC537
Pr ^a	CHOH	3.2–3.5 (CH ₂)	5.70 (CH)	–	CDCl ₃	94T5425
Me	CHNHMe	2.94	5.22 (CH)	7.62–7.86	CDCl ₃	94T5425
Me	C=O	3.20	–	7.6–8.2	CDCl ₃	93JHC353
Et	C=O	(3.8 (CH ₂))	–	7.6–8.2	CDCl ₃	93JHC353
CH ₂ Ph	C=O	(4.87 (CH ₂))	–	7.73–8.01	CDCl ₃	86CCC1304
CH ₂ COMe	C=O	(4.47 (CH ₂))	–	7.88–8.01	CDCl ₃	86CCC1304
CH ₂ OCOPh	C=O	6.2 (CH ₂)	–	7.4–8.2	CDCl ₃	93JHC353

Table 9 Proton NMR data on reduced isothiazoles (20).

Substituent		Chemical shift (ppm)				Solvent	Ref.
X	R ¹	CH ₂ -3	CH ₂ -4	CH ₂ -5	R ¹		
SO	CH ₂ Ph	3.18, 3.38	2.20, 2.63	2.92–3.06	4.19, 4.50 (CH ₂) ^a	CDCl ₃	93JOC696
SO	CH ₂ CO ₂ Me	3.37, 3.57	2.38, 2.74	2.95–3.15	3.87, 4.26 (CH ₂) ^b	CDCl ₃	93JOC696
SO	H(D)	3.34, 3.75	2.16, 2.48	2.79, 2.95	4.78 (NH)	CDCl ₃	93JOC696
SO ₂	Me	3.19 or 3.24	2.34	3.19 or 3.24	2.68 (Me)	CDCl ₃	82JA7108
SO ₂	Me ₂ (quaternary) ^c	3.95	2.63	3.95	3.25 (N ⁺ Me ₂)	CD ₃ CN	82JA7108

^a ²J = 15 Hz. ^b ²J = 18 Hz. ^c FSO₃[−] salt.**Table 10** Carbon-13 NMR chemical shifts of isothiazoles.

Substituent				Chemical Shifts, δ (ppm)			Solvent	Ref.
1	3	4	5	3	4	5		
–	H	H	H	157.0	123.4	147.8	CDCl ₃	75CJC836
–	CN	H	Me	139.1	126.6	166.9	CDCl ₃	82H(19)221
–	Me	H	CN	167.4	131.5	133.2	CDCl ₃	82H(19)221
–	Me	CN	H	167.6	109.3	157.0	CDCl ₃	82H(19)221
–	H	H	C(OH)Ph ₂	157.1	122.7	176.7	CDCl ₃	88CJC1617
–	CH=CMe ₂	H	NMe ₂	165.8	101.4	175.9	CDCl ₃	92M133
–	C ₆ H ₅	H	SEt	167.8	121.1	162.4	CDCl ₃	87S349
O ₂	OEt	NH ₂	CO ₂ Et	159.9	146.5	101.6	DMSO	83JOC763
O ₂	NH ₂	NH ₂	CO ₂ Et	156.9	148.7	101.4	DMSO	83JOC763

chemical shifts for the heterocyclic carbons of 1,2-benzisothiazoles and 1- or 3-oxo derivatives are given in Table 11. In the 3-oxo compounds the C-3 resonance is shifted significantly upfield from typical ketones or esters because of conjugation of the carbonyl group with the ring π electron system.

Table 11 Carbon-13 NMR chemical shifts of 1,2-benzisothiazoles and 1- or 3-oxides.

Substituent							Chemical shift, δ (ppm)			Solvent	Ref.
1	2	3	4	5	6	7	3	3a	7a		
—	—	Me	H	H	H	H	162.8	NA	152.0	CDCl ₃	87JA7137
—	—	Me	H	H	H	COMe	161.1	129.7	150.3	CDCl ₃	91JHC749
—	—	Me	H	H	H	OMe	162.9	NA	153.0	CDCl ₃	87JA7137
—	—	(CH ₂) ₄ CN	H	H	H	H	165.1	134.1	152.0	CDCl ₃	88JCS(P1)2141
—	—	Ph	H	OMe	OMe	H	163.5	128.0	148.3	CDCl ₃	88T2985
—	H	=O	H	OMe	OMe	H	166.9	119.2	142.3	DMSO	88T2985
—	^a	=O	H	Me	H	H	165.4	119.9	137.6	CDCl ₃	93JHC141
=O	H	=O	H	H	H	H	169.1	128.9	149.8	DMSO	88T2985
=O	H	=O	H	OMe	OMe	H	168.9	121.8	142.9	DMSO	88T2985

NA, not assigned.

^a2',3'-O-Isopropylidene- β -D-ribofuranose.

Saccharin, its salts, and related compounds have been extensively studied by many techniques, including ¹³C NMR, and data are summarized in Table 12. The chemical shift of C-3 in particular appears to be sensitive to the degree of ionization. It should be noted that there is some confusion in the literature over the assignments of carbon signals of the benzene ring. Fortunately the INADEQUATE spectrum of saccharinate ion in D₂O/H₂O has been published in full, and these assignments are therefore certain (87MI 305-01).

Table 12 Carbon-13 NMR chemical shifts of saccharin and related compounds.

Compound	Chemical shift, δ (ppm)							Solvent	Ref.
	3	3a	4	5	6	7	7a		
Saccharin	161.0	127.9	125.1	134.7	135.5	121.2	139.5	DMSO	84CHEC(6)131
Saccharin-Na salt	168.2	134.6	122.5	131.1	131.6	119.1	145.3	DMSO	91JST185
Saccharin-Na salt	172.2	132.2	123.5	134.0	133.5	120.3	141.7	H ₂ O/D ₂ O	87MI 305-01
Saccharin-Hg salt	163.8	128.9	124.5	134.0	134.8	120.8	142.3	DMSO	91JST185
N-Substituted (12)	159.1	126.8	121.9	135.8	125.6 ^a	136.4 ^a	137.8	DMSO	83LA2021
3-Anil (21)	156.8	128.3	123.5	133.7	121.4 ^a	133.3 ^a	140.9	DMSO	87JCED391

^aThese signals may be incorrectly assigned—see text.



3.05.3.2.3 NMR of other nuclei

The increasing use of two-dimensional techniques in ¹H and ¹³C NMR, and the structural and conformational information available from nuclear Overhauser effect (nOe) experiments, have resulted in fewer applications of the NMR of other nuclei than might have been expected. Chemical shifts in ¹⁴N and ¹⁵N NMR for some isothiazoles and 1,2-benzisothiazoles and saccharin are given in CHEC-I (84CHEC-I(6)131), and there are reference data on other heterocycles (83HCA1537, 84OMR(22)215). Coupling constants are given in Table 13. In general, ²J_{N,H} values of 10–14 Hz are seen across formal double bonds when the nitrogen lone pair of electrons and a C—H bond are in

a *cis* configuration to each other, as is isothiazoles. The values for isothiazoles are similar to isoxazoles, but significantly less than in thiazole where $^2J_{3,2}$ and $^3J_{3,4}$ are both about 10.5 Hz, confirming the extensive π electron delocalization in this case.

Table 13 Nitrogen-15 NMR chemical shifts and coupling constants for isothiazoles <83HCA1537>.

Substituents			Chemical shift, δ (ref. MeNO ₂) (ppm)	$^2J_{2,3}$	$^3J_{2,4}$	$^3J_{2,5}$
3	4	5				
H	H	H	-81.8	14.2	1.86	1.32
H	Me	H	-81.8	14.4	-	1.3
H	Me	H	-87.0			
H	H	Me	-86.6	14.5	2.2	-
Me	CO ₂ H	H	-86.6	-	-	1.5

An empirical correlation between the ^{14}N chemical shift (δ_{N}) and residual π electron density at the nitrogen (q^{π}) has been proposed ($\delta_{\text{N}} = 456 + 81.5 q^{\pi}$). Calculated and experimental values for isothiazole and 1,2- and 2,1-benzisothiazoles are in reasonable agreement <87KGS544>.

NMR spectra of other nuclei have been reported. A problem with ^{33}S NMR is the broadness of the signal because of the adjacent nitrogen atom; isothiazole absorbs at +53.7 ppm (reference (NH₄)₂SO₄) <84CJC981>. The saccharinate anion has been examined by ^{17}O NMR; the chemical shifts for O-1 (155 ppm) and O-3 (275 ppm) (reference H₂O) are consistent with extensive contribution from resonance forms such as $=\text{C}-\text{O}^-$, whereas the sulfur oxygens show little evidence for delocalization of the negative charge onto them <87MI 305-01>.

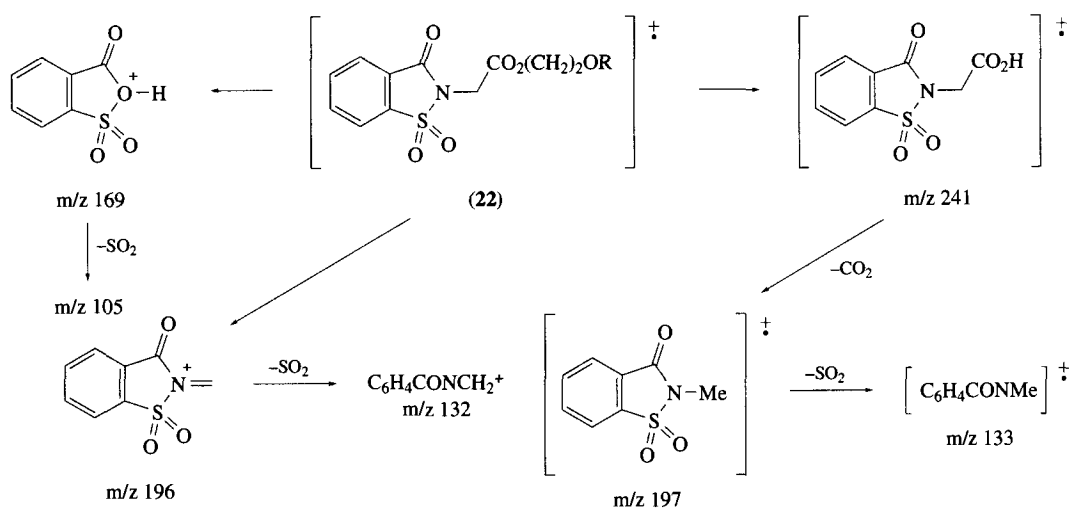
3.05.3.3 Mass Spectroscopy

Aromatic isothiazoles and benzisothiazoles are characterized by strong molecular ions, and typical fragmentation pathways are given in CHEC-I <84CHEC-I(6)131>. A feature of 1,1-dioxides is the ready abstraction of SO or SO₂, resulting in weaker molecular ions. In general, standard electron impact techniques are appropriate for many isothiazoles, but softer techniques, notably fast atom bombardment (FAB), are more suitable for quaternary salts (see, for example, McKinnon and Abouzeid <91JHC749>). Further fragmentation schemes for 1,2 and 1,1-benzisothiazoles and a sultam derivative are discussed below.

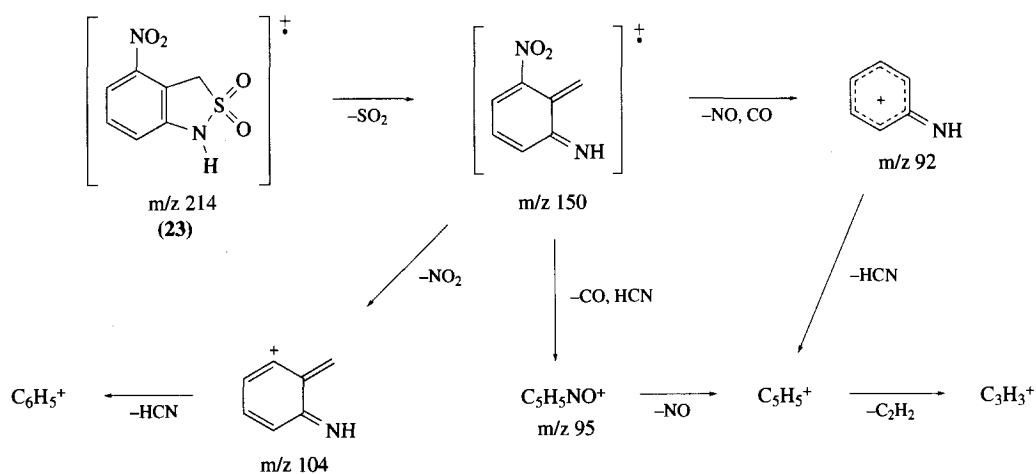
The fragmentation of *N*-substituted saccharin derivatives has been examined in some detail <86CCC1304>. A simplified fragmentation pathway is shown for one such derivative, (22), in Scheme 1. The molecular ion is relatively weak (1–12%) because of the ready fragmentation of the side chain, which gives rise to the most intense peaks. Loss of SO₂ occurs from many of the fragment ions. The fragmentation of a series of 4- or 6-nitro- 2,1-benzisothiazoline-2,2-dioxides has been studied in detail by a range of techniques (collision-induced decomposition, mass-analysed ion kinetic energy, and linked-scan techniques) and shows a number of characteristic features such as intense molecular ions, loss of SO₂, and weak ions from loss of O, OH, or NO₂ from the nitro groups <93OMS(28)853, 93RCM763>. The proposed pathway for the NH parent compound (23) is shown in Scheme 2; the fragmentation schemes for *N*-substituted derivatives are given in the original papers. In the example shown, the molecular ion intensity under electron impact is 98% of that of the base peak (m/z 92). Molecules of this type undergo thermal elimination of SO₂ at about 200°C, but the mass spectrum showed loss of SO₂ at much lower temperatures, confirming that this loss is also electron impact induced. Analysis of metastable peaks showed that there are indeed two mechanisms for loss of SO₂ from the molecular ion under electron impact <93RCM763>.

Loss of SO₂ also dominates the mass spectra of sultams (24) <93RRC27>. The molecular ion intensity is very dependent on the nature of the *N*-substituent, ranging from intense when R = Ar to very weak where β -cleavage of the side chain is possible (e.g., R = CH₂CH₂CO₂H), or where a rearrangement involving the sultam ring hydrogens at position 3 is possible (e.g., R = CH₂COX). The fragmentation of the parent molecule (24; R = H) is shown in Scheme 3; the base peak is at m/z 30.

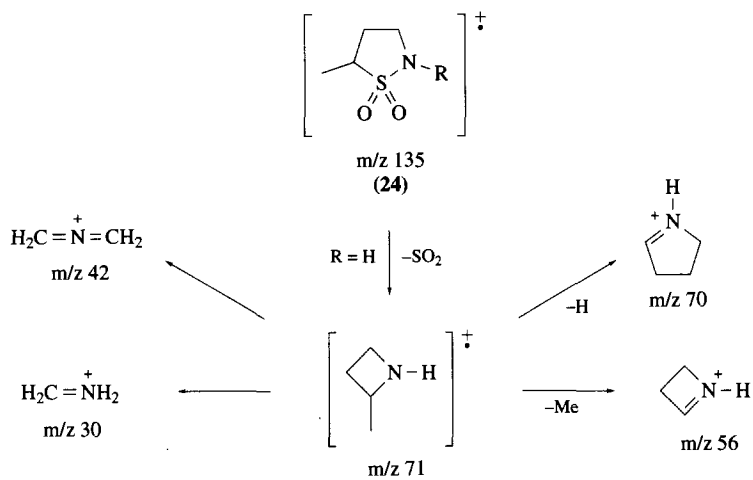
The negative ion mass spectrum of isothiazole has been studied in detail <92MI 305-01>. A main conclusion from a study of collision-induced activation and charge reversal negative ion spectra of isothiazole and its 3-, 4-, and 5-methyl derivatives is that reaction with NH₂⁻ gives rise to depro-



Scheme 1



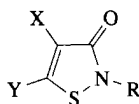
Scheme 2



Scheme 3

tonation predominantly from the 5 position. The most intense fragment ion arises from loss of HCN, or MeCN in the case of the 3-Me derivative. There is no evidence for any interconversion of isothiazole and thiazole under negative ion conditions, although they can be interconverted photochemically.

Gas chromatography-mass spectroscopy has been used for quantitative analysis of 2-substituted isothiazol-3-ones, (**25**) which are constituents of "Kathon" preservative agents. The fragmentation pathways are discussed, for example, by Matissek and Wittkowski <84MI 305-01> and Favretto et al. <91MI 305-01>. The molecular ions are intense, with loss of CO being an important fragmentation pathway. Both α and β cleavage are important processes for (**25d**).



- (**25a**) X = Y = H, R = Me
 (**25b**) X = H, Y = Cl, R = Me
 (**25c**) X = Y = Cl, R = Me
 (**25d**) X = Y = H, R = *n*-octyl

3.05.3.4 Ultraviolet Spectroscopy

The ultraviolet spectra of substituted isothiazoles and 1,2- and 2,1-benzothiazoles are described in CHEC-I <84CHEC-I(6)131>. Isothiazole itself has an absorption maximum in ethanol solution at 244 nm ($\log \epsilon = 3.72$), 1,2-benzisothiazole has maxima at 205 nm, 222 nm, 252 nm, 297 nm, and 302 nm, and 2,1-benzisothiazole maxima at 203 nm, 221 nm, 288 nm, 298 nm, and 315 nm. The widespread use of HPLC techniques with ultraviolet detection for detection of preservative agents has led to a considerable body of literature on the ultraviolet spectra of isothiazolin-3-ones (**25**) (Table 14).

Table 14 Ultraviolet absorption of isothiazole-3-ones (**25**)
 <87MI 305-02> (solvent: methanol/water, 8:2 v/v).

Compound	$\lambda_{\max}$ (nm)	$\log \epsilon$	$\lambda_{\max}$ (nm)	$\log \epsilon$
(25a)		NR	275	3.90
(25b)	217	3.78	276	3.84
(25c)	227	3.64	281	3.92
(25d)		NR	279	3.92

NR, not reported.

Data for saccharin and its anion are given in Table 15 <84MI 305-02>; these have also been used for analytical purposes.

Table 15 Ultraviolet absorption of saccharin <84MI 305-01>.

Solvent	$\lambda_{\max}$ (nm)	$\log \epsilon$	$\lambda_{\max}$ (nm)	$\log \epsilon$	$\lambda_{\max}$ (nm)	$\log \epsilon$
Methanol	226	3.93	276	2.98	285	2.89
0.1 N NaOH	234.5	3.81	268	3.21		

In the case of divalent metal (M) complexes ($[M(\text{saccharinate})_2(\text{H}_2\text{O})_4]$, M = Mn, Fe, Cr, Ni, or Cu) the ultraviolet spectra and magnetic properties are consistent with octahedral coordination, with the two saccharin molecules *trans* to each other, coordinated through nitrogen. The ligand field splittings are very similar to the hexa-aquo complexes, suggesting little distortion from octahedral coordination, and the metals are in a high-spin electronic configuration <90PO1383>.

3.05.3.5 Infrared and Raman Spectroscopy

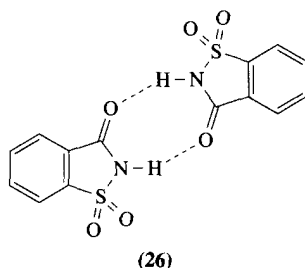
In many isothiazoles the most intense absorptions occur near 840 cm^{-1} and 750 cm^{-1} , and a table of the most characteristic bands is given in CHEC-I (84CHEC-I(6)131). A detailed analysis of the infrared and Raman spectra of 1,2- and 2,1-benzisothiazole has subsequently been published (83PS(16)313). These molecules have 36 fundamental vibrations, of which 25 are in the plane of the molecule and 11 out of plane. The heterocyclic C(3)—H vibration occurs at 3042 cm^{-1} (1,2-benzisothiazole) and 3092 cm^{-1} (2,1-benzisothiazole), these values being very similar to those of 4,5- and 3,4-disubstituted isothiazoles, respectively. Characteristic intense out-of-plane C—H vibrations ($\delta(\text{C—H})$) for the aromatic hydrogens occur at 749 cm^{-1} and 757 cm^{-1} for 1,2- and 2,1-benzisothiazoles, respectively.

Among the most characteristic and structurally useful infrared absorption bands are the symmetric and anti-symmetric S=O vibrations of 1,1-dioxides and C(3)=O vibration of isothiazol-3-ones. The symmetric S=O stretching vibration of 1,1-dioxides, near 1170 cm^{-1} , is particularly insensitive to substituents, and the asymmetric vibration is usually in the range $1300\text{--}1350\text{ cm}^{-1}$. The exocyclic C(3)=O bond is very sensitive to conjugation and charge density in the heterocyclic ring, as can be seen from Table 16. The mercury saccharinate complex is of interest because the mercury is covalently bound; in other metal coordinate complexes the C=O value falls, as expected, to below 1650 cm^{-1} , reflecting the essentially anionic character of the complexed saccharinate. The carbonyl groups of 5- and 7-acetyl-1,2-benzisothiazoles have absorptions at 1685 cm^{-1} and 1655 cm^{-1} , respectively. These are shifted to lower frequency by adjacent sulfur groups (91JHC749). The carbonyl absorption of the quaternary 2,3-dimethyl-7-acetyl-1,2-benzisothiazolium perchlorate (18) is at 1645 cm^{-1} ; this lower frequency has been ascribed to a bond between the carbonyl oxygen and sulfur involving hypervalent sulfur (91JHC749).

Table 16 Infrared absorption frequency of exocyclic C(3)=O vibrations.

Compound	$\nu(\text{C}=\text{O})$ (cm^{-1})	Ref.
<i>N</i> -Methyl saccharin	1750	93JHC353
Saccharin	1725	88JST(174)467
Saccharin anion	1640	84CC1583
Saccharin-mercury salt	1700	88JST467
<i>N</i> -Methyl isothiazol-3-one	1660	64TL1477
(17)	1620	85EJM447

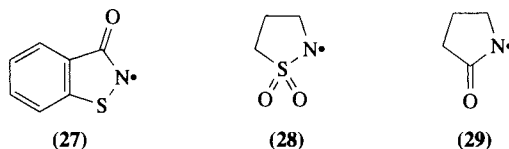
The hydrogen bonding of saccharin, thiosaccharin, and their salts have been examined in detail (86JST(142)275, 92JST(267)197). Saccharin exists in the solid state as a symmetric dimer (26), and there are three bonds in the N—H stretching region (3090 cm^{-1} , 2970 cm^{-1} , and 2700 cm^{-1}), one of which is an overtone vibration. Thiosaccharin on the other hand, exists as in a weakly hydrogen-bonded network structure, and has only one N—H absorption, at 3360 cm^{-1} . In the salts, the 1,1-dioxide oxygen atoms take part in hydrogen bonds with water of crystallization. Infrared spectroscopy has also been used to examine polymorphism in thiosaccharin (93JST(293)113).



3.05.3.6 Other Techniques

This section briefly describes some results from ESR experiments on benzisothiazol-3-ones (27) and sultams (28). These radicals were prepared by photolysis in degassed solutions in the presence of a suitable peroxide. The large hyperfine splittings of (27) in ^{17}O - and ^{33}S -enriched compounds

suggest extensive delocalization of the free electron onto the oxygen and sulfur atoms. This delocalization is consistent with a planar geometry for (27) <88JOC2850>. On the other hand, the low hyperfine coupling of (28) suggests little spin delocalization, and it is worth noting that the spin delocalization to the S-oxide is much less than in the related carbonyl compound (29) <83JOC537>.

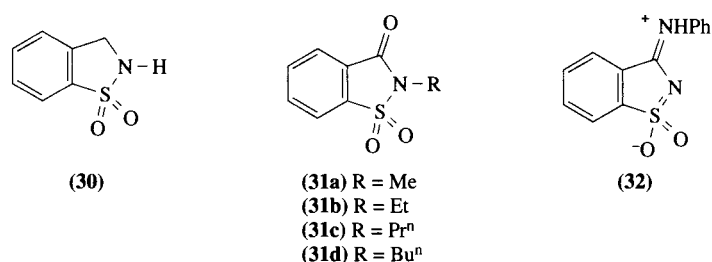


Mossbauer spectroscopy has been applied to several metal complexes but will not be discussed here (see, for example, Ng et al. <91JOM(403)101>), and x-ray photoelectron spectroscopy is briefly discussed in Section 3.05.2.2.

3.05.4 THERMODYNAMICS

3.05.4.1 Melting and Boiling Points

The melting and boiling points for some model isothiazoles and benzisothiazoles are given in CHEC-I <84CHEC-I(6)131>. In summary, the parent molecules have low melting points (isothiazole and 2,1-benzisothiazole are liquids, b.p. 113°C and 242°C, respectively; 1,2-benzisothiazole melts at 37°C). Isothiazole undergoes several glassy transitions in the solid phase before melting at -71°C <85MI 305-01>. Substituents which can introduce hydrogen bonding increase the stability of the crystalline state and raise the melting point. Thus, saccharin which exists as the symmetric hydrogen-bonded dimer (26) in the solid state, melts at 228°C, whilst (30) and (31a) melt at 110–112°C and 129–130°C, respectively <83JOC537, 93JHC353>. It is interesting to compare melting points of the series (31a)–(31d) (129°C, 92°C, 71°C, and 38°C, respectively); although the molecular weight increases, the increasing bulk of the R group prevents any interaction of the polar groups in the crystalline state, and thus the melting points decrease <93JHC353>. Introduction of further polar groups (e.g., (31): R = CH₂COPh, m.p. 191–193°C; R = COPh, 163–165°C; R = CH₂CH₂SOMe, 127–128°C) results in an increase in melting point <86CCC1304, 89JPS903, 93JHC353>. 1,2-Benzisothiazol-3-(2*H*)-one itself melts at 158–160°C. Saccharin anils (21) have very high melting points (317°C for (21)), consistent with charge delocalization giving rise to polar species such as (32) <87JCED391>. Sultams are low melting solids (e.g., (8; R = Me), 46–49°C) whilst the quaternary salts, as expected, have much higher melting points <82JA7108>.



3.05.4.2 Solution Properties

Isothiazole has a solubility of about 3.5% in water and is miscible with most organic solvents. The benzisothiazoles are insoluble in water but soluble in strong acids (salt formation), and soluble in organic solvents. The solubility of substituted compounds is very dependent on the possibilities of stabilizing the crystal by internal hydrogen bonding, and upon the *pK* (as an acid or base) of any ionizable groups. The former point is illustrated by (12), where the aqueous solubility of the single enantiomers (1.2 g l⁻¹) is some six times greater than that of the racemate because the racemic molecules crystallize as strongly hydrogen-bonded dimers which are not favored for the single enantiomers <83LA2021>. Saccharin has a solubility in water of 0.2 g l⁻¹ at 20°C, rising to 1.3 g l⁻¹

at 75°C, and sodium saccharin has a solubility of 100 g l⁻¹ at 20°C, rising to 254 g l⁻¹ at 75°C <84MI 305-02>.

The partition behavior of compounds between aqueous phases and octanol is now a routine measurement or calculation used in life sciences research as a model for membrane transport, particularly across the 'blood-brain' barrier. The effect of counterions on the partition of saccharin has been extensively studied to investigate permeation of, and solubility in, lipid membranes <89PHA66, 90PHA191>.

The p*K*_a values of a range of isothiazoles are given in CHEC-I <84CHEC-I(6)131>. Isothiazole itself has a p*K*_a of -0.5, and 2,1-benzisothiazole a p*K*_a of -0.05. Compared with benzoic acid (p*K*_a 4.2), isothiazole has the effect of strengthening the acidity of attached carboxylic acid groups; the p*K*_a values of isothiazole 3-, 4-, and 5-carboxylic acids being 3.67, 3.45, and 2.60, respectively. The p*K*_a of saccharin in water is 1.6, and this value rises to 4.25 in water-saturated octanol, where ionization of the N—H proton is more difficult <89MI 305-01>. 4-Hydroxyisothiazole-3-one 1,1-dioxides (**40a**) have p*K*_a values around 3.3–3.7 (in 50% EtOH), and 4-hydroxyisothiazoline 1,1-dioxides (**41a**) in the region 4.2–4.7 <84JOC2212, 85AP(318)304>.

3.05.4.3 Aromaticity

In recent years the definitions and criteria of aromaticity have been examined in detail, and there are several authoritative reviews which give background to the theoretical, experimental, and statistical criteria used for isothiazole and related compounds <85T1409, 87KGS544, 90IJQ843, 90JPR885, 92JPO74, 93AHC(56)303, 93QSAR146>. In all treatments isothiazole is clearly a planar aromatic molecule, and its degree of aromaticity by most models is similar to that of thiazole and pyrazole, and higher than isoxazole and oxazole. Comparative data are given in Table 17, where the theoretical or experimental criteria used are as follows:

- Bird index: calculated from statistical deviation of bond orders from bond length measurements; higher values imply higher aromaticity, on a scale of 0–100 <85T1409>.
- Effective resonance energy (*Δ*ε*π*L*): the energy difference calculated between the eigenvalues of the lowest π delocalized molecular orbital and the corresponding eigenvalues of the lowest π localized orbitals using Boys localization procedure <90IJQ843>.
- The π ring current contribution to the out-of-plane component of the magnetic susceptibility, χ_⊥ <87ZN(A)49>.
- The calculated induced π electron ring current as a fraction (*I*) of that calculated for benzene, using the PPP method <87KGS544>.

There are numerous other measures, including heats of formation and ¹⁵N chemical shift. These are listed by Katritzky and Barczynski <90JPR885>.

Table 17 Comparative aromaticity criteria for isothiazole, thiazole, pyrazole, and isoxazole.

	<i>Bird Index</i>	*Δ <i>ε</i> π <i>L</i>	χ _⊥	<i>I</i>
Isothiazole	59	-0.107	-37.2	0.621
Thiazole	64	-0.100	-39.5	0.902
Pyrazole	73	-0.100	-33.3	—
Isoxazole	47	-0.075	-26.0	—
Oxazole	38	-0.069	-22.5	—

Another possible criterion of aromaticity, the tendency of ¹*J*_{c,c} coupling constants in ¹³C NMR to converge toward that of benzene (56 Hz) as the degree of aromaticity increases (i.e., single/double bond fixation decreases), has since been proposed <94MRC62>. The ¹*J*_{c,c} coupling constants of isothiazole are ¹*J*_{3,4} 52.5 Hz and ¹*J*_{4,5} 62.2 Hz. These compare with the more divergent pair ¹*J*_{3,4} 48.7 Hz and ¹*J*_{4,5} 67.7 Hz for the less aromatic isoxazole. Similarly, ¹*J*_{4,5} for thiazole (62.1 Hz) is closer to that of benzene than that of ¹*J*_{4,5} for oxazole (70.8 Hz). This model is interesting, but other factors, including geometry, contribute to these coupling constants.

Alternation of bond orders has been used to show that isothiazole 1-oxide and the 1,1-dioxide are not aromatic, but are better described as ylides. The degree of bond fixation in the oxides

calculated by molecular orbital techniques is markedly greater, as shown in Table 18. The small calculated dipole moment of isothiazole compared with the sulfoxides also indicates a much higher degree of π electron delocalization in the parent compound $\langle 92\text{JPO}74 \rangle$.

Table 18 Bond orders and calculated dipole moments of isothiazole and its 1-oxides $\langle 92\text{JPO}74 \rangle$.

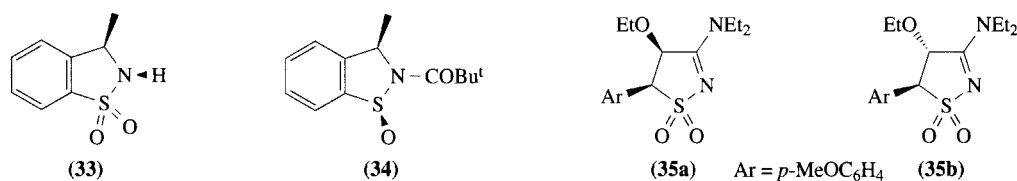
	Calculated bond order					Dipole moment (D)
	S—N	N—C	C(3)—C(4)	C(4)—C(5)	C—S	
Isothiazole	1.40	1.68	1.49	1.92	1.57	2.9 ^a
Isothiazole-1-oxide	0.99	1.87	1.22	2.13	1.09	6.06
Isothiazole-1,1-dioxide	0.91	1.91	1.13	2.18	1.00	6.90

^aMeasured value 2.4 D.

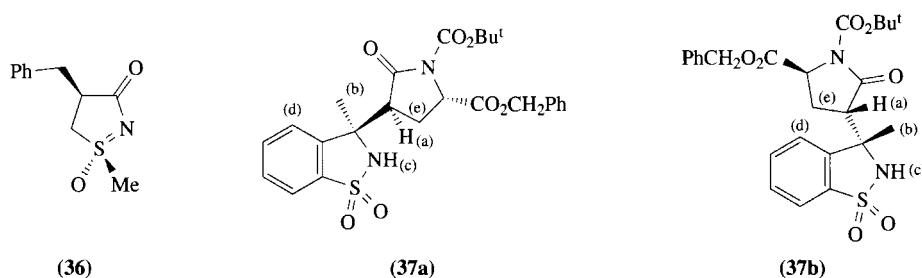
3.05.4.4 Conformations

Isothiazole and the benzisothiazoles are planar molecules, and the 1,1-dioxides, saccharin and thiosaccharin, and their salts, are all planar, apart, of course, from the oxygen atoms on sulfur. Calculations on isothiazole-1-oxide show that the heterocyclic ring has an envelope conformation, with the sulfur atom 22 pm above, and the oxygen atom 85 pm below, the plane of the other four atoms of the ring. This, of course, would result in a significant dipole moment, calculated to be 1.27 D, perpendicular to the plane of the ring $\langle 92\text{JPO}74 \rangle$.

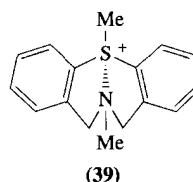
X-ray studies of the 1,2-benzisothiazoline-1,1-dioxide (**33**) show that in the crystalline state the molecule is nonplanar, and exists as an equimolar mixture of two conformers having the nitrogen atom 3 pm or 51 pm above the plane of the ring. The N—H and C—Me bonds lie in a *cis* configuration, allowing the nitrogen lone pair of electrons to bisect the angle between the S—O bonds. The existence of two conformers in the crystalline state implies significant flexibility. The conformation of (**33**) is in contrast to that of the *N*-acyl derivative, where the nitrogen lone pair is involved in conjugation $\langle 90\text{TL}4117 \rangle$. The sulfonamide (**34**) has a planar endocyclic nitrogen, and the S=O and C—Me bonds are in a *cis* configuration $\langle 90\text{TL}4117 \rangle$. Proton NMR studies on the substituted 3-aminoisothiazoline 1,1-dioxides (**35a**) and (**35b**) enable ready distinction of the *cis* and *trans* isomers, the $^3J_{4,5}$ coupling constants being 8.2 Hz and 1 Hz, respectively, implying a dihedral angle close to 90° in (**35b**) $\langle 93\text{T}9117 \rangle$.



There are many examples of the use of nOe measurements from NMR to establish conformations. The existence of an nOe interaction between the Me and benzylic CH₂ groups has been used to confirm the geometry of (**36**) $\langle 88\text{SC}769 \rangle$. Studies of nOe interactions between various hydrogen atoms of (**37**) have been used to confirm both the stereochemistry and the conformations of (**37a**) and (**37b**) $\langle 91\text{TL}2679 \rangle$. For example, in (**37a**) there is an nOe between H(a) and both CH₃(b) and NH(c), whereas in (**37b**) the nOe is only between H(a) and CH₃(b). Similarly in (**37b**), but not (**37a**), there is an nOe between the aromatic hydrogen, (d) and both H(a) and one of the adjacent methylene hydrogen atoms (e).



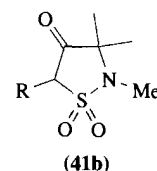
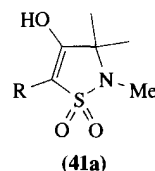
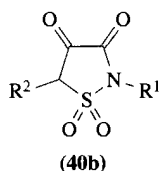
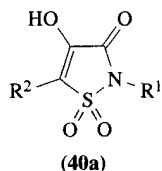
Fully saturated isothiazoles normally exist in an envelope conformation. X-ray studies of dehydromethionine (**38**) show that C-3 lies out of the plane of the other four ring atoms, and on the same face of the ring as the S—Me group. However, the NMR studies in solution suggest rapid equilibrium between the conformers <82JCS(P1)1283>. A combination of ^1H and ^{13}C NMR, x-ray studies, and theoretical calculations has been used to show that the dibenzo[*b,g*]thiazocinium salts exist as ammoniosulfuranes, with fairly rigid conformations as shown in (**39**), with the sulfur atom having a distorted trigonal bipyramidal geometry <86JA6320>. The increasing use of bornanesultams as chiral auxiliary agents depends on their having fairly rigid and predictable conformations <93TL4321>.



3.05.4.5 Tautomerism

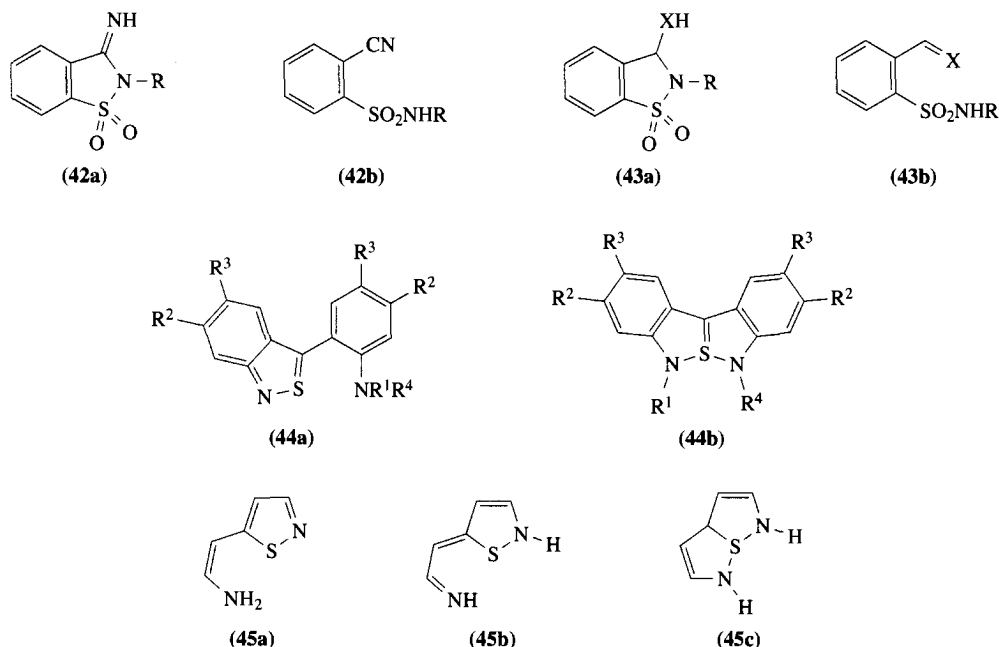
3-Hydroxyisothiazole exists as the hydroxy tautomer in nonpolar solvents, but more polar solvents result in a greater contribution of the 3-keto tautomer. Spectroscopic studies indicate that at least some 5-hydroxy isothiazoles exist in the 5-keto form. 1,2-Benzisothiazol-3-one, 2,1-benzisothiazol-3-one, and saccharin all exist in the keto form. The 3-amino derivatives of isothiazole and 1,2-benzisothiazole exist in the 3-amino form, as do their 1-oxides. 5-Phenyl-isothiazol-3-thiol exists in the SH form <84CHEC-I(6)131>. Comparison of the ultraviolet spectra of methyl 3-methoxy- and methyl 3-hydroxyisothiazole 5-carboxylate and the 3-one (**17**) indicates that this 3-hydroxyisothiazole also exists as the 3-hydroxy tautomer in methanol solution <85EJM447>.

Theoretical calculations on five-membered heterocycles, taking into account the heteroatoms and nature of substituents, indicate that for five-substituted isothiazoles, NH and SH substituents should exist in the isothiazole tautomeric form, whereas the 5-hydroxy group should exist as isothiazol-5-ones, in agreement with experiment <81AQ105>. 5-Aryl-4-hydroxyisothiazol-3-one 1,1-dioxides have been shown to exist as the 4-hydroxy tautomer rather than the possible 3,4-diketo tautomer (**40a**) $\rightleftharpoons$ (**40b**) ($\text{R}^1 = \text{Me}$, $\text{R}^2 = \text{Ph}$ or $\text{R}^1 = \text{H}$, $\text{R}^2 = \text{Ph}$) on the basis of ^{13}C NMR, infrared ($\text{C}=\text{O}$ 1710 cm^{-1}), and pK_a measurements (pK_a (4-OH) 3.3–4). One particular diketo compound (infrared, $\text{C}=\text{O}$ 1750 cm^{-1}) was, however, identified <84JOC2212>. Isothiazolidin-4-one 1,1-dioxides (**41**) exist in the solid state predominantly in the keto form (**41b**). In solution the tautomeric equilibrium depends on substituents and solvent; (**41**) ($\text{R} = \text{H}$) exists as the keto form in CDCl_3 , but (**41**) ($\text{R} = \text{CO}_2\text{Et}$) exists as the enol (**41a**) in this solvent. The 5-phenyl derivative (**41**) ($\text{R} = \text{Ph}$) favors the keto form in CDCl_3 but the enol in DMSO. These sultams show less tendency to enolize than the corresponding sultones <85AP(318)304>.



Studies of *o*-cyano benzene sulfonamides (**42a**) and (**42b**) by NMR and infrared spectroscopy show that an equilibrium exists between the ring-chain tautomers (**42a**) and (**42b**) in dioxane to which has been added 10% triethylamine, and the equilibrium favors the ring-opened tautomer. Both tautomers are stable in dioxane alone. In the case of the equivalent benzamide, however, the cyclic form is always favored because of the higher nucleophilicity of the amide nitrogen atom <83KGS1635>. A range of spectroscopic techniques, including CP/MAS solid state ^{13}C NMR, has been used to examine the tautomerism of (**43**). In the solid state the cyclic form (**43a**) is favored, and AM1 calculations and mass spectroscopy suggest that the ring-opened form (**43b**) is favored in the gas phase. In solution there is an equilibrium, depending on both the solvent (more polar solvents favoring the cyclic structure) and substituents. The cyclic form (**43a**) is preferred for $\text{R} = \text{Me}$

and $X = \text{NMe}$, and $R = \text{Pr}$ and $X = \text{O}$, whilst the open chain form (43b) is favored for $R = \text{Bu}^t$ and $X = \text{NBu}^t$, and $R = \text{Pr}^i$ and $X = \text{NPr}^i$ <94T5425>. NMR has been used to examine which of the tautomeric forms of (44) is preferred for different substituents. The tautomer (44b), which involves a hypervalent sulfur atom, is stable when $R^1, R^2, R^3 = \text{H}$ and $R^4 = \text{CH}_3\text{CO}$, but only the unsymmetric structure (44a) was obtained for $R^1, R^2, R^3, R^4 = \text{H}$ <88JHC1095>. This type of problem has also been examined using molecular orbital calculations, and the isothiazole structure (45a) is calculated to be more stable than the alternatives (45b) or the hypervalent structure (45c) <91JA6449>.



3.05.5 REACTIVITY OF CYCLIC CONJUGATED RINGS

3.05.5.1 General Survey of Activity

Since the last review <84CHEC-I(6)131> the phototransformations of methyl and phenyl isothiazoles have been re-examined (see Section 3.05.5.2). A range of alkylating agents is used for quaternizing isothiazoles <84CHEC-I(6)131>. Strong acids and Lewis acids give adducts, and *N*-bonded ligands are formed with transition metal salts. Oxaridines are obtained by oxidation of some isothiazoles (see Section 3.05.5.3). Isothiazoles with a potential ring NH are readily alkylated and in some cases halogenated at the ring nitrogen. Electrophilic substitution of mononuclear isothiazoles occurs at C-4, with the 3 position being relatively inert to attack. Nitration occurs at C-4, usually in good yield. Various conditions are used for halogenations, and the yields of 4-halo derivative can be poor due to the formation of perhalogeno compounds. Electron-releasing groups in the 3 or 5 position facilitate halogenation. 2-substituted isothiazolin-3-ones are more reactive to halogenation, giving initially the 4-halo compound, then the 4,5-dihalo derivative, and with excess halogen, addition across the double bond occurs, to give the tetrahalo compound. The electrophilic substitution of benzisothiazoles occurs in the benzene ring (see Section 3.05.7). The ring sulfur atom is readily oxidized to the sulfoxide or sulfone <84CHEC-I(6)131, 91HCA1059>. Mononuclear isothiazoles are oxidized to isothiazolin-3-one 1,1-dioxides (see Section 3.05.5.5).

The C-5 position of the isothiazole ring is more susceptible to nucleophilic attack than C-3. In contrast to the isothiazolium and 1,2-benzisothiazolium salts, nucleophilic attack occurs at C-3 of 2,1-benzisothiazolium salts. Nucleophilic attack of saccharin derivatives takes place at the carbonyl group (see Section 3.05.5.6). Some reactions previously considered to be by nucleophilic attack at C-5 or C-3 are now explained by attack at the ring sulfur. 2-Methylisothiazol-3-one is shown to exist in equilibrium in hydrochloric acid with the sulfenyl chloride (see Section 3.05.5.7).

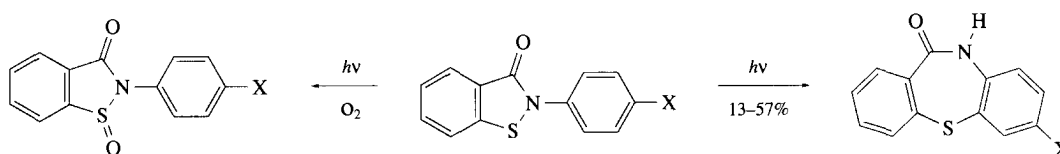
Deprotonation at C-5 occurs with organolithium compounds (see Section 3.05.5.8). Few reactions with radicals and carbenes are known (see Section 3.05.5.9). Isothiazolium salts are ring opened by

reducing agents. Several papers on the chemical reduction and asymmetric hydrogenation of 1,2-benzisothiazole compounds to the dihydro derivative have appeared. Some electrochemical reactions are reported (see Section 3.05.5.10).

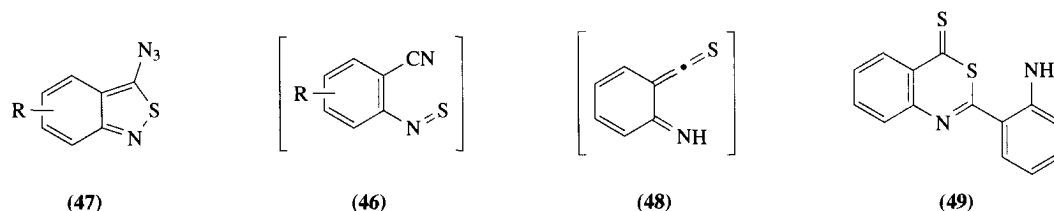
Since the last review a considerable amount has been published on cycloaddition reactions. Isothiazolin-3-one 1,1-dioxides can act as dipolarophiles or dienophiles (see Section 3.05.5.11).

3.05.5.2 Thermal and Photochemical Reactions

Reinvestigation of the phototransformations of methyl- and phenyl-monosubstituted isothiazoles and thiazoles has led to an understanding of the permutation pathways and mechanism. The methylisothiazoles rearrange in neutral and acid solution but, unlike earlier work, no methylisothiazole $\rightarrow$ methylisothiazole transpositions are observed. With the phenylisothiazoles the 4-phenylisothiazole is the terminal product <93JOC3407, 94JA2292>. Photoisomerization of 2-aryl-1,2-benzisothiazolin-3-ones gives dibenzo[*b,f*][1,4]thiazepin-(11*H*)-ones, and in the presence of oxygen the 2-aryl-1,2-benzisothiazol-3(2*H*)-one 1-oxide is obtained (Scheme 4) <83CC765, 85BCJ3131>. 2-Naphthyl-, 2-pyridyl-, and 2-pyrazinyl-1,2-benzisothiazolin-3-ones on irradiation similarly rearrange to give dibenzothiazepinone derivatives <86H(24)919, 86BCJ1601>. The reactions of the transient 6-cyanothionitrosobenzenes (**46**), generated by photolysis or thermolysis of 3-azido 2,1-benzisothiazoles (**47**), have been investigated <84CC374, 89CL2083, 91TL7459, 92JA1830>. On heating, 1-methyl-2,1-benzisothiazolin-3-thione gives, via the thioketene (**48**), the 3,1-benzothiazine-4-thione (**49**) <82JOC5255>.

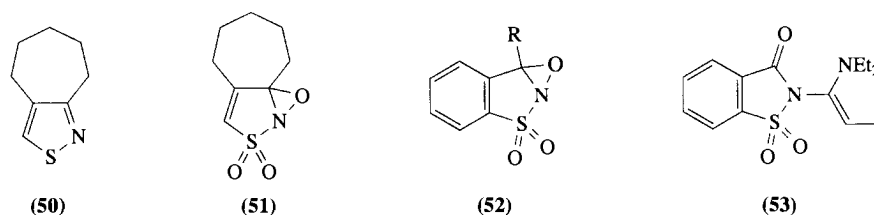


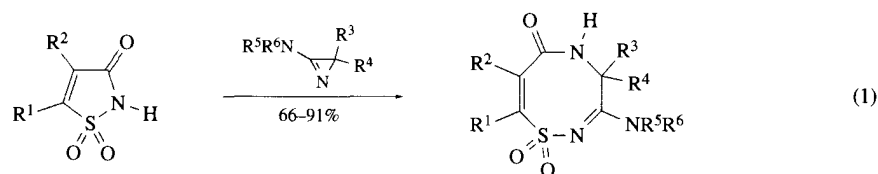
Scheme 4



3.05.5.3 Electrophilic Attack at Nitrogen

Attempts to prepare the *N*-oxide of isothiazole derivatives by direct oxidation have been unsuccessful <72JCS(P1)2305>, but 3-phenylisothiazole 2-oxide and 3-alkylamino-1,2-benzisothiazole 2-oxides have been obtained indirectly <70CB3166, 85T1885>. The oxidation of the cyclohepta[*c*]isothiazole (**50**) with hydrogen peroxide yields the oxaridine 1,1-dioxide (**51**) <91HCA1059>. 3-Alkyl-1,2-benzisothiazoles with MCPBA give the oxaridines (**52**), and the use of a chiral 3-alkyl substituent leads to pure diastereomers <90JOC1254, 91JOC809>. The *N*-alkylation of saccharin with *O*-alkylisourea under neutral conditions and with alkyl iodides using a microwave oven is described <86S332, 94SC301>. Palladium(0)-catalysed *N*-allylation and *N*-fluorination using cesium fluorosulfate are also reported <84BCJ3021, 91T7447>. *N,N*-Diethylprop-1-ynamine adds to saccharin to afford the enamine (**53**) <84CC1583>. The reaction of 3-amino-2*H*-azirine with isothiazolin-3-ones leads to 4*H*-1,2,5-thiadiazocin-6(5*H*)-one 1,1-dioxides (Equation (1)) <91HCA1002>.



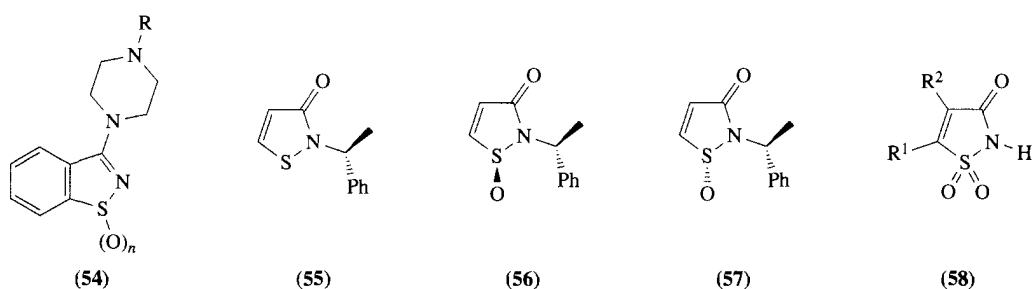


3.05.5.4 Electrophilic Attack at Carbon

Since 1982 there have been very few references to electrophilic substitution, although several reviews have appeared on halogenations and nitrations $\langle 85\text{AHC}(38)105, 90\text{AHC}(47)139, 94\text{AHC}(59)245 \rangle$.

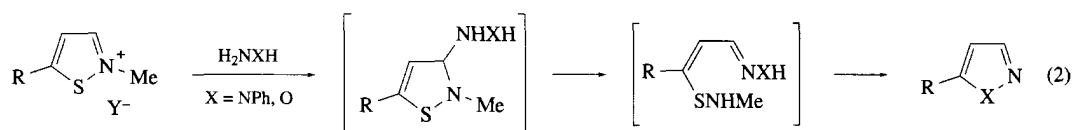
3.05.5.5 Electrophilic Attack at Sulfur

Oxidation of 3-piperazin-1-yl-1,2-benzisothiazole (**54**) ($n = 0$) with nitric acid or MCPBA at low temperatures gives the 1-oxide (**54**) ($n = 1$), while MCPBA at room temperature, oxone and sodium periodate afford the 1,1-dioxide (**54**) ($n = 2$) $\langle 91\text{JMC}3316 \rangle$. The oxidation of 2-[(*S*)-1-phenylethyl]isothiazolin-3-one (**55**) with MCPBA yields a mixture of the diastereomer 1-oxides (**56**) and (**57**) (in a ratio of 2.2:1) which are easily separated $\langle 89\text{TL}3061 \rangle$. 3-Unsubstituted isothiazoles on treatment with hydrogen peroxide in acetic acid are transformed to isothiazolin-3-one 1,1-dioxides (**58**) $\langle 91\text{HCA}1059 \rangle$.

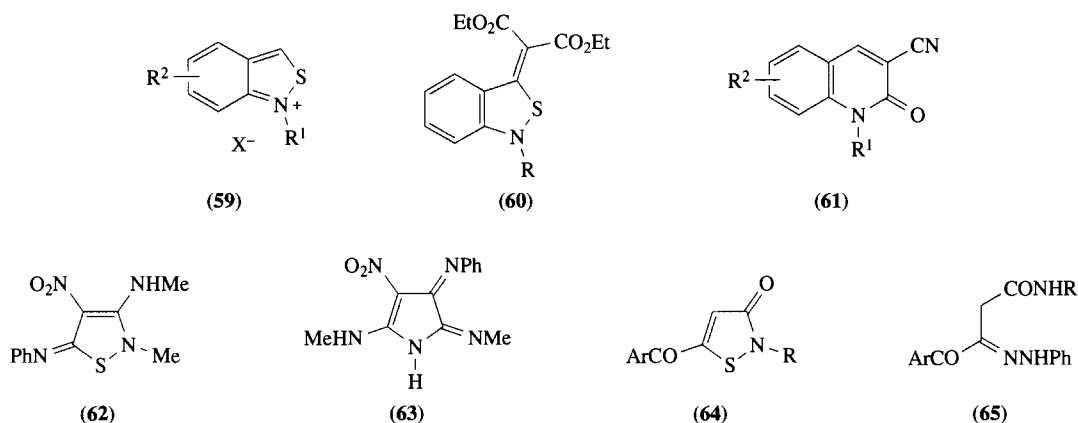


3.05.5.6 Nucleophilic Attack at Carbon

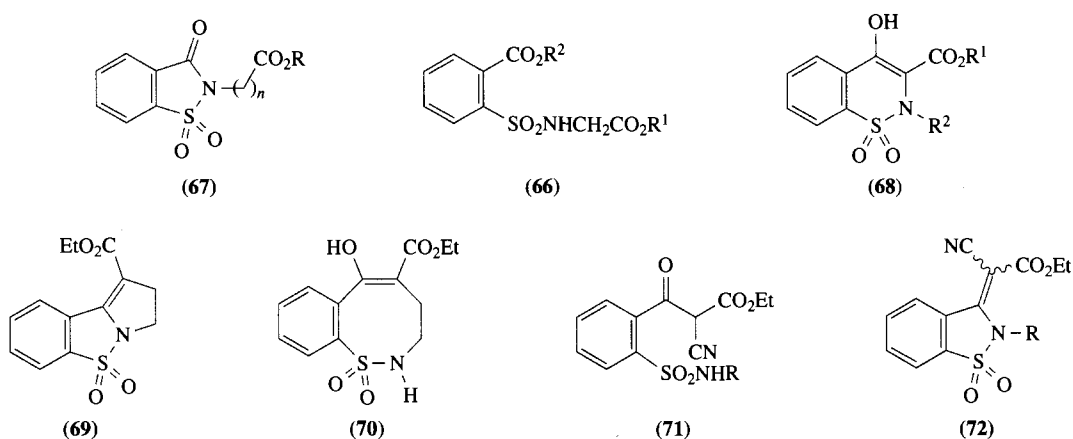
In contrast to the isothiazolium and 1,2-benzisothiazolium salts, the reaction of nitrogen, sulfur, and oxygen nucleophiles occurs at C-3 of 2,1-benzisothiazolium salts. Carbanions also react at this carbon atom, and the quaternary salt (**59**) ($\text{R}^2 = \text{H}, \text{R}^1 = \text{Me}$) with diethyl malonate, for example, affords the benzisothiazole derivative (**60**) and 2-methylaminobenzaldehyde, while with ethyl acetoacetate, quinolones (**61**) are obtained. 2,1-Benzisothiazolium salts may be regarded as synthetic equivalents of 2-aminobenzaldehydes $\langle 82\text{CJC}440, 83\text{JHC}1707 \rangle$. The nitro isothiazole (**62**) is thought to undergo initial attack by the cyanide ion at C-5 to generate the pyrrole (**63**) $\langle 83\text{JCS}(P1)1953 \rangle$. It is suggested that phenylhydrazine reacts with 2-substituted-5-arylisothiazolin-3-ones (**64**) in refluxing ethanol by an initial attack at C-5, to explain the formation of 3-phenylhydrazono-3-aryl-*N*-substituted propionamides (**65**) $\langle 85\text{JHC}1465 \rangle$. The minor components, 5-substituted pyrazole or isoxazole, resulting from the reaction of phenylhydrazine or hydroxylamine with isothiazolium salts, are probably formed by initial reaction at C-3 (Equation (2)) $\langle 85\text{T}1885 \rangle$.



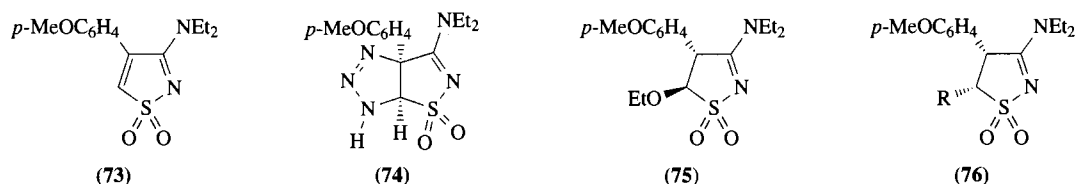
The nucleophilic attack of 2-substituted saccharins occurs at the carbonyl group and results in ring opening of the sulfonamide. The sulphonamides (**66**) from the 2-alkoxycarbonylmethyl deriva-



tives (67) ($n = 1$) can undergo a Dieckmann recyclization to produce the benzothiazine (68) ($R^2 = H$). This ring enlargement forms the basis for the synthesis of the anti-inflammatory drugs piroxicam and isoxicam [80JHC1281, 85AHC(38)105]. Depending on the reaction conditions the 2-ethoxycarbonylbutyl compound (67) ($R = Et$, $n = 3$) yields the pyrrolobenzisothiazoline (69) or benzothiazocine (70) [92AQ265]. The condensation of α -chloroacetate with 2-methylsaccharin gives the *N*-methylbenzothiazine (68) ($R^1, R^2 = Me$) [83JOC3601]. Ethyl cyanoacetate in the presence of potassium *t*-butoxide reacts with 2-alkylsaccharins to afford the sulfonamide (71), which cyclizes in acetic anhydride to the benzisothiazol-3-ylidine (72) [92JMC4613].



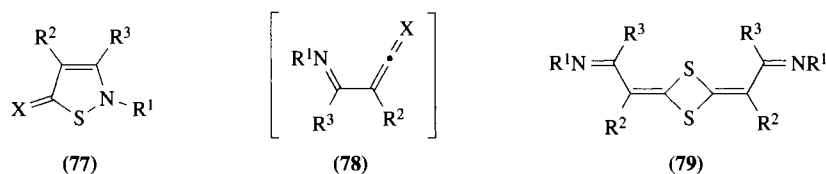
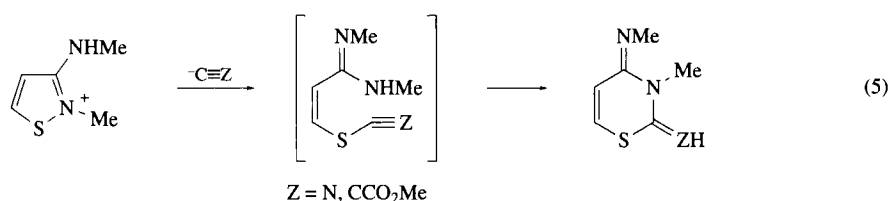
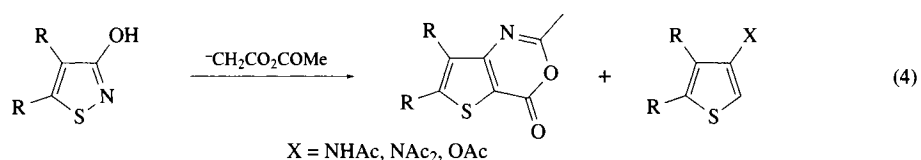
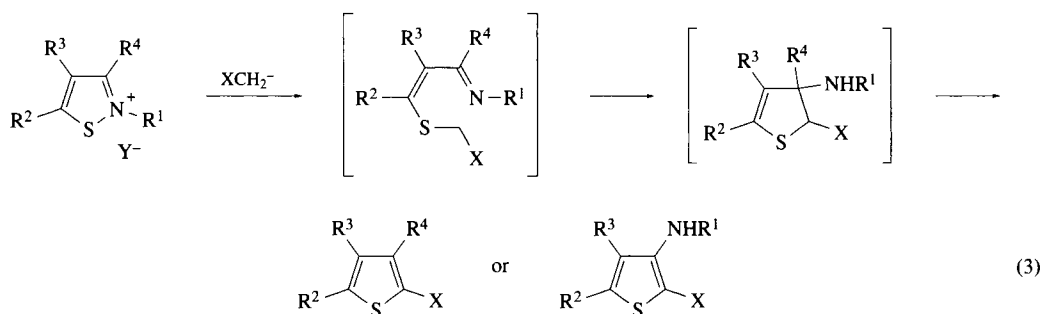
Sodium azide, ethanol, and acetone react with 3-diethylamino-4-(4-methoxyphenyl)isothiazole 1,1-dioxide (73) to give the triazoline (74), *trans*-4,5-dihydro-4-(4-methoxyphenyl)-5-ethoxyisothiazole 1,1-dioxide (75), and some of the *cis* isomer (76) ($R = OEt$) and the *cis*-5-(2-oxopropyl) compound (76) ($R = CH_2COMe$), respectively [93T9117].



3.05.5.7 Nucleophilic Attack at Sulfur

Many reactions, which lead to ring cleavage, often followed by rearrangement and recyclization, are now explained by an initial nucleophilic attack at the sulfur atom rather than at C-3 or C-5. Thus, the reaction of carbanions with a variety of isothiazolium or 1,2-benzisothiazolium salts

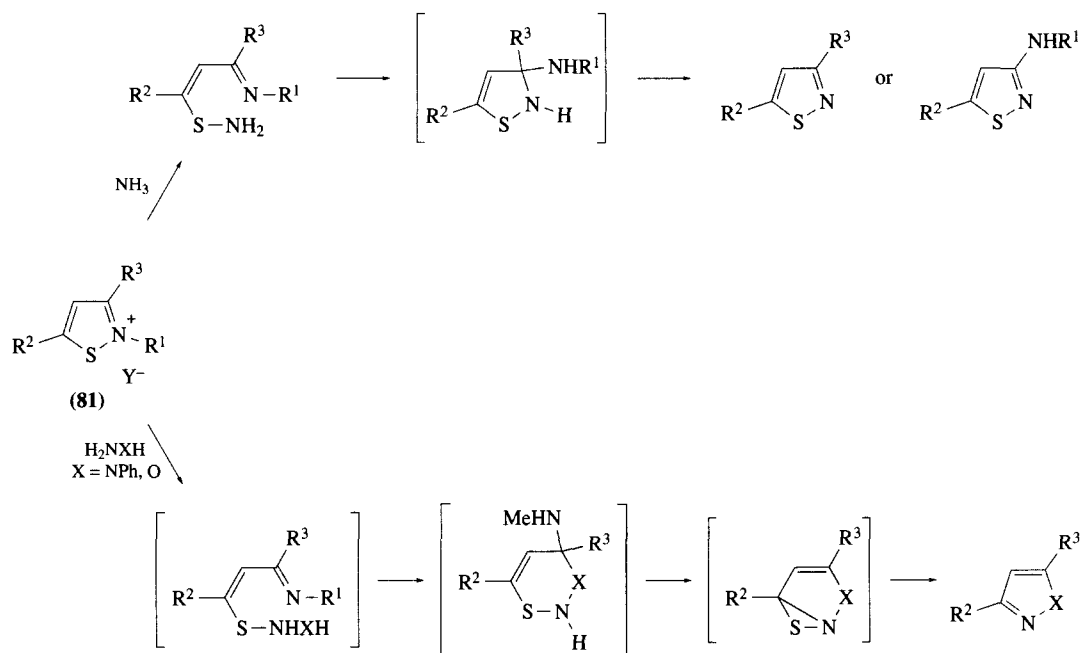
yields the 3-amino thiophene or the desamino compound depending on whether R^4 is a better leaving group than NHMe (Equation (3)) <73CJC3081, 77CJC1123>. When the anion of ethyl acetate is used, both thiophene products ($X = \text{CO}_2\text{Et}$) are obtained <84CJC1580>. Similarly the 3-hydroxyisothiazoles ($R = \text{Ph}$, $\text{RR} = (-\text{CH}=\text{CH}-)_2$) are transformed into several thiophene compounds on treatment with acetic anhydride in the presence of dbu (Equation (4)) <85JHC1497>. Nucleophilic attack with cyanide or methyl ethyne carboxylate leads to ring expansion to give the thiazine (Equation (5)) <79TL1281>. Tributylphosphane or cyanide react with 2-substituted isothiazolin-5-ones or 5-thiones (77) ($X = \text{O}$, S) to produce the imidoyl ketenes (78) ($X = \text{O}$, S). The ketene (78) ($X = \text{O}$) is trapped with alcohols or amines to afford acrylic acid derivatives, while the thioketene dimerizes to the 1,3-dithietane (79) <85CB851>.



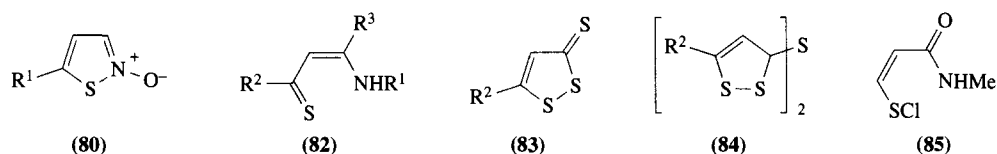
The reaction of isothiazolium salts with nitrogen nucleophiles also takes place initially at the sulfur atom <85T1885>. For example, the reaction with ammonia gives, via ring opening, the dequaternized starting material or the 3-alkylaminoisothiazole depending on whether R^3 is a good leaving group (Scheme 5). The reaction with phenylhydrazine leads to pyrazoles and with hydroxylamine to isoxazoles (Scheme 5), and also the isothiazole *N*-oxide (80). With (81) ($R^3 = \text{H}$) a minor product is also formed by nucleophilic attack at the sterically unhindered C-3 (see Section 3.05.5.6). Benzylamine reacts with the quaternary salts ($R^1 = \text{Me}$) to give a mixture of the methylamino and benzylamino thiones (82), ($R^1 = \text{Me}, \text{Bn}$).

Earlier work recognized that sulfur nucleophiles also react at the ring sulfur <73CJC3081>. Thus, hydrogen sulfide or benzenethiol with the isothiazolium salt (81) ($R^1 = \text{alkyl}$, $R^3 = \text{H}$) give the alkylamino thione (82) ($R^1 = \text{alkyl}$, $R^3 = \text{H}$) and the aryl salts (81) ($R^1 = \text{Ar}$) yield the 1,2-dithioles (83) and (84).

Recent evidence, using trapping with norbornene and 1-octyne, shows that in hydrochloric acid at 80°C 2-methylisothiazolin-3-one exists in equilibrium with the ring-opened sulfenyl chloride (85) <94H(38)1205>.

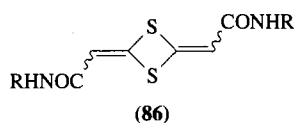


Scheme 5



3.05.5.8 Nucleophilic Attack at Hydrogen Attached to Carbon

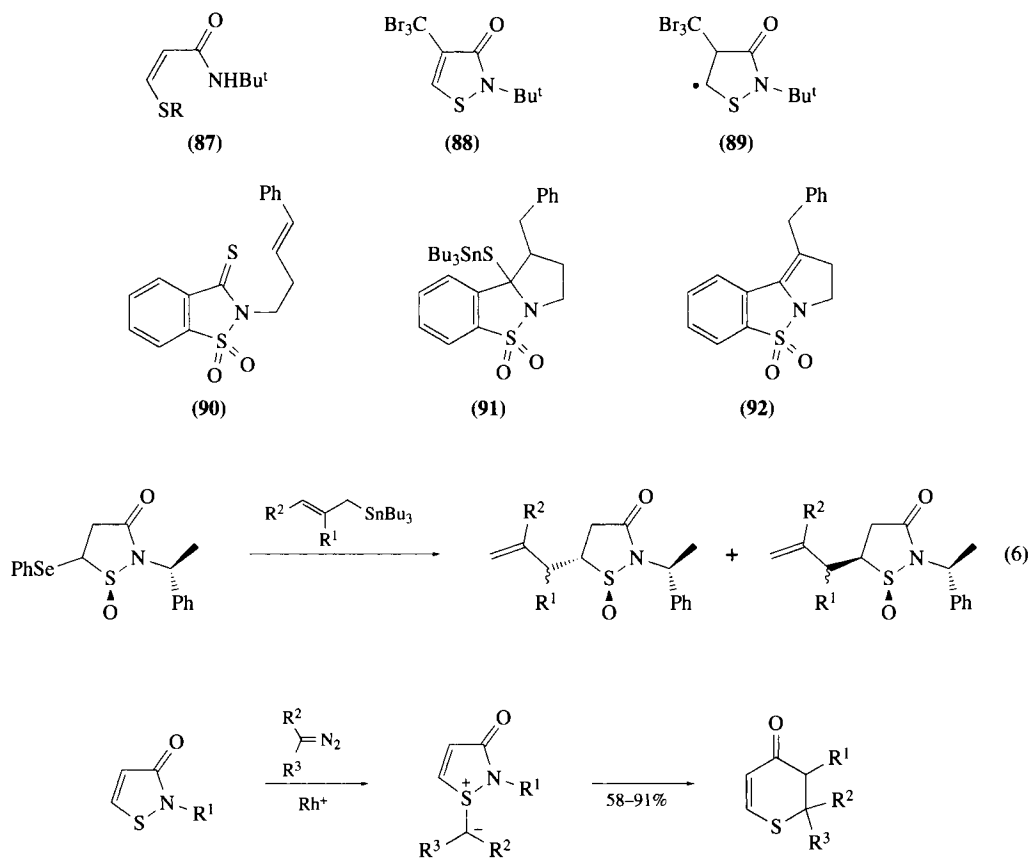
Under basic conditions, ring deprotonation occurs reversibly at C-5 in isothiazoles, and in also isothiazolium salts where the exchange is more rapid. Organolithium compounds deprotonate isothiazoles at C-5 or the equivalent 3 position in 2,1-benzisothiazoles $\langle 84\text{CHEC-I}(6)131 \rangle$. The *N*-substituted isothiazolin-3-ones are readily deprotonated to the 5-anion, which attacks the ring sulfur of a second molecule to yield 2,4-bismethylene-1,3-dithietanes **(86)** $\langle 70\text{T1493} \rangle$.



3.05.5.9 Reactions with Radicals and Carbenes

The reaction of 2-*t*-butylisothiazolin-3-one with various free radicals has been examined. The phenyl and arylsulfide radicals attack at the sulfur to give the ring-opened compounds **(87)** (*R* = Ph) and **(87)** (*R* = PhS), respectively. However, the reaction with the tribromomethane radical yields the 4-tribromomethyl isothiazolidinone **(88)** probably via the 5-isothiazolidin-3-onyl radical **(89)** $\langle 81\text{T2181} \rangle$. The free radical generated by treating 2-(4-phenylbut-3-enyl)-1,2-benzisothiazolin-3-thione 1,1-dioxide **(90)** with tri-*n*-butylstannane cyclizes to **(91)**, which on treatment with TFA yields the pyrrolinodihydrobenzisothiazole **(92)** $\langle 92\text{JOC6803} \rangle$. The 5-seleno compound, prepared from 2-((*S*)-1-phenylethyl)isothiazolin-3-one 1-oxide, gives the 5-isothiazolidinyl radical, which with 2-alkenyl tributyl tin derivatives produces the 5-(2-alkenyl)isothiazolidinones (Equation (6)). The stereoselectivity of the radical addition is solvent-dependent $\langle 91\text{SL101} \rangle$. Rhodium(II)-catalyzed

addition of diazo compounds to 2-substituted isothiazolin-3-ones affords, via trapping of a carbene, the intermediate sulfonium ylides, which undergo ring expansion to 3,4-dihydro-1,3-thiazin-4-ones (Scheme 6) <83CC643>.

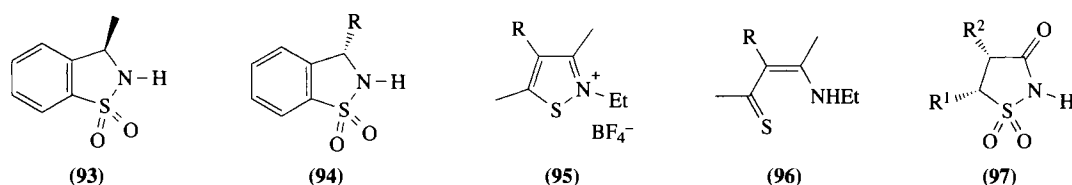


Scheme 6

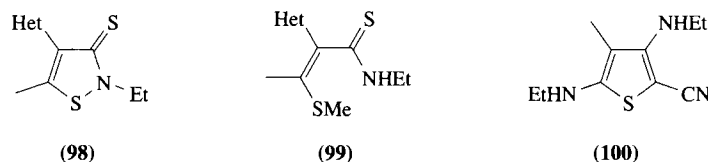
3.05.5.10 Reduction and Electrochemistry

Thiosaccharin is reduced by the borane–dimethyl sulfide complex to 2,3-dihydro-1,2-benzisothiazole 1,1-dioxide <90JCR(S)106>. Sodium borohydride reduces 3-substituted 1,2-benzisothiazole 1,1-dioxides to the 2,3-dihydro derivatives <83JOC537>. Asymmetric hydrogenation of the 3-methyl compound using $\text{Ru}_2\text{Cl}_4[(R)\text{-BINAP}]_2\text{NEt}_3$ as the catalyst yields (*R*)-dihydro-(**93**). The analogous (*S*)-BINAP affords the (*S*) derivative (**94**) (*R* = Me) <90TL4117>. Similar hydrogenation of the 3-*t*-butyl compound produces only traces of the racemic dihydro derivative, but reduction using lithium aluminum hydride–(+)-*N*-methylephedrine–3,5-dimethylphenol gives the (*S*)-dihydro product (**94**) (*R* = Bu^t) <91TL4893>. Reductive cleavage of 3,5-dimethyl isothiazolium salts (**95**) occurs with sodium borohydride or lithium aluminum hydride to yield β -enamino thioketones (**96**) <88SC1847>. Hydrogenation of isothiazolin-3-one 1,1-dioxides in acetic acid, using palladium–charcoal as the catalyst, gives the *cis*-isothiazolidin-3-ones (**97**) <91HCA1059>.

Electrochemical reduction of 5-(pyrazin-2-yl)- or 5-(pyrimidin-5-yl)-4-methylisothiazolin-3-one

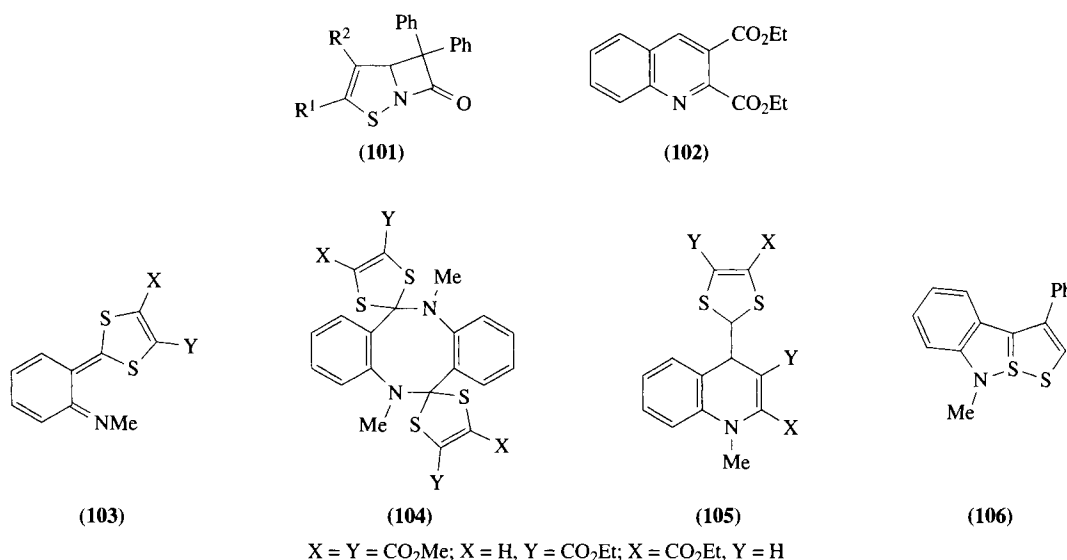


(98) in DMF gives, following methylation, the thioamide (99). In acetonitrile the thiophene (100) is also obtained <91JCS(P1)1763>. Electrochemical oxidation of 5-amino-3-methylisothiazole produces the azobisisothiazole, and with 2-phenyl-1,2-benzisothiazolin-3-one the sulfoxide is obtained <88JIC490, 94EA661>.



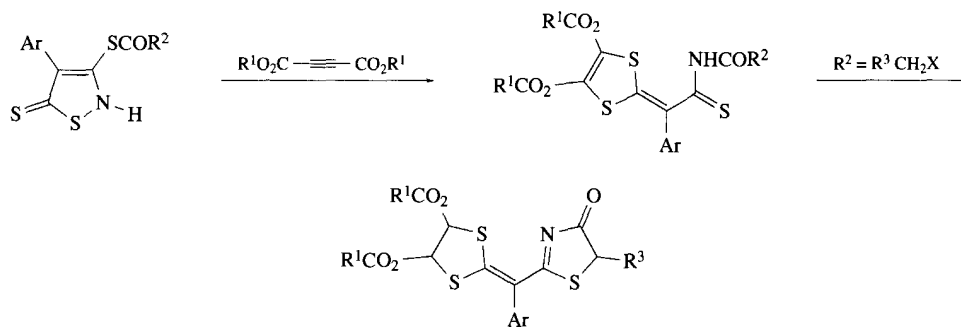
3.05.5.11 Cyclic Transition State Reactions with a Second Molecule

Isothiazoles are reported to yield the lactam (101) on reaction with diphenyl ketene <85BSB149>. Ethyne dicarboxylate esters add to 2,1-benzisothiazole to generate quinoline esters (102), and benzyne reacts to yield acridine <83H(20)489, 88JCS(P1)2141>. 2-Methyl-2,1-benzisothiazolin-3-thione with acetylene esters forms 2-iminobenzoquinone methides (103), which dimerize to give diazocines (104) or further react with the ethyne ester to yield diadducts (105). The initial adduct formed with phenylethyne and 2-methyl-2,1-benzisothiazolin-3-thione rearranges to produce 1,2-dithiole[3,2b] 2,1-benzisothiazole (106) <87CJC1247>. The cycloaddition of dimethyl acetylene dicarboxylate with 3-acylthio-4-aryl-3-isothiazolin-5-thiones yielding 1,3-dithioles has been extended to include 3-halogenoacylthio derivatives, which can undergo intramolecular cyclization to afford the thiazolyl dithiole (Scheme 7) <82JCS(P1)1239>.

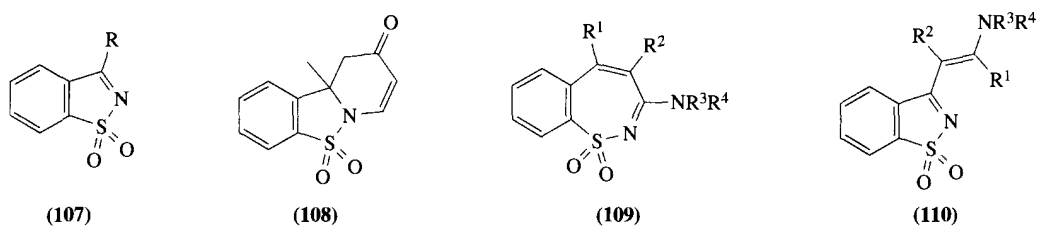


The cycloaddition of 1-methoxy-3-trimethylsilyloxy-1,3-butadiene with 3-methyl-1,2-benzisothiazole 1,1-dioxide (107) (R = Me) affords the pyridone (108) <84H(22)671>. An improved synthesis of 1,2-benzisothiazole 1,1-dioxide has led to the preparation of the benzothiazepine (109) (R¹ = H) by cycloaddition of the ynamine followed by ring expansion <83CC520>. Addition of *N,N*-dialkylprop-1-ynamines to 3-substituted 1,2-benzisothiazole 1,1-dioxide (107) (R = SMe, SPh, SePh) gives mainly the imine-vinylamine (110) with only small amounts of the benzothiazepine (109) <85CC845>.

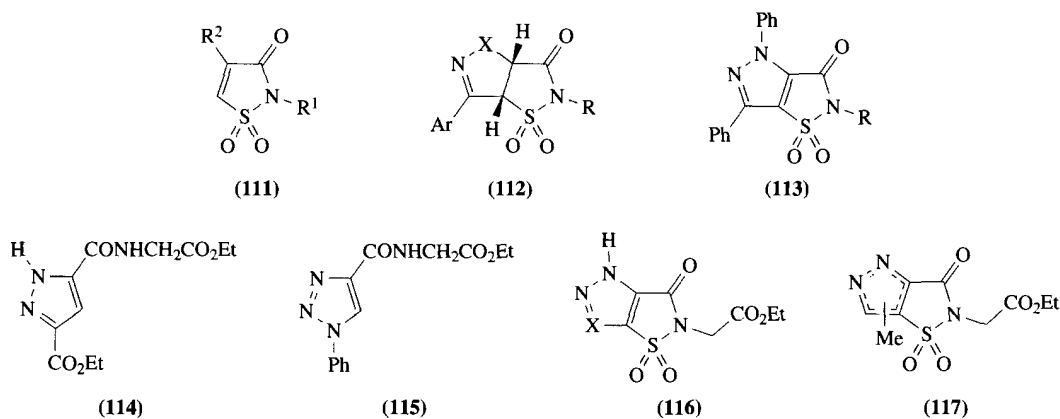
Isothiazolin-3-one 1,1-dioxides are dipolarophiles, which with 1,3-dipoles form cyclic adducts where the regioselectivity is controlled by the carbonyl group <89HCA1416>. Thus, (111) (R² = H) with diphenylnitrile imine and 4-chlorobenzonitrile oxide gives the pyrazolothiazolone (112) (X = NPh, Ar = Ph) and the isoxazolothiazolone (112) (X = O, Ar = 4-ClC₆H₄), respectively. When the bromo derivative (111) (R² = Br) is used, dehydrobromination takes place to give the aromatic system (113). The adducts of (111) (R¹ = CH₂CO₂Et, R² = H) with ethyl diazoacetate and



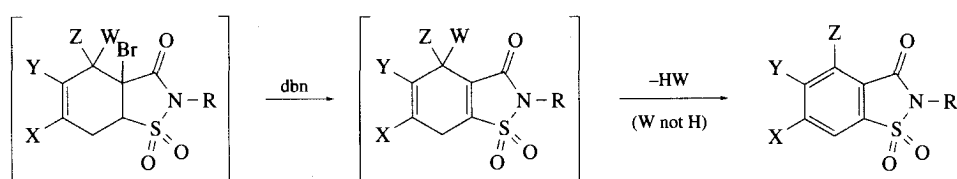
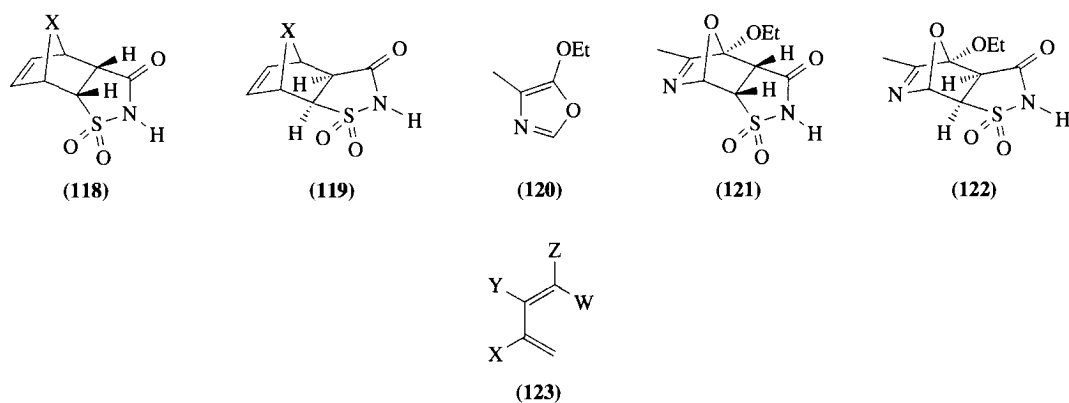
Scheme 7



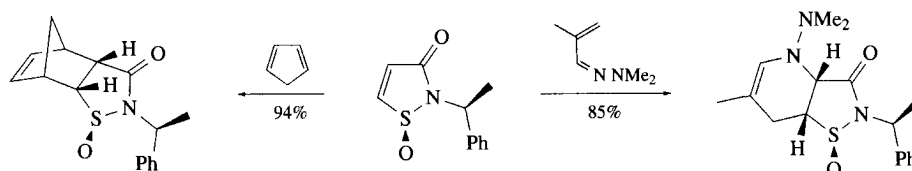
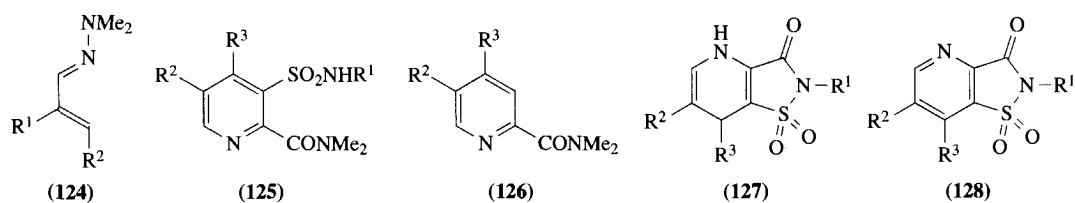
azidobenzene are unstable, and the pyrazole (114) and the triazole (115) are obtained. The adduct of ethyl diazoacetate with the bromo compound (111) ($R^1 = \text{CH}_2\text{CO}_2\text{Et}$, $R^2 = \text{Br}$) aromatizes to the pyrazole (116) ($X = \text{CHCO}_2\text{Et}$). With diazomethane only a low yield of a mixture of methyl pyrazoles (117) is obtained, presumably from the reaction of diazomethane with the pyrazole (116) ($X = \text{CH}$).



Isothiazolin-3-one 1,1-dioxides are also versatile dienophiles, and reaction with various cyclic dienes has been further explored. The *endo* adduct (118) is predominantly obtained, except in the case of furan when the *exo* compound (119) ($X = \text{O}$) is the major product (89JMC1024). The oxazole (120) reacts at room temperature with (111) ($R^1 = \text{H}$) to afford the *endo* (121) and *exo* (122) (major product) adducts (90HCA69). Examples are reported of the reaction of 4-bromoisothiazolin-3-one 1,1-dioxides with hydroxylated 1,3-butadienes (123) ($X, Y, Z, W = \text{H}, \text{AcO}, \text{MeO}, \text{TMS-O}$), giving an adduct which on dehydrobromination aromatizes to the saccharin derivative (Scheme 8) (90HCA69). Depending on the reaction conditions the picolinamide (125) or (126) and the 4-azasaccharin (127) or (128) are obtained on cycloaddition of the unsaturated hydrazone (124) with (111) ($R^2 = \text{H}$) (89HCA1435). The reaction of 2-((*S*)-1-phenylethyl)isothiazolin-3-one (*S*)-1-oxide with 1-azadiene and cyclopentadiene gives the corresponding cycloadducts with excellent diastereoselectivity ($\geq 96\%$) (Scheme 9) (89TL3061).

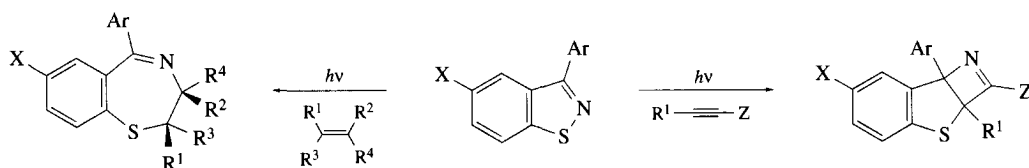


Scheme 8



Scheme 9

The photocycloaddition reactions of 3-aryl-1,2-benzisothiazole with alkenes is regio- and stereo-specific and yields 2,3-dihydro-1,4-benzothiazepines (Scheme 10) <81T3377>. When electron-rich alkynes are used, then substituted 3,4-benzo-2,6-thiazabicyclo[3.2.3]hepta-3,6-dienes are the major product (Scheme 10) <83JOC1275>.

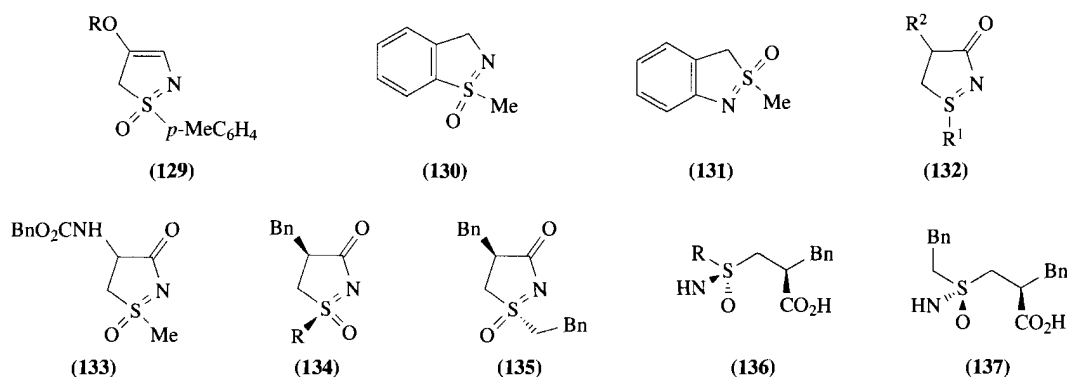


Scheme 10

3.05.6 REACTIVITY OF NONCONJUGATED RINGS

3.05.6.1 Compounds not in Tautomeric Equilibrium with Aromatic Compounds

The double bonds of the cyclic sulfoximines, 5*H*-1 λ^4 -1-(4-methylphenyl)isothiazole 1-oxide (**129**), 3*H*-1 λ^4 -1-methyl-1,2-benzisothiazole 1-oxide (**130**), and 3*H*-2 λ^4 -1-methyl-2,1-benzisothiazole 1-oxide (**131**) although in conjugation do not include all the atoms in the isothiazole ring <71JA7333, 84CHEC(6)131>. The enol (**129**) (*R* = H) is acidic and reacts with diazomethane to give the 4-methoxy derivative (**129**) (*R* = Me). The cyclic sulfilimides (**132**) (*R*¹ = Me, CH₂Bn; *R*² = NH₂, Bn) and the cyclic sulfoximides (**133**) and (**134**) (*R* = Me, CH₂Bn) are known and are examples of exocyclic conjugation where it is not possible to have tautomeric equilibrium with an aromatic system <84JMC228, 88SC769, 90JOC5791, 92JMC4875>. Oxidation of the *S*-benzylmethyl compound (**132**) (*R*¹ = CH₂Bn, *R*² = Bn) with MCPBA gives a mixture of the *cis*-(**134**) (*R* = CH₂Bn) and *trans*-(**135**) sulfoximides, which are readily separated. In contrast, the oxidation of the *S*-methyl derivative (**132**) (*R*¹ = Me, *R*² = Bn) is reported to be stereospecific, yielding only the *cis* product (**134**) (*R* = Me). Acid hydrolysis of the cyclic sulfoximides (**134**) and (**135**) affords the sulfoximino propionic acids (**136**) (*R* = Me, CH₂Bn) and (**137**), respectively.



3.05.6.2 Compounds in Tautomeric Equilibrium with Aromatic Compounds

The tautomerism of ketones, thiones and imines is discussed in Section 3.05.4.5, and such compounds are considered under the aromatic tautomer.

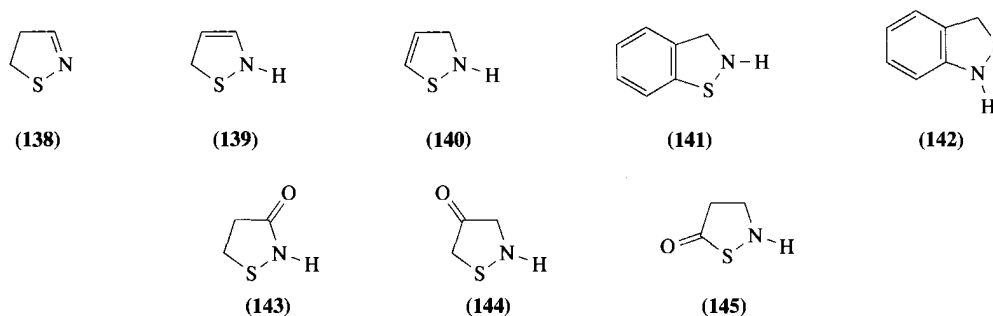
3.05.6.3 Dihydro Compounds

3.05.6.3.1 Structural types

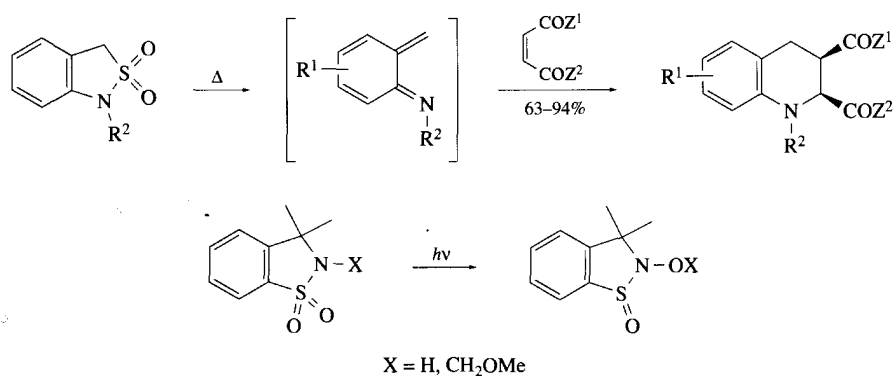
Derivatives of the dihydroisothiazoles, represented by 2-isothiazoline (**138**), 3-isothiazoline (**139**), 4-isothiazoline (**140**), 2,3-dihydro-1,2-benzisothiazole (**141**) and 1,3-dihydro-2,1-benzisothiazole (**142**), are known (see Section 3.05.9 and CHEC-I <84CHEC-I(6)131>). Isothiazolidin-3-one (**143**), isothiazolidin-4-one (**144**), and isothiazolidin-5-one (**145**) may be regarded as dihydroisothiazoles. The isothiazolidin-3-ones are readily prepared from isothiazolin-3-one 1,1-dioxides by cycloaddition reactions (see Section 3.05.5.11), halogenation <76JHC1095, 76JHC1321, 89HCA1416, 91HCA1059>, and hydrogenation (see Section 3.05.5.10).

3.05.6.3.2 Thermal and photochemical reactions

The thermolysis of 2,1-benzothiazoline 2,2-dioxides generates aza-*o*-xylenes which are trapped in situ with maleic acid derivatives to give *cis*-1,2,3,4-tetrahydroquinoline-2,3-dicarboxylic acid products (Scheme 11) <91SL571>. 3,3-Dimethyl-2,3-dihydro-1,2-benzisothiazole 1,1-dioxide compounds



are converted into the 2-hydroxy-3,3-dimethyl-2,3-dihydro-1,2-benzisothiazole 1-oxide derivatives (Scheme 11) <87AG(E)146>. Photolysis of *N*-halo compounds produces free radicals (see Section 3.05.3.6) <83JOC537>.



Scheme 11

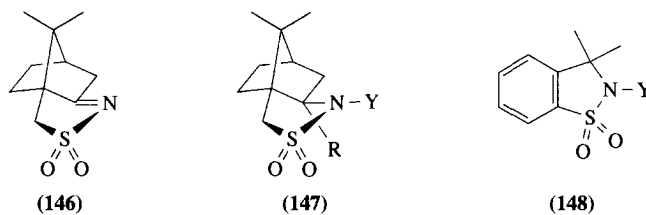
3.05.6.3.3 Aromatization

Depending on the substituents in the 4 and 5 positions, aromatization can occur in situ with 2-isothiazolines and isothiazolidin-3-ones (see Sections 3.05.5.11 and 3.05.9.2.2). Dehydrochlorination of the 4-chloro-2-isothiazolines with potassium carbonate gives the isothiazole (see Section 3.05.9.1.3). The *trans*-4,5-dibromoisothiazolin-3-one 1,1-dioxide is dehydrobrominated on treatment with pyridine to 4-bromoisothiazolin-3-one 1,1-dioxide. The compounds formed by the cycloaddition reactions of 2-substituted isothiazolin-3-one 1,1-dioxides can be aromatized using ddq, manganese dioxide or nickel dioxide <89HCA1416>. 2-Acetyl-3-acetoxyl-2,3-dihydro-1,2-benzisothiazole 1,1-dioxide (see Section 3.05.9.1.2) aromatizes with sulfuric acid to 1,2-benzisothiazole 1,1-dioxide <83CC520>.

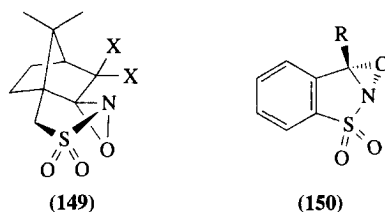
3.05.6.3.4 Other reactions

The camphorylsulfinylimine (**146**) with lithium aluminum hydride is reduced to the (2*R*)-10,2-bornane sultam (**147**) (*R* = *Y* = H), and reaction with methyl magnesium iodide in the presence of copper(I) chloride gives the methyl analog (**147**) (*R* = Me, *Y* = H) <88TL6087>. The fluorination of 3,3-dimethyl-2,3-dihydro-1,2-benzisothiazole 1,1-dioxide (**148**) (*Y* = H) gives the *N*-fluoro com-

pound (**148**) ($Y = F$), which is a useful and safe fluorinating agent <88TL6087, 89HCA1248, 91TL1779>. The electrochemical reduction of *N*-fluoro derivatives has been examined <92T1595>.

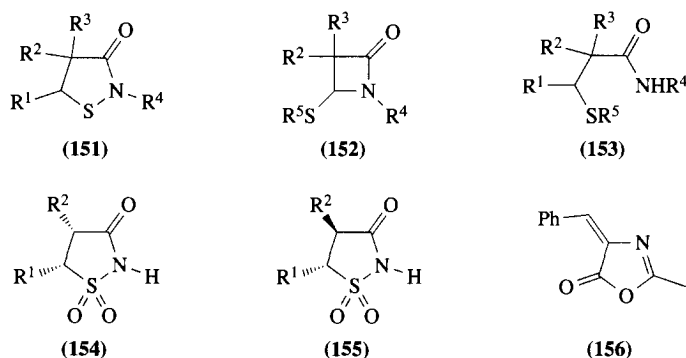


(2*R*,8*aS*)-10-Camphorylsulfonyloxaziridine (**149**) ($X = H$), which is readily prepared from 1*S*-10-camphorsulfonic acid via oxidation of the camphorylsulfonylimine (**146**), is a stereoselective oxidizing agent particularly useful for the asymmetric synthesis of α -hydroxy carbonyl compounds from enolates <92TL161, 93OSC(8)104>. Substituents (**149**) ($X = Cl, OMe$; $XX = O$) are found to modify the selectivity <88JCS(P1)1753, 90JOC3715, 91JOC1143>. The (2*R*,3*S*) 3-substituted 1,2-benzisothiazole 1,1-dioxide oxides (**150**) and their (2*S*,3*R*) isomers are in general less effective than the camphor sulfonyloxaziridines (**149**), but may have advantages in the epoxidation of alkenes <91JOC809>.

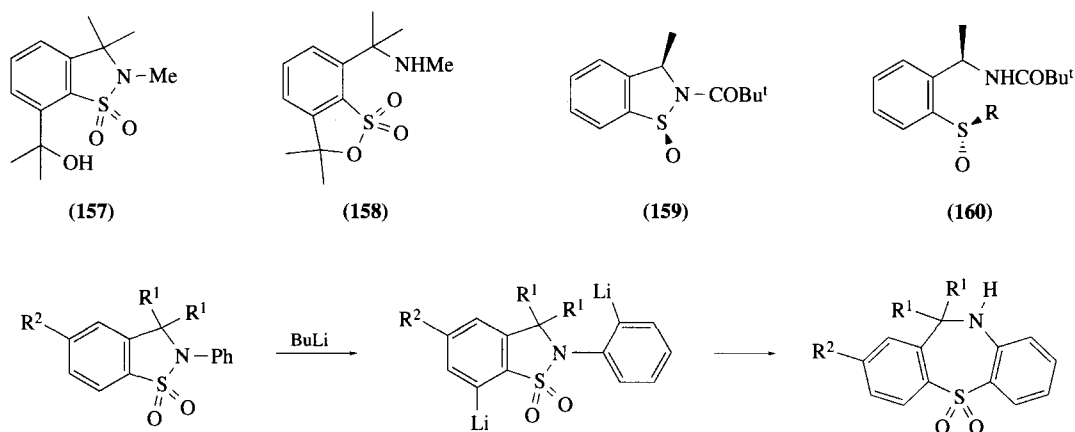


The oxidation of 2-alkyl-2,3-dihydro-1,2-benzisothiazole with peracetic acid affords the 1,1-dioxide <86TL5703>. The nitration of 2,3-dihydro-3,3-dimethyl-1,2-benzisothiazole 1,1-dioxide (**148**) ($Y = H$) yields the *N*-nitro-7-nitro compound, which with sulfuric acid produces the 7-nitro derivative <92T1595>. 2,3-Dihydro-2,1-benzisothiazole 1,1-dioxide on nitration gives the 5,7-dinitro derivative, while the 1-ethoxycarbonyl analog yields the 5-nitro compound <86JHC1645>.

The 4-aryl-4-hydroxy-3-dialkylamino-2-isothiazolines (see Section 3.05.9.1.3) are converted with thionyl chloride to the 4-chloro derivatives <92T3227>. The reactions of isothiazolidin-3-ones (**151**) have been studied as a route to β -lactams. The 5-chloro compound (**151**) ($R^1 = Cl$), obtained from the reaction of sulfonyl chloride with (**151**) ($R^1 = H$), undergoes nucleophilic attack at the sulfur with an alkyl lithium (R^5Li) to yield the lactam (**152**). The benzoate (**151**) ($R^1 = PhCO_2$), prepared by treating (**151**) ($R^1 = H$) with *t*-butyl perbenzoate, ring opens with hydrogen bromide to afford the sulfonyl bromide (**153**) ($R^1 = Br, R^5 = Br$), which with sodium hydroxide cyclizes to the 5-bromo compound (**151**) ($R^1 = Br$). Benzenethiol reacts with 2-*t*-butyl-4,4-diphenylisothiazolidin-3-one (**151**) ($R^1 = H, R^2 = R^3 = Ph, R^4 = Bu^t$) to give the disulfide (**153**) ($R^1 = H, R^2 = R^3 = Ph, R^4 = Bu^t, R^5 = SPh$) <85JCS(P1)153>. Attempts to generate the 5-isothiazolidinyl radical by hydrogen or bromine abstraction from (**151**) ($R^1 = H, Br; R^2 = R^3 = Ph; R^4 = Bu^t$) have been reported <81T2181>. The *cis*-4,5-disubstituted isothiazolidin-3-one 1,1-dioxides (**154**) ($R^1 = Me, Ph; R^2 = Me, NH_2, NHAc$) isomerize to the corresponding *trans* compounds (**155**) <72JOC3781, 91HCA1059>. Both *cis*-(**154**) ($R^1 = Ph, R^2 = NHAc$) and *trans*-(**155**) ($R^1 = Ph, R^2 = NHAc$) rearrange in acetic anhydride and pyridine to 4-benzylidene-2-methyl-2-oxazolin-5-one (**156**).



2,3,3-Trimethyl-7-(1-methyl-1-hydroxyethyl) 1,2-benzisothiazole 1,1-dioxide (**157**) cyclizes in acid to the sultone (**158**). The reaction is reversed with a base <84JOC3445>. The *cis*-(*S*)-2-*t*-butylcarbonyl-3-methyl-1,2-benzisothiazole 1-oxide (**159**) ring opens with alkylolithiums and Grignard reagents to give (**160**) <91JCS(P1)3383>. The dilithiated compound, obtained on treating the 2,3-dihydro-1,2-benzisothiazole 1,1-dioxide with butyllithium, yields on hydrolysis the dibenzo[*b,f*][1,4]thiazepine derivative (Scheme 12) <83T2073>.

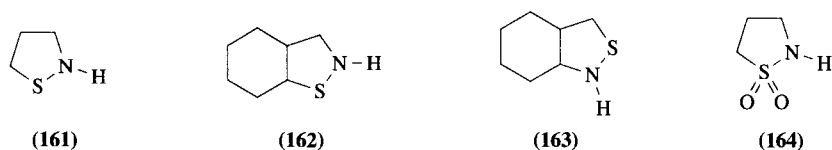


Scheme 12

3.05.6.4 Tetrahydroisothiazoles

3.05.6.4.1 Structural types

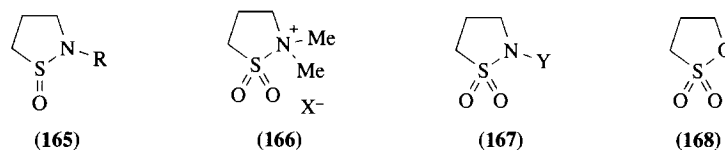
The tetrahydroisothiazoles, as represented by structure (**161**), are named isothiazolidines. The fully reduced benzisothiazoles are often referred to as hexahydro-1,2-benzisothiazole (**162**) and hexahydro-2,1-benzisothiazole (**163**). The 1,1-dioxides are also known as sultams, for example 1,3-propanesultam (**164**).



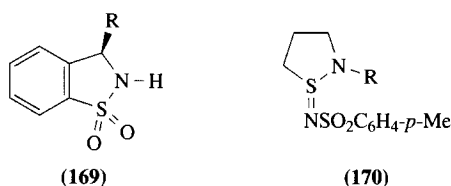
3.05.6.4.2 Reactions at the ring nitrogen

The reaction of fluorine with the 10,2-bornane sultams (**147**) ($R = H, Me$; $Y = H$) gives the *N*-fluoro derivatives (**147**) ($Y = F$) which are enantioselective fluorinating agents <88TL6087>. *N*-Alkylation of isothiazolidine 1-oxide (**165**) ($R = H$) is readily carried out using phase transfer conditions or via the monoanion generated with organolithium compounds. The sulfonation of (**165**) ($R = H$) with pyridine-sulfur dioxide affords the *N*-sulfonated isothiazolidine 1-oxide (**165**) ($R = SO_3H$) <93JOC696>. 2-Methylisothiazolidine 1,1-dioxide yields the quaternary salt (**166**) on treatment with methyl fluorosulfate or methyl triflate <82JA7108>. The nitration of isothiazolidine 1,1-dioxide (**167**) ($Y = H$) gives the *N*-nitro compound (**167**) ($Y = NO_2$), which is stable. The treatment of (**167**) ($Y = H$) with dinitrogen tetroxide yields the *N*-nitroso derivative (**167**) ($Y = NO$),

which on thermal decomposition in the presence of sodium bicarbonate gives 3-hydroxypropane-sulfonic acid as the main product, the sultam (167) ($Y = H$), and the sultone (168) (87JOC2162).



(2*R*)-10,2-Bornane sultam (147) ($R = Y = H$) is one of the most versatile chiral auxiliaries and is used via *N*-acylation for asymmetric synthesis (90PAC1241, 93T293). It is prepared by the reduction of the camphorylsulfonylimine (146) (93OSC(8)110), and is now commercially available in kilogram quantities. The saccharin-derived toluenesultams (169) are also used as chiral auxiliaries but to a lesser extent (91TL4893, 94TL3509).

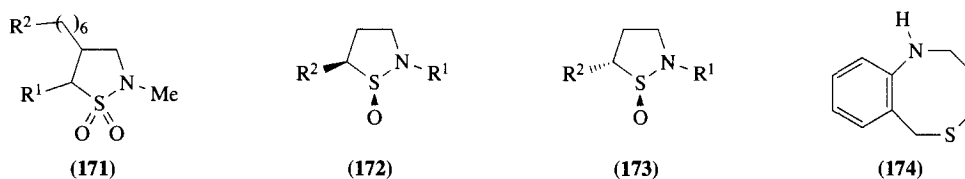


3.05.6.4.3 Reactions at the ring sulfur

N-Alkylisothiazolidines are oxidized with sodium periodate to the 1,1-dioxides (167) ($Y = \text{alkyl}$) and react with chloramine-T to give the sulfimide (170) (85H(23)1897). The 2,2-dimethylisothiazolidinium 1,1-dioxide salt (166) ring opens with alcohols (ROH) to give betylates, *N*-dimethylpropylsulfonates ($RSO_2(CH_2)_3NMe_2$) (82JA7108). Acid hydrolysis of *N*-benzyl-*S*-methylisothiazolidinium salts gives quantitatively the *N*-benzyl-3-methylsulfonylpropylamines ($ArCH_2NH(CH_2)_3SOMe$), while alkaline hydrolysis yields the aldehydes ($ArCHO$) and 3-methylthiopropylamine (82JHC1515).

3.05.6.4.4 Other reactions

The photolysis of *N*-halo isothiazolidine produces the cyclic sulfonamidyl radical (see Section 3.05.3.6) (83JOC537). The aldehyde (171) ($R^1 = CHO$), obtained on reaction of the sultam (171) ($R^1 = H$) with butyllithium and ethyl formate, exists in tautomeric equilibrium with its hydroxymethylene form, and is used for the synthesis of prostaglandin analogs (83TL1647). The deprotonation of isothiazolidine 1-oxide occurs at the 5 position as well as the nitrogen with *s*-butyllithium. Quenching with deuterium oxide gives the *syn*-(172) ($R^1 = R^2 = D$, 79% yield) and *anti*-(173) ($R^1 = R^2 = D$, 21% yield) deuterated compounds. The benzylation of the dianion yields the 5-benzylisothiazolidine 1-oxides (172) and (173) ($R^1 = H$, $R^2 = Bn$, *anti*:*syn* 82:18). With benzophenone the *syn*-5-(1,1-diphenyl-1-hydroxymethyl)isothiazolidine 1-oxide (173) ($R^1 = H$, $R^2 = Ph_2COH$) is selectively formed (93JOC696). Ring expansion takes place when *N*-phenyl-*S*-methylisothiazolidinium chloride is treated with sodium ethoxide, to give 5,1-benzothiazocine (174) (84H(22)1045).



3.05.7 REACTIVITY OF SUBSTITUENTS ATTACHED TO RING CARBON ATOMS

3.05.7.1 General Survey of Reactivity

The reactivity of substituents has been well covered previously $\langle 84\text{CHEC-I(6)131} \rangle$. In the benzisothiazoles, electrophilic substitution takes place in the fused benzene ring, the position of substitution being governed by substituents present in this ring, the isothiazole ring having little effect. The 5 and 7 positions are mainly substituted in 1,2-benzisothiazole and 2,1-benzisothiazole $\langle 84\text{CHEC-I(6)131, 90AHC(47)181, 94AHC(59)245} \rangle$. The carbon-linked substituents undergo normal reactions. The 3- and 4-methyl groups are less active than the 5-methyl group in isothiazoles, with the 5-methyl group forming an anion more readily than the 3-methyl group in 3,5-dimethylisothiazole (see Section 3.05.7.3). Phenyl substituents, especially in the 3 position, are deactivated by the isothiazole ring. The order for ease of decarboxylation of isothiazole carboxylic acids is $5 > 3 > 4$.

Nitro groups are reduced to amines by catalytic or by chemical methods. The aminoisothiazoles form diazonium salts which undergo the usual reactions. Nonaqueous diazotization is reported for the preparation of derivatives (see Section 3.05.7.4).

The 3- and 5-hydroxy isothiazoles and the corresponding thiol compounds are either *O*- and *S*- or *N*-alkylated. Hydroxy compounds are readily converted to chloro derivatives. 3-Methoxy groups are reported not to be displaced by nucleophiles $\langle 84\text{CHEC-I(6)131} \rangle$, yet both alkoxy groups in a 3,4-diethoxy isothiazole can be displaced (see Section 3.05.7.5). 3-Methoxy-1,2-benzisothiazole and the 3- and 5-alkylthio groups in isothiazoles undergo displacement reactions. New reactions at the carbonyl group of saccharin derivatives have been reported (see Section 3.05.7.5).

In halo isothiazoles the order of activity for nucleophilic displacement is $5 > 4 > 3$. Attempts to displace the 3-halo in 1,2-benzisothiazoles leads to ring cleavage, whereas the 3-halo group in 2,1-benzisothiazoles is displaced $\langle 84\text{CHEC-I(6)131} \rangle$. The relative reactivities of the chloro groups in a 3,4-dichloroisothiazole have been explored (see Section 3.05.7.7).

Isothiazoles lithiate preferentially at the 5 position, and this enables various functions to be introduced at this position. The preparation of an isothiazole Grignard reagent and its reactions are reported (see Section 3.05.7.8).

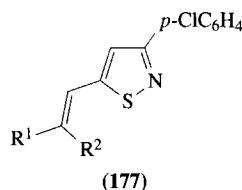
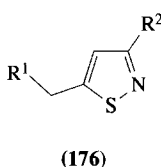
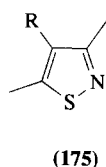
Ring carbon substituents involved in intramolecular reaction with the isothiazole ring system are discussed in Section 3.05.7.9.

3.05.7.2 Fused Benzene Rings

The nitration of 3,5-dimethyl-1,2-benzisothiazole to the 4-nitro and 7-nitro products has been described $\langle 91\text{JHC347} \rangle$. Friedel-Crafts acylation of 3-methyl-6-methylthio-1,2-benzisothiazole gives the 7-acetyl derivative whereas the 5-methylthio analog fails to acylate $\langle 91\text{JHC445} \rangle$.

3.05.7.3 Carbon-linked Substituents

Since the last review $\langle 84\text{CHEC-I(6)131} \rangle$, only a few significant reactions with alkyl and aryl groups have appeared. The reaction of 3,5-dimethylisothiazole (**175**) ($R = H$) with LDA and an alkyl halide leads to 5-alkyl-3-methylisothiazole (**176**) ($R^1 = \text{alkyl}$, $R^2 = \text{Me}$, 53–82% yield). With an excess of LDA a mixture of the monoalkylated (**176**) ($R = \text{alkyl}$, $R^2 = \text{Me}$) and 3,5-dialkylated (**176**) ($R^1 = \text{alkyl}$, $R^2 = \text{CH}_2R^1$) products is obtained $\langle 90\text{SC617} \rangle$. Various bases with 4-substituted methyl 3,5-dimethylisothiazole (**175**) ($R = \text{CH}_2X$; $X = \text{CN, CO}_2\text{Et, 4-MeOC}_6\text{H}_4\text{SO}_2$) generate selectively the carbanion in the 4 position, which undergoes alkylation, acylation, 1,2-additions, or Michael-type reactions to give a range of 4-substituted products $\langle 87\text{G461} \rangle$. The condensation of 5-methyl-(4-chlorophenyl)isothiazole (**176**) ($R^1 = H$, $R^2 = 4\text{-ClC}_6\text{H}_4$) with 4-chlorobenzaldehyde in the presence of potassium *t*-butoxide gives the (*E*)-alkene (**177**) ($R^1 = 4\text{-ClC}_6\text{H}_4$, $R^2 = H$), which on irradiation yields a 3:2 mixture with the (*Z*)-isomer (**177**) ($R^1 = H$, $R^2 = 4\text{-ClC}_6\text{H}_4$) $\langle 85\text{JA2721} \rangle$.



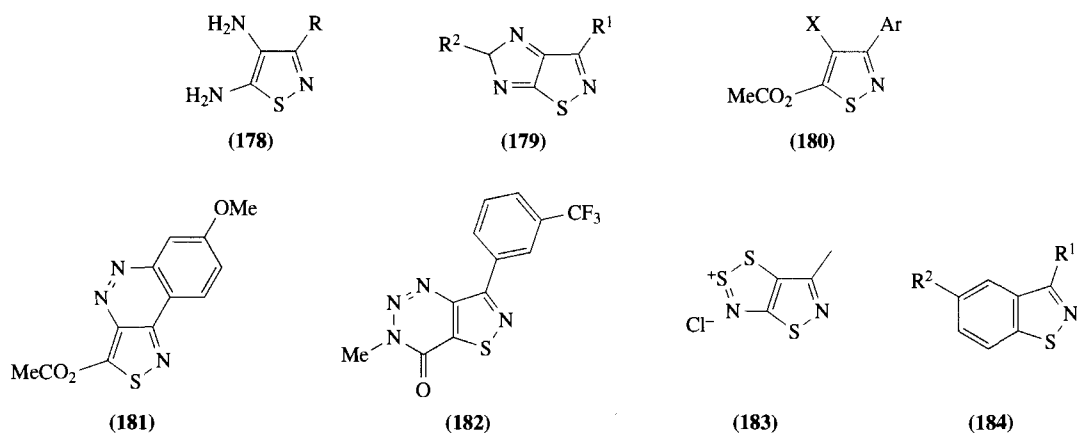
4-Hydroxymethyl-3,5-dimethylisothiazole (**175**) ($R = CH_2OH$) and 5-hydroxymethyl-3-methoxyisothiazole (**176**) ($R^1 = OH$, $R^2 = OMe$) are converted with thionyl chloride to the corresponding chloromethyl compounds. The reaction of the 4-chloromethyl derivative (**175**) ($R = CH_2Cl$) with triphenyl phosphine gives the ylide (**175**) ($R = CH_2P^+Ph_3$), which with aldehydes yields 4-alkenyl isothiazoles (**175**) ($R = CH=CHR^1$). Alkenes are also obtained by the dehydration of the alcohol (**175**) ($R = CHR^1OH$) $\langle 85EJM447, 88JHC235 \rangle$. The oxidation of 3-methyl-5-vinylisothiazole with potassium permanganate gives the 3-methyl 5-carboxylic acid $\langle 87H(26)1587 \rangle$. 5-Methylisothiazole is oxidized with selenium dioxide in low yield (8%) to the 5-carboxylic acid, while the 3-methyl analog fails to give any carboxylic acid $\langle 85H(23)127 \rangle$.

The isothiazole 3- and 5-carboxylic acids with sulfur tetrafluoride and hydrogen fluoride yield the corresponding trifluoromethyl derivatives $\langle 91JFC(55)173 \rangle$. 5-Acetamido-4-nitroisothiazole-3-carboxylic acid and 4-amino-3-phenylisothiazole-5-carboxylic acid are readily decarboxylated $\langle 85JHC1497, 93JHC1379 \rangle$. Phosphorus oxychloride in DMF converts both the amide groups in 5-aminoisothiazole-3,4-dicarboxamide into nitrile groups $\langle 88S449 \rangle$. Sodium borohydride reduces the methyl 3-methoxyisothiazole-5-carboxylate to the alcohol (**176**) ($R^1 = OH$, $R^2 = OMe$) $\langle 85EJM447 \rangle$.

The reaction of 4-formyl-3,5-dimethylisothiazole (**175**) ($R = CHO$) with sodium borohydride and organometallic compounds (R^1MgX or R^1_3Al) gives the alcohols (**175**) ($R = CH_2OH$) and (**175**) ($R = CHR^1OH$), respectively. The Wittig reaction on the aldehyde yields the alkenes (**175**) ($R = CH=CHR^1$) $\langle 88JHC235 \rangle$. 2-Alkyl-5-arylisothiazolin-3-ones are debenzoylated with sodium hydroxide (see Section 3.05.9.2.1) $\langle 87H(25)569 \rangle$. On heating 2-alkyl-5-arylisothiazolin-3-ones with phenylhydrazine in ethanol the 3-phenylhydrazono-3-arylopropionamides are formed (see Section 3.05.5.6), but at room temperature, 1,2,3-thiadiazoles are obtained (see Section 3.05.7.9). The reaction of Grignard or organolithium reagents with the 4-nitrile derivative (**175**) ($R = CN$) is a convenient synthesis of 4-acyl-3,5-dimethylisothiazoles (**175**) ($R = COR^1$). The nitrile with dibal or tibia affords the aldehyde (**175**) ($R = CHO$) $\langle 88JHC235 \rangle$.

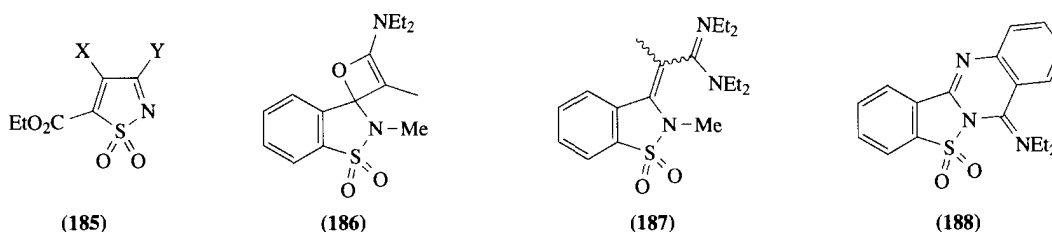
3.05.7.4 Nitrogen-linked Substituents

3,4-Diamino-3-methylisothiazole (**178**) ($R = Me$) on reaction with diethoxymethyl acetate gives a low yield of 3-methylimidazo[4,5-*d*]isothiazole (**179**) ($R^1 = Me$, $R^2 = H$). The diamines (**178**) ($R = H, Me$) readily cyclize with thiocarbonyldimidazole to yield after methylation the 5-methylthioimidazo[4,5-*d*]isothiazoles (**179**) ($R^1 = H, Me$; $R^2 = MeS$) $\langle 93JHC1379 \rangle$. Nonaqueous diazotization converts methyl 4-amino-3-arylisothiazolecarboxylates to the desamino and halo compounds (**180**) ($X = H, Cl, Br, I$). When the aryl group is 3-methoxyphenyl the isothiazole[4,3-*c*]cinnoline (**181**) is obtained. 4-Amino-3-(3-trifluoromethylphenyl)isothiazole-5-*N*-methylcarboxamide yields the fused triazinone (**182**) $\langle 87JHC243 \rangle$. The hetero-Herz reaction with 5-amino-3-methylisothiazole and sulfur monochloride affords the isothiazolothiadiazole (**183**) $\langle 84JOC1224 \rangle$. The acetamidines (**184**) ($R^1 = NHC(=NH)R$) are prepared from 3-amino-1,2-benzisothiazole (**184**) ($R^1 = NH_2$) by reaction with alkyl or aryl cyanides (RCN) in the presence of tin(IV) chloride. The formamidines (**184**) ($R^1 = N=CHNMe_2$) are obtained by reaction with *N,N*-dimethylformamide dimethyl acetal $\langle 93EJM955 \rangle$.



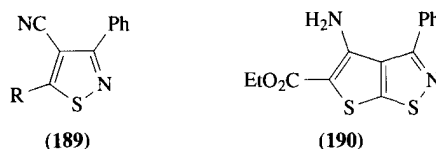
3.05.7.5 Oxygen-linked Substituents

4,5-Diphenylisothiazolin-3-one with acetic anhydride at room temperature gives the 2-acetyl derivative quantitatively, while at 130 °C the *O*-acetyl compound is also obtained (85JHC1497). The reaction of ethyl 4-hydroxyisothiazolin-3-one-5-carboxylate 1,1-dioxide with phosphorus pentachloride gives the 3,4-dichloro compound (185) ($X = Y = \text{Cl}$). The 4-ethoxy group in ethyl 3,4-diethoxyisothiazole-3-carboxylate 1,1-dioxide (185) ($X = Y = \text{OEt}$) is first displaced by amines to give (185) ($X = \text{NR}^1\text{R}^2$, $Y = \text{OEt}$). Further reaction with ammonia affords the diamine ($X = \text{NR}^1\text{R}^2$, $Y = \text{NH}_2$) (83JOC763). *N,N*-Diethylprop-1-ynamine reacts with the carbonyl group of *N*-methylsaccharin to yield the spiro-oxete (186) and the amide (187) (84CC1583). An intramolecular azawittig reaction with *N*-(2-azidobenzoyl)saccharin and triethyl phosphite gives 1,2-benzisothiazolo[3,2-*b*]quinazolin-7-one 5,5-dioxide (188) (90TL6561).



3.05.7.6 Sulfur-linked Substituents

The methylthio group in 4-cyano-5-methylthio-3-phenylisothiazole (189) ($R = \text{SMe}$) undergoes displacement with various nucleophiles to afford the 5-substituted compounds (189) (e.g., $R = \text{OEt}$, OH , NHNH_2 , I). The ethoxycarbonyl methylthio derivative (189) ($R = \text{SCH}_2\text{CO}_2\text{Et}$) is cyclized to the 3-phenylthieno[3,2-*d*]isothiazole (190) (82AJC393, 89AJC1291). 2-Substituted isothiazolin-5-thiones are converted with propylene oxide to the corresponding isothiazolin-5-ones (85CB851).



3.05.7.7 Halogen Substituents

Ethyl 3,4-dichloroisothiazole-5-carboxylate 1,1-dioxide (185) ($X = Y = \text{Cl}$) reacts with ethanol in the presence of silica gel to yield the 4-chloro-3-ethoxy compound (185) ($X = \text{Cl}$, $Y = \text{OEt}$), which with ethanol and triethylamine gives the 3,4-diethoxy derivative (185) ($X = Y = \text{OEt}$). In contrast, the reaction of ammonia with the 3,4-dichloro or 4-chloro-3-ethoxy derivatives (185) ($X = \text{Cl}$, $Y = \text{Cl}$, OEt) occurs preferentially at C-4 to give (185) ($X = \text{NH}_2$, $Y = \text{Cl}$, OEt) (83JOC763). The first reported isothiazole Grignard reagent, 3,5-dimethyl-4-isothiazoyl magnesium iodide (175) ($R = \text{MgI}$), is obtained from the 4-iodo compound (175) ($R = \text{I}$) by ethylmagnesium bromide exchange (87SC1207). An attempt to cross-couple 5-bromo-3-methylisothiazole with styrene using palladium(II) acetate and triphenyl phosphine as a catalyst resulted in the formation of 3,3'-dimethyl-5,5'-biisothiazole (81CPB3543).

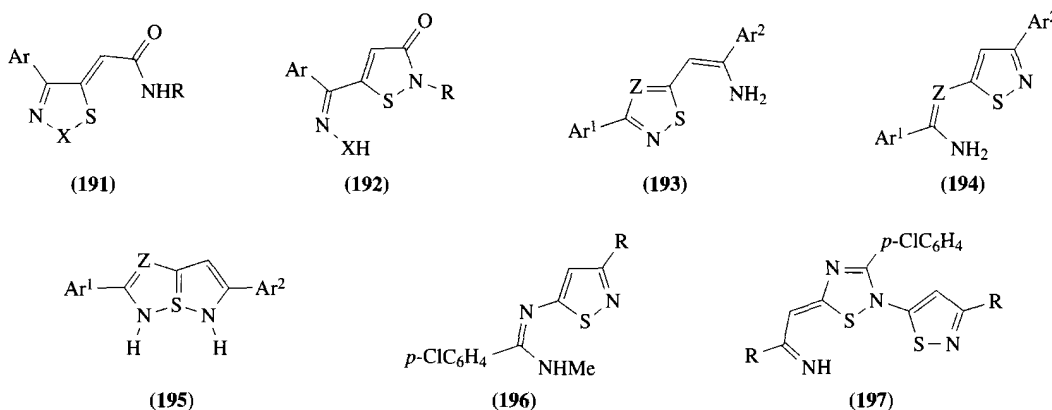
3.05.7.8 Metal Substituents

5-Lithioisothiazoles with various benzaldehydes and benzophenones produce secondary and tertiary carbinols (85JMC1245, 87CJC1617). 3,5-Dimethyl-3-isothiazoyl magnesium iodide is inert to

alkyl halides, but alkylation takes place with benzyl and allyl halides to afford (**175**) ($R = \text{Bn, allyl}$). Ketones ($R^1R^2C=O$) with the Grignard reagent give the tertiary alcohols (**175**) ($R = CR^1R^2OH$) $\langle 87SC1207 \rangle$.

3.05.7.9 Reaction of Substituents Involving Ring Transformations

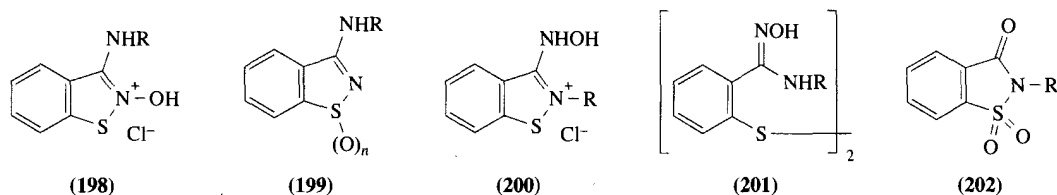
Appropriately 5-substituted isothiazoles undergo rearrangement involving initial attack at the ring sulfur $\langle 79JCS(P1)2340, 93AHC(56)49 \rangle$. Treatment of 2-alkyl-5-arylisothiazolin-3-ones with hydroxylamine or arylhydrazines (Ar^1NHNH_2) results in the formation of 1,2,5-oxathiazoles (**191**) ($X = O$) or 1,2,3-thiadiazoles (**191**) ($X = NAr^1$) via the oxime (**192**) ($X = O$) or hydrazone (**192**) ($X = NAr^1$) $\langle 84JHC1679 \rangle$. The reaction of 5-aminoisothiazoles with aryl nitriles ($ArCN$) affords directly the 1,2,4-thiadiazole (**193**) ($Z = N$) via the amidine (**194**) ($Z = N$). The 10-*S*-3 sulfurane (**195**) ($Z = N$) is considered to be the intermediate $\langle 81H(15)1155, 83PS(16)111 \rangle$. 3-Aryl-5-methylisothiazole with LDA and aryl nitriles ($ArCN$) yields both of the 5-(2-amino-2-arylvinyl)-3-aryl-isothiazole derivatives (**194**) and (**193**) ($Z = CH$), and the equilibrium between the two forms via the sulfurane (**195**) ($Z = CH$) has been explored $\langle 84TL4561, 85JA2721 \rangle$. The condensation of 5-aminoisothiazoles with *N*-methyl-4-chlorobenzimidazolyl chloride has been shown to produce two main products, the amidine (**196**) and the thiadiazolyl isothiazole (**197**) generated from a sulfurane-type intermediate $\langle 92H(33)763 \rangle$.



3.05.8 REACTIVITY OF SUBSTITUENTS ATTACHED TO RING HETEROATOMS

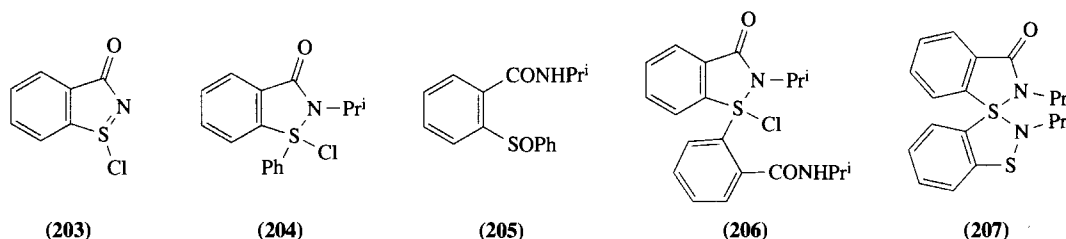
3.05.8.1 Ring Nitrogen

The 3-alkylamino-1,2-benzisothiazole 2-oxide (**198**) like pyridine *N*-oxides is reduced with phosphorus trichloride or thionyl chloride to the deoxy compound (**199**) ($n = 0$). The *N*-oxide (**198**) rearranges in methanol to the 3-hydroxylamine compound (**200**) and in formic acid to the sulfoxide (**199**) ($n = 1$). In the presence of a base, (**198**) ring opens to give the disulfide (**201**) $\langle 70CB3166 \rangle$. The reaction of *N*-hydroxymethylsaccharin (**202**) ($R = CH_2OH$) with aroyl chlorides or alkyl halides in the presence of a base proceeds by a retro-ene-type fragmentation of the *N*-hydroxymethyl group followed by formation of the *N*-aroyl- or *N*-alkylsaccharins $\langle 93JHC353 \rangle$. Dithiocarboxylation of *N*-alkoxycarbonyl or *N*-benzoylmethylsaccharin using carbon disulfide and sodium hydride followed by alkylation with methyl iodide gives the dithio acetal (**202**) ($R = CR^1=C(SMe)_2$; $R^1 = \text{Ph, OMe, OEt}$), which on reaction with hydrazine yields the 2-hydrazino-3,3-bis(methylthio) derivatives ($H_2NN=CR^1CH(SMe)_2$) $\langle 90LA927 \rangle$.



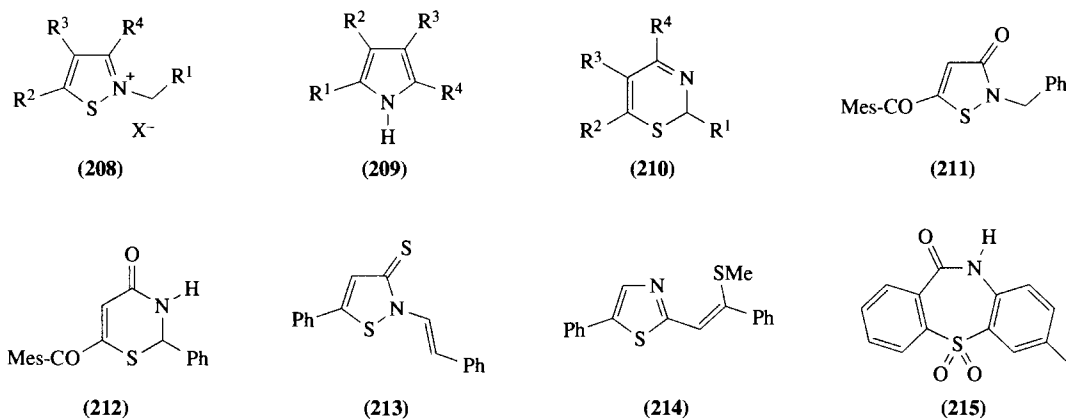
3.05.8.2 Ring Sulfur

A few reactions involving substituents on the ring sulfur have been reported. On hydrolysis the *S*-chloro compound (**203**) gives 1,2-benzisothiazol-3-one 1-oxide <78ZOR862>. 1-Chloro-1-phenyl-2-isopropyl-1,2-benzisothiazol-3-one (**204**) on treatment with a base gives the benzamide (**205**). The 1-chloro-1-(2-(*N*-isopropylcarbamoyl)phenyl) derivative (**206**) with potassium hydride yields (**207**) <78JA953>.



3.05.8.3 Reaction of Substituents Involving Ring Transformations

Several ring transformations involving the substituent on the ring nitrogen of isothiazoles are known. When the 2-alkoxycarbonylmethyl or 2-cyanomethyl isothiazolium salts (**208**) ($R^1 = CO_2R^2$, CN) are heated in the presence of triethylamine the pyrrole-2-carboxylic acid is formed (**209**) ($R^1 = CO_2R^2$, CN) by spontaneous extrusion of sulfur from the intermediate 1,3-thiazine (**210**) ($R^1 = CO_2R^2$, CN) <93AG(E)712>. The 2-phenacylisothiazolium salts with pyridine (**208**) ($R^1 = COPh$) give the 2-benzoyl-1,3-thiazine (**210**) ($R^1 = COPh$) <85SB149>. A similar reaction is reported for 2-phenacyl-1,2-benzisothiazol-3-one, which yields the benzothiazine (**210**) ($R^1 = COPh$, $R^2R^3 = -CH=CHCH=CH-$, $R^4 = OH$) <76JOC1325>. 2-Benzyl-5-mesitylisothiazolin-3-one (**211**) rearranges with sodium ethoxide to the 1,3-thiazin-4-one (**212**) <85JHC1635>. The reaction of 5-phenyl-[(*E*)-2-styryl]isothiazolin-3-thione (**213**) with triethyloxonium tetrafluoroborate gives the 2-styrylthiazole (**214**) <88JOC5374>. Halogen-metal exchange using butyllithium transforms 2-(2-bromo-4-phenyl)saccharin into the dibenzo[*b,f*][1,4]thiazepin derivative (**215**) <83T2073>.



3.05.9 RING SYNTHESSES CLASSIFIED BY THE NUMBER OF RING ATOMS IN EACH COMPONENT

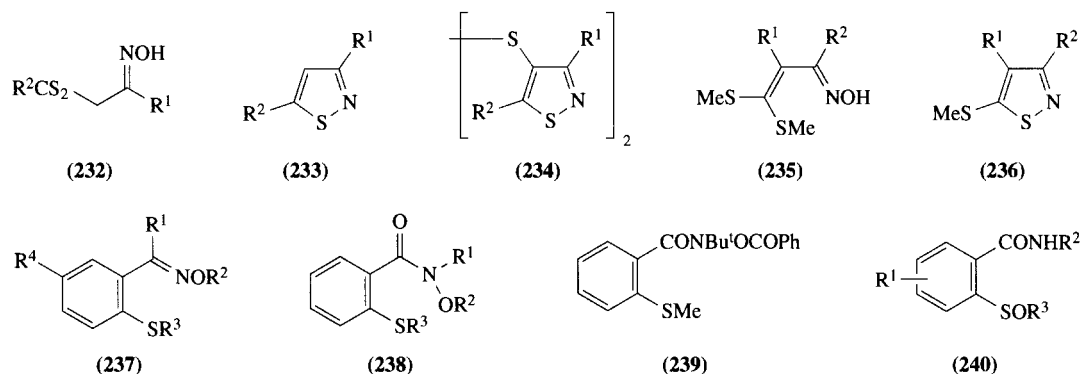
3.05.9.1 Formation of One Bond

3.05.9.1.1 Formation of a nitrogen-sulfur bond

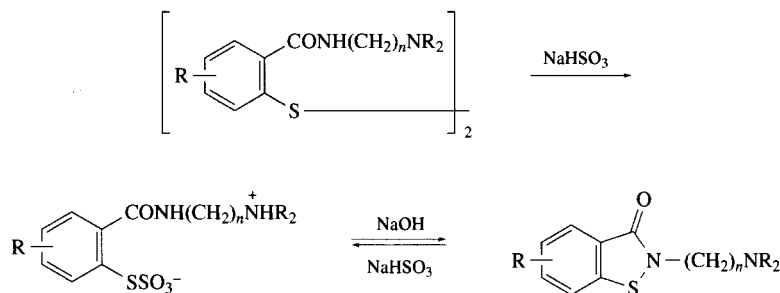
The oxidative cyclization of an appropriate γ -thio amine derivative to form the nitrogen-sulfur bond is the most convenient method of synthesizing substituted isothiazoles. For example, on

Oximes are useful intermediates in the synthesis of isothiazoles. The aryl dithiocarboxylate derivatives of the 2-hydroxyimino alkyl compounds (**232**) ($R^2 = Ar$) cyclize on reaction with tosyl isocyanate to 3,5-disubstituted isothiazoles (**233**) ($R^2 = Ar$). The dialkyldithiocarbamates (**232**) ($R^1 = NR_2$) yield the bis(4-isothiazolyl) disulfides (**234**) ($R^2 = NR_2$), and the trithiocarbonates (**232**) ($R^2 = SR^1$) produce a mixture of (**233**) ($R^2 = SR^1$) and (**234**) ($R^2 = SR^1$) $\langle 84CL1691, 87S349 \rangle$. The oxime dithioacetals (**235**) cyclize with thionyl chloride to give 5-methylthio isothiazoles (**236**) $\langle 89JOC1088 \rangle$. The oximes of 2-acyl thioanisole derivatives (**237**) are converted into 1,2-benzisothiazoles by acetic anhydride in pyridine $\langle 88CJC1405 \rangle$. The thermal cyclization of the oxime derivatives (**237**) ($R^2 = ArCO, Me_2NCS$) produces 3-substituted 1,2-benzisothiazoles, while the corresponding hydroxamic acid compounds (**238**) afford the 2-substituted 1,2-benzisothiazolin-3-ones only with the *t*-butylthio derivative (**238**) ($R^3 = Bu^t$) $\langle 82PS(12)357 \rangle$. One of the products from the thermal decomposition of *N,O*-diacyl-*N-t*-butylhydroxylamine (**239**) is 2-*t*-butylbenzisothiazol-3-one, which is also obtained from the Pummerer reaction on *N-t*-butyl-2-methylsulfinyl benzamide (**240**) ($R^1 = H, R^2 = Bu^t, R^3 = Me$) with thionyl chloride $\langle 81BCJ1781 \rangle$. This reaction is a general route

to 2-alkyl or 2-aryl derivatives <82BCJ1183>. Trichloromethyl chloroformate is the preferred reagent for methoxy substituents as the cyclization fails when thionyl chloride is used <91JMC3316>. Further modifications have been the thermal rearrangement of *t*-butyl sulfoxides or treatment of the benzyl sulfoxides with trichloroacetic anhydride <92TL153>. The cyclization of appropriate 2-alkylthioaryl ketoximes by simultaneous or consecutive ring formation is used to produce benzo diisothiazoles <91JHC445>.

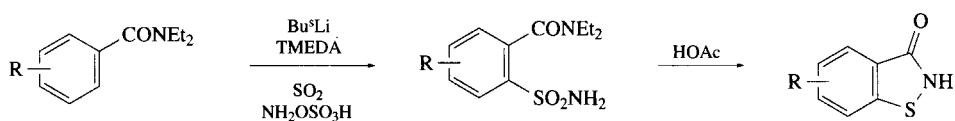


2-Carboxamido-6-nitrobenzenethiols in aqueous dioxan give the 7-nitrobenzisothiazolones <88JCS(P1)691>. 1,2-Benzisothiazol-3-ones may be prepared from Bunte salts or vice versa (Scheme 13) <85JMC1661, 85TL1753>.

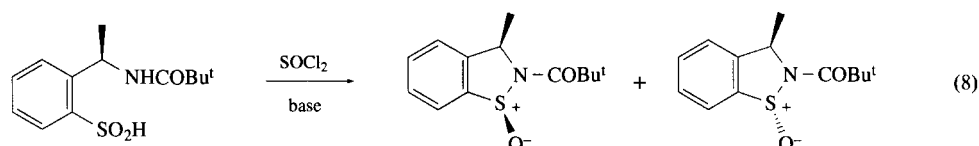


Scheme 13

A method for the synthesis of substituted saccharins has been developed via the *ortho* lithiation of *N,N*-diethylbenzamides (Scheme 14) <91TL7179>. The stereoselectivity of the cyclization of the (*R*)-sulfinic acid with thionyl chloride is found to be dependent on the base used, DMAP giving only the (*S*)-*cis* cyclic sulfinamide (Equation (8)) <91JCS(P1)3383>.



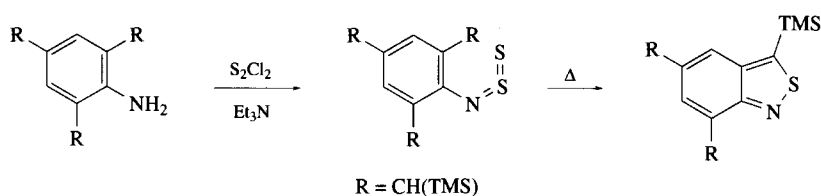
Scheme 14



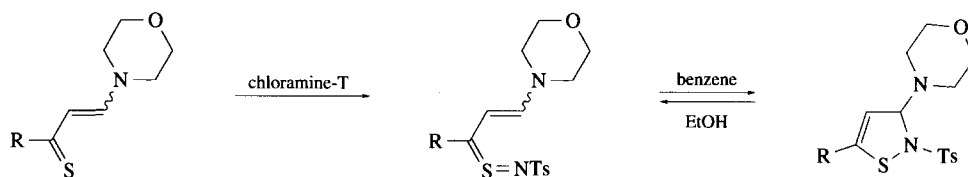
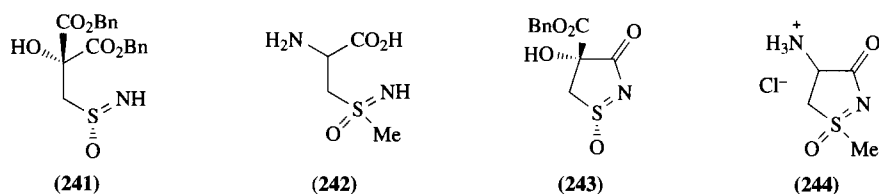
3.05.9.1.2 Formation of a bond adjacent to a heteroatom

An example of the formation of the sulfur-carbon bond is the cyclization of the *N*-thiofinylaniline to the 2,1-benzisothiazole (Scheme 15) <87CL2293>. There are more cases of nitrogen-carbon bond

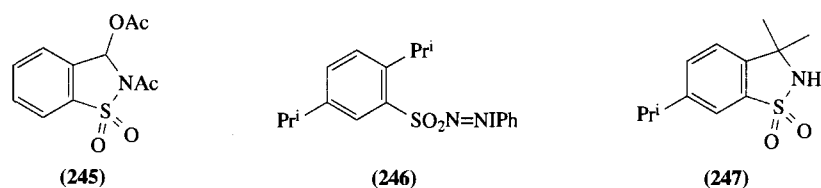
formation. The sulfoximine (**241**) and *S*-methylcysteine sulfoximine (**242**) produce the isothiazol-3-one 1-oxides (**243**) and (**244**) <84JMC228, 92JMC4875>. The reaction of the enamino thione with chloramine-T produces the thione *S*-imide, which undergoes a reversible cyclization to the thiazoline (Scheme 16) <83TL4435>. 1,2-Benzisothiazole 1,1-dioxide is conveniently prepared by the oxidation of 2-sulfonamidotoluene with chromium trioxide in acetic acid and treatment of the formed *N,O*-diacetyl derivative (**245**) with sulfuric acid <83CC520>. Metalloporphyrins or cytochrome P-450 catalyze an intramolecular nitrene C—H insertion in the imidoiodo sulfonamide derivative (**246**) to give the dihydrobenzisothiazole 1,1-dioxide (**247**) <83JA6728, 85JA6427>.



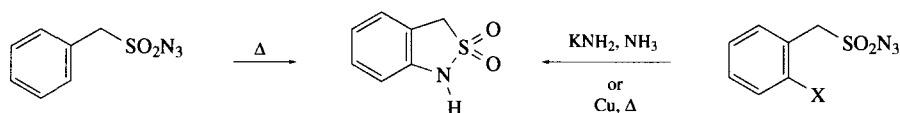
Scheme 15



Scheme 16



Flash vacuum pyrolysis of toluenesulfonyl azide gives 2,1-benzisothiazole 2,2-dioxide, which is also obtained from 2-halo- α -toluenesulfonamides on treatment with potassium amide and liquid ammonia, or by heating with copper (Scheme 17) <87H(26)2327, 86JHC1645>.

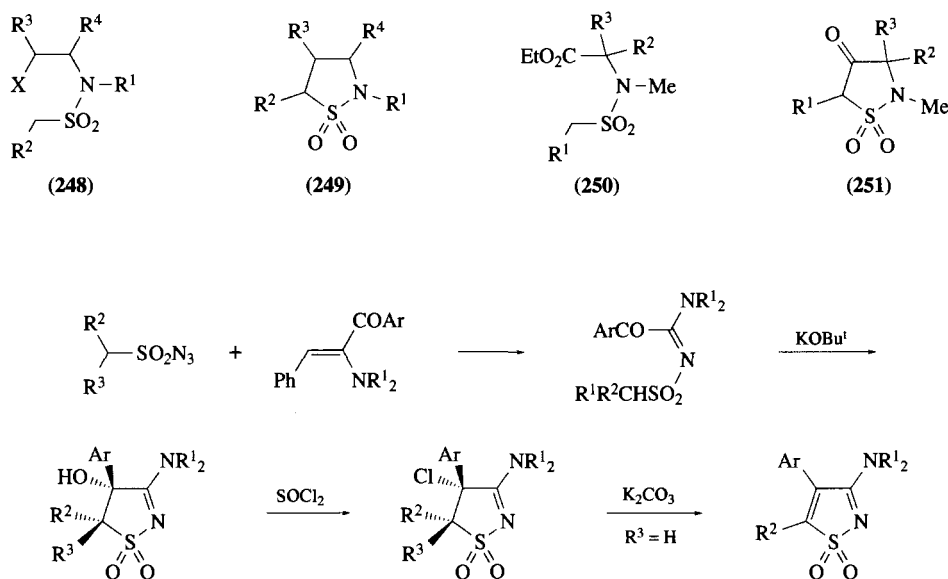


Scheme 17

3.05.9.1.3 Formation of a carbon–carbon bond

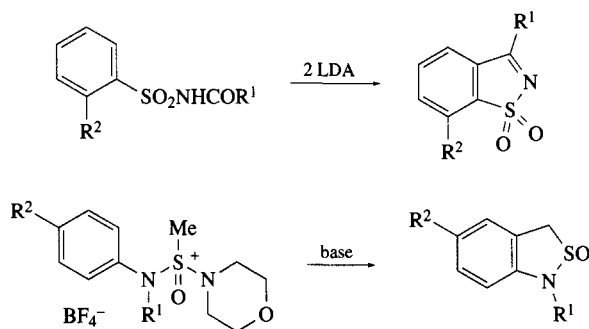
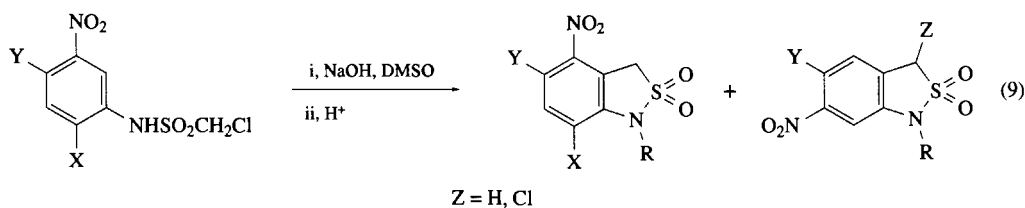
Substituted 1,3-propanesultams (**249**) are prepared via butyllithium-mediated cyclization of *N*-(2-bromoalkyl)-*N*-methylalkanesulfonamides (**248**) ($X = \text{Br}$, $R^1 = \text{Me}$) or the *N,O*-dimesylates of

substituted 2-amino alcohols (**248**) ($X = \text{MeSO}_2\text{O}$, $R^2 = \text{H}$) <73S667, 91S859>. Dieckmann condensation of methane sulfonamidopropionate esters (**250**) affords the isothiazolidin-4-one 1,1-dioxides (**251**) <85AP(318)304>. The cyclization of *N*-alkyl sulfonylamidines, formed by 1,3-dipolar addition of the azide to the enamine, gives the isothiazoline, which after treatment with thionyl chloride provides a new route to 3-aminoisothiazole 1,1-dioxides (Scheme 18) <92T3227>.



Scheme 18

The treatment of *N*-alkyl(3-nitrophenyl)chloromethylsulfonamides with a strong base leads to the benzosultam derivatives (Equation (9)) <84TL4791, 92S571>. 1,2-Benzisothiazole 1,1-dioxides are obtained by the *ortho* lithiation of *N*-acylbenzenesulfonamides (Scheme 19) <92JOC5328>. The reaction of diamino sulfoxonium salts with a base gives the 1-alkyl-1,3-dihydro-2,1-benzisothiazole 2-oxide (Scheme 19), probably via rearrangement of an intermediate ylide <85CL333, 90BCJ3223>.

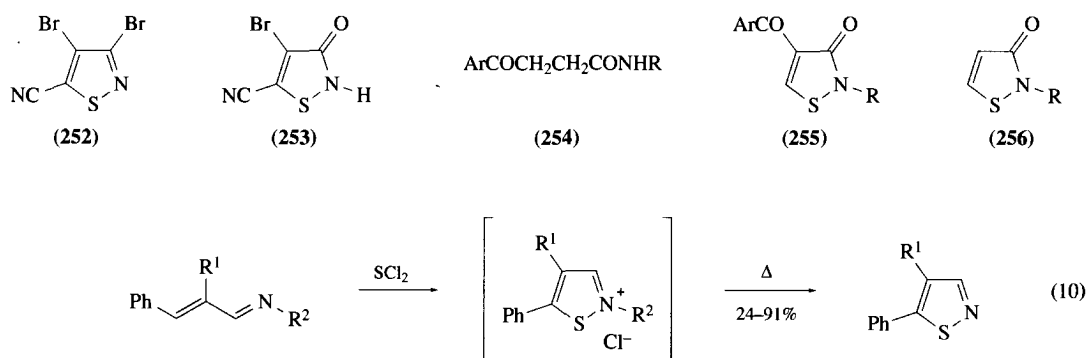


Scheme 19

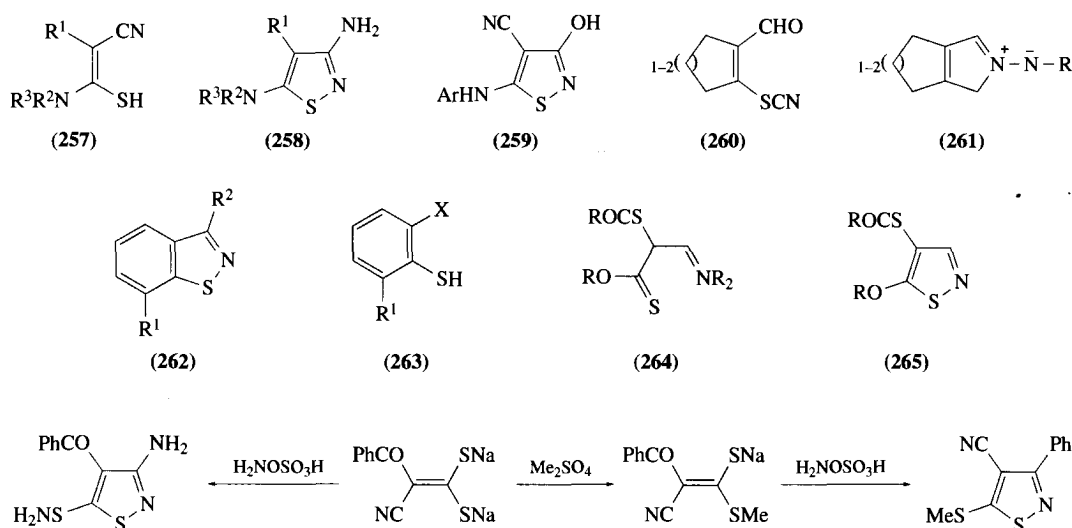
3.05.9.2 Formation of Two Bonds

3.05.9.2.1 From [4 + 1] atom fragments

The reaction of dicyanoethyne with sulfur dioxide and hydrogen bromide gives a 35% yield of 3,4-dibromo-5-cyanoisothiazole (**252**) <82ZOR675>. A similar reaction with ethyne dicarboxamide affords 4-bromoisothiazol-3-one-5-carboxamide (**253**) <83ZOR1337>. The reaction of *N*-substituted 3-aroilpropionamides (**254**) with thionyl chloride results in the formation of 5-aroil isothiazolin-3-ones (**255**), which on treatment with sodium hydroxide give the 2-substituted isothiazolin-3-ones (**256**) <85JHC1635, 87H(25)569>. The addition of sulfur dichloride to 1-alkyl-4-phenyl-1,3-butadienes yields the isothiazolium salts, which on heating afford the 5-phenylisothiazoles (Equation (10)) <83PS(16)119>.



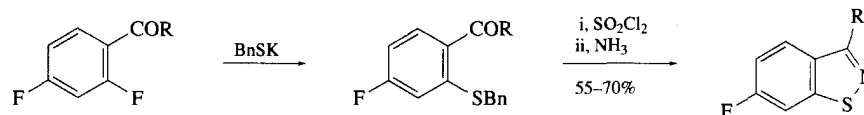
The amination of 3-amino-3-thioacrylonitriles (**257**) using chloramine is a general synthesis of 3-amino 5-substituted isothiazoles (**258**). The cyclization of the cyano acetamide (**257**) ($\text{R}^1 = \text{H}_2\text{NCO}$, $\text{R}^2\text{R}^3\text{N} = \text{ArNH}$) yields only the 3-hydroxy-4-cyano-5-arylaminoisothiazole (**259**) <88JHC759>. The addition of hydrazine derivatives to thiocyanatovinylaldehydes (**260**) produces the 2-imine derivatives (**261**) <93TL1909>. The 1,2-benzisothiazoles (**262**) ($\text{R}^1 = \text{H}$, NH_2 ; $\text{R}^2 = \text{Cl}$, OMe , NO_2) are obtained on treatment of the benzenethiols (**263**) ($\text{X} = \text{CHO}$, CN) with chloramine <83JCS(P1)2973, 84JCS(P1)385>. 2-Dialkylaminomethylene dithionates (**264**) condense with hydroxyamine-*O*-sulfonic acid to give 5-alkoxyisothiazole 5-thionocarboxylate (**265**) <93AP57>. The dithiolate disodium salt with hydroxyamine-*O*-sulfonic acid cyclizes to 3-amino-4-benzoyl-5-aminothioisothiazole, whereas the monomethyl compound gives 4-cyano-3-phenyl-5-methylthioisothiazole (Scheme 20) <84T381>.



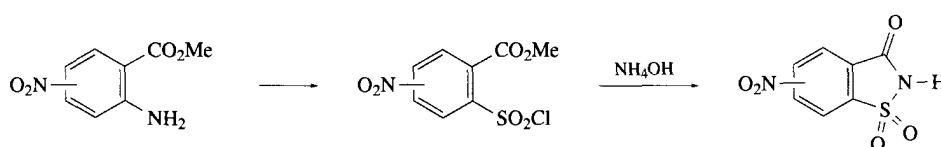
Scheme 20

6-Fluorobenzisothiazoles are prepared by the selective displacement of the 2-fluoro group in the 2,4-difluorophenyl ketone with benzyl thiol followed by reaction with sulfur chloride and ammonia (Scheme 21) <93TL6525>. An alternative synthesis of nitrosaccharins is the treatment of nitro

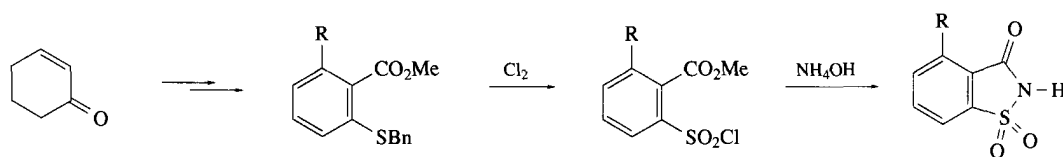
2-chlorosulfonylbenzoate esters with ammonia (Scheme 22) <86JHC1253>. A general route to 4-alkyl- or 4-aryl-substituted saccharins starts from cyclohexenone to prepare the intermediate trisubstituted benzene derivative, which is reacted with chlorine to give the sulfonyl chloride, followed by treatment with ammonium hydroxide (Scheme 23) <91BMC733>. The 3-amino or 3-hydroxy benzisothiazole 1,2-dioxides are obtained on reaction with either 2-formylbenzenesulfonyl chloride or its pseudo isomer (Equation (11)) <94T5425>.



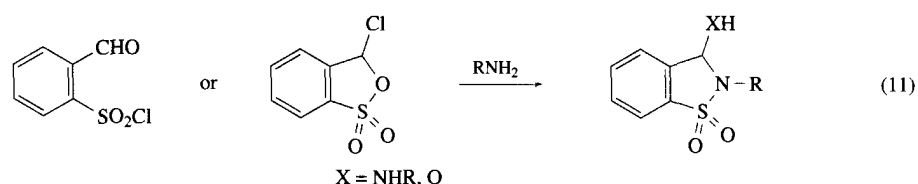
Scheme 21



Scheme 22



Scheme 23

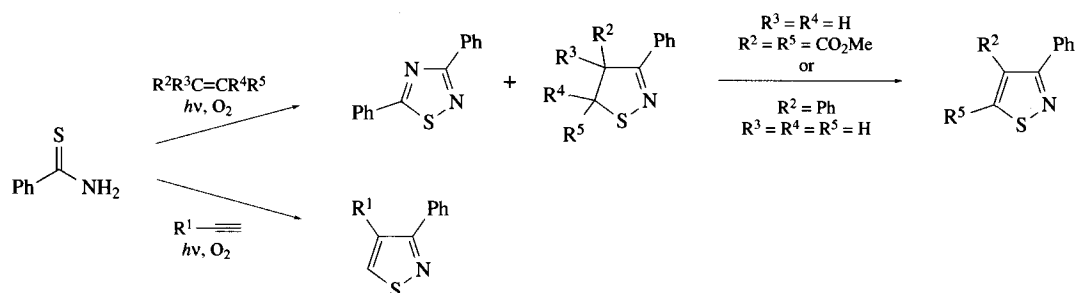


The synthesis of the fused isothiazole systems 2,1-benzisothiazolo[2,3-*b*]-2,1-benzisothiazole, 8-methylbenzo[1,2-*c*:5-*d'*]diisothiazole, and 3-methylbenzo[1,2-*c*:6,5-*d'*]diisothiazole uses the standard reaction of *N*-sulfinylmethanesulfonamide with 2-toluidines to obtain the 2,1-benzisothiazole ring <85CJC882, 88JHC1095, 91JHC347>.

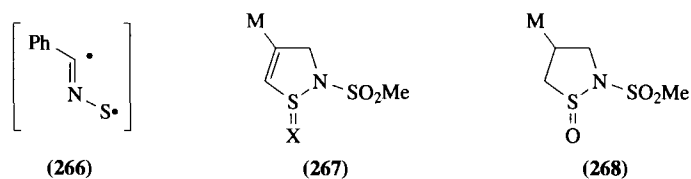
3.05.9.2.2 From [3 + 2] atom fragments

The photoreaction of phenyl carbothioamides under aerobic conditions in the presence of alkenes or alkynes yields isothiazoles and 3,5-diphenyl-1,2,4-thiadiazole (Scheme 24). It has been postulated that the biradical (**266**) is the reactive intermediate rather than the nitrile sulfide <84TL409, 90H(30)983>. Solutions of cyclotrithiazyl chloride in suluryl chloride behave as the reagent “NSCl₃” in reacting with methacrylonitrile to give 4-cyanoisothiazole <90CJC650>. Metal propargyl (MCH₂C≡CR) and η^1 allyl (MCH₂C=CH₂) complexes (e.g., M = CpFe(CO)₂, CpMo(CO)₃) react with *N*-sulfinyl sulfonamide (MeSO₂NSO) to give the isothiazole complexes (**267**) (X = O) and (**268**), respectively.

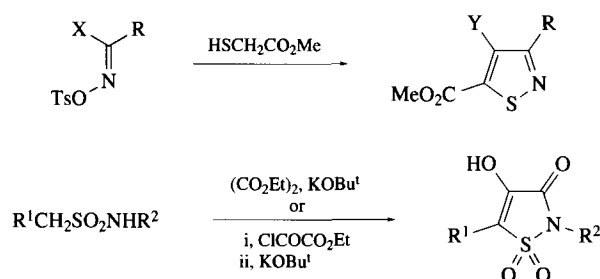
The propargyl complex with the sulfur bis(sulfonylimide) ($\text{MeSSO}_2\text{N})_2\text{S}$) gives the isothiazole (**267**) ($\text{X} = \text{NSO}_2\text{Me}$) <86OM846>.



Scheme 24

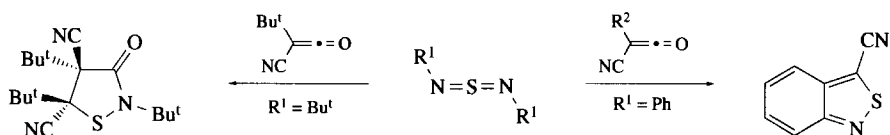


Further examples of the reaction of oxime tosylates ($\text{X} = \text{CN}$, CO_2Et) with methyl 2-thioacetate to give 4-amino or 4-hydroxy isothiazole 5-carboxylate esters ($\text{Y} = \text{NH}_2$ or OH , respectively) are described (Scheme 25) <86CPB701, 87JHC243, 92TL6523>. The condensation of methane or arylmethane sulfonyl amides with diethyl oxalate or reaction with ethyl oxalyl chloride gives the 4-hydroxyisothiazolin-3-ones (Scheme 25) <83JOC763, 84JOC2212>.

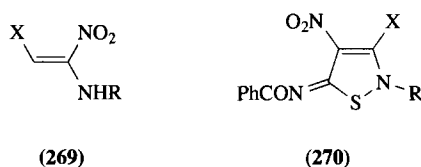


Scheme 25

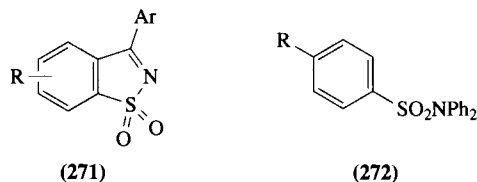
The treatment of di-*t*-butyl diimide with *t*-butylketene produces the isothiazolidin-3-one and diphenyl diimide with chlorocyanoketene gives 3-cyano-2,1-benzisothiazole (Scheme 26) <83H(20)187>. The reaction of benzoyl isothiocyanate with nitroketene *S,N*- and *N,N*-acetals (**269**) ($\text{X} = \text{MeS}$, R^1NH) yields the 3-methylthio and 3-amino-3-isothiazolines (**270**) ($\text{X} = \text{MeS}$, R^1NH) <82S65>.



Scheme 26

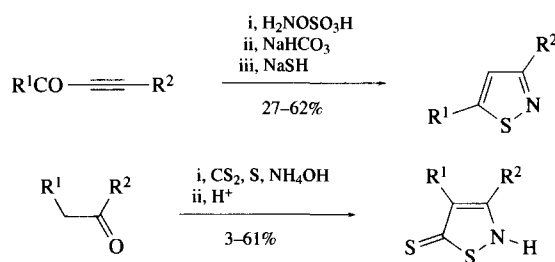


Heating benzophenones with chlorosulfonyl isocyanate affords 3-aryl-1,2-benzisothiazole 1,1-dioxides (**271**) <89SC417>, which are also synthesized by a one-pot reaction from *ortho*-lithiated *N,N*-diphenylbenzenesulfonamides (**272**) with aromatic nitriles (ArCN) <89S394>.



3.05.9.3 Formation of Three Bonds

A one-pot synthesis of 4-substituted isothiazoles from 1-acyl alkynes is described where sulfur is added as the last atom fragment (Scheme 27) <87H(26)1587, 89H(29)97>. The reaction of ketones with carbon disulfide, sulfur, and ammonium hydroxide followed by treatment with acid gives the 3,4-dialkyl-substituted isothiazolin-5-thiones (Scheme 27) <79JCR(S)410, 88BCJ4443>.

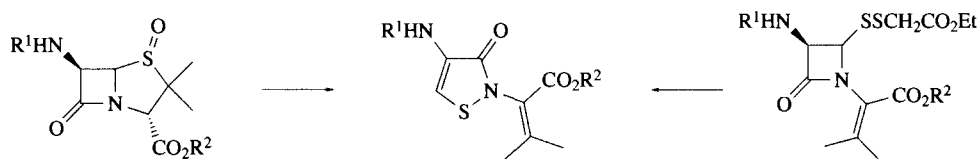


Scheme 27

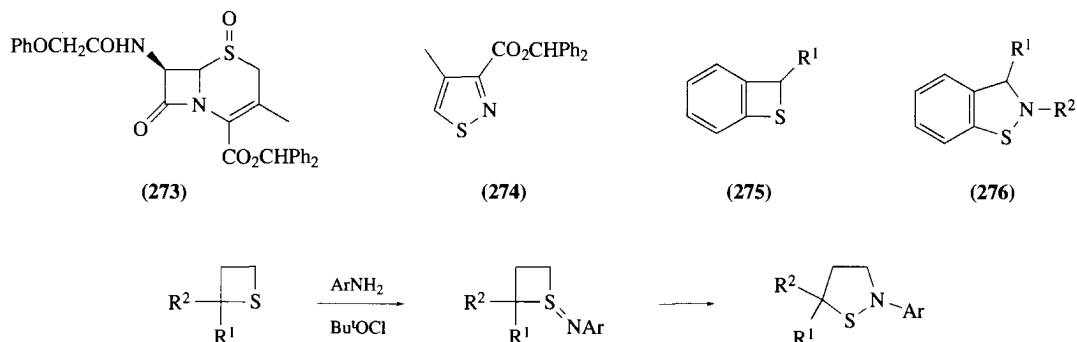
3.05.10 RING SYNTHESIS BY TRANSFORMATION OF ANOTHER RING

3.05.10.1 From Four-membered Heterocycles

Penicillin sulfoxides are converted on heating with trimethyl orthoacetate or excess ethyl 2-thioacetate into isothiazolin-3-ones. The azetidinone disulfide, formed when one equivalent of ethyl 2-thioacetate is used, rearranges on heating with *N,N*-dimethylaniline to the isothiazolinone (Scheme 28) <85H(23)809, 85TL3179>. The reaction of the benzhydryl ester of cephalosporin V (**273**) with 4-*t*-butyl iodobenzene dichloride leads to the 4-methylisothiazole 3-carboxylate ester (**274**) <89CC1348>. Primary amines react with benzothiete (**275**) to give the 2,3-dihydro-1,2-benzisothiazoles (**276**) <84AG(E)244>. The reaction of thietanes with anilines and tertiary butyl hypochlorite yields the *N*-arylimides, which rearrange to *N*-arylisothiazolidines (Scheme 29) <85M1153>.



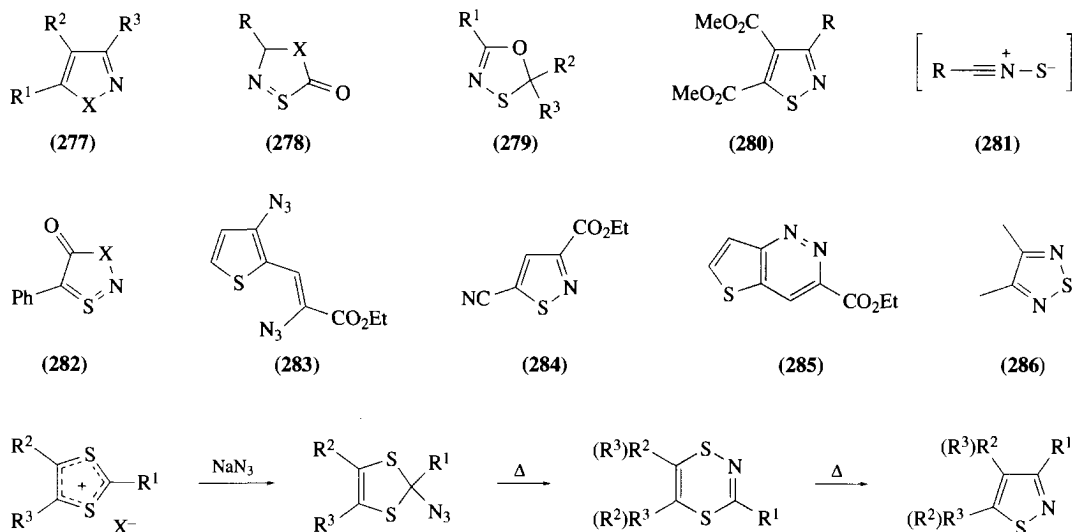
Scheme 28



Scheme 29

3.05.10.2 From Other Five-membered Heterocycles

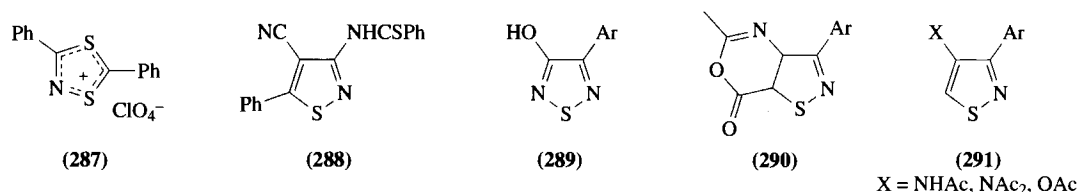
The treatment of the zirconium metallocycle (277) ($X = \text{ZrCp}_2$) in situ with sulfur chloride affords the isothiazole (277) ($X = \text{S}$) <87JA7137, 88JA2310>. The thermal fragmentation of 1,3,4-oxathiazol-2-ones (278) ($X = \text{O}$), 1,3,4-diathiazol-2-ones (278) ($X = \text{S}$), and 1,3,4-oxathiazoles (279) in the presence of DMAD yields dimethyl isothiazole-4,5-dicarboxylates (280) via the generated nitrile sulfide (281) <82TL5453, 85JCS(P1)1517, 87JCS(P1)2339>. The cycloaddition of 5-phenyl-1,3,2-dithiazol-4-one (282) ($X = \text{S}$) to DMAD to yield dimethyl 5-phenylisothiazole-3,4-dicarboxylate is much slower than the corresponding oxathiazolone (282) ($X = \text{O}$) <89JCS(P1)2489>. The thermal decomposition of ethyl 2-azido-3-(3-azido-2-thienyl)propenoate (283) results in the formation of ethyl 5-cyanoisothiazole-3-carboxylate (284) together with the thienopyridazine (285) <84JCS(P1)915>. The addition of benzyne to 3,4-dimethyl-1,2,5-thiadiazole (286) gives 3-methyl-1,2-benzisothiazole <82CC299>. 2-Substituted 1,3-dithiol-2-yl-azides, prepared from the 1,3-dithiolium salts, give on thermolysis the 1,4,2-dithiazines, which extrude sulfur to give the isothiazoles (Scheme 30) <83TL3729>. The 1,4,2-dithiazolium salt (287) with malononitrile gives the isothiazole (288) <89BCJ1086>. 3-Hydroxy-1,2,5-thiadiazole (289) is transformed on reaction with acetic anhydride in the presence of dbu into the isothiazoles (290) and (291) <85JHC1497>.



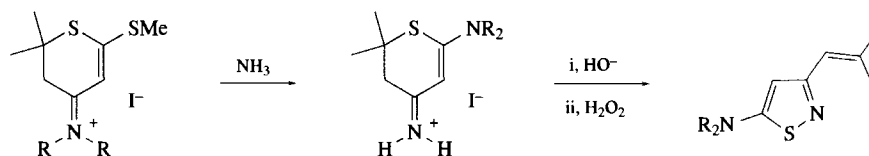
Scheme 30

3.05.10.3 From Six-membered Heterocycles

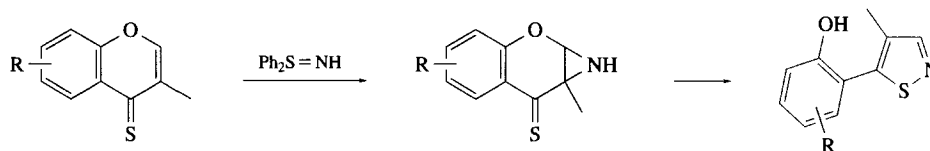
Treatment of 4-dialkylamino-2-methylthiopyran iodides with ammonia leads to 4-amino-2-dialkylaminothiopyranylum iodides, which on hydrolysis and oxidative cyclization afford 5-



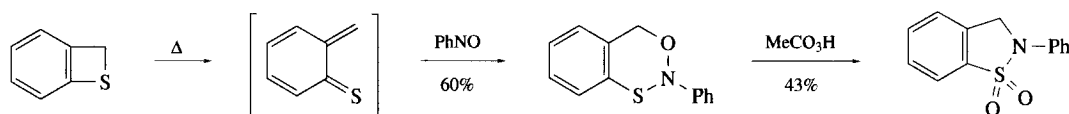
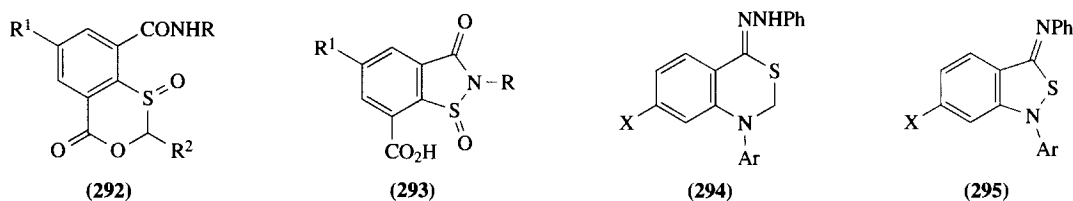
dialkylamino-3-(2-methyl-1-propenyl)isothiazoles (Scheme 31) ^[92M133]. The reaction of diphenylsulfilimine with 3-methylbenzopyran-4(*H*)-thione gives the 4-methylisothiazole (Scheme 32) ^[88JCR(S)349]. Heating the carboxamides of 3,1-benzoxathin-4-one (**292**) gives 1,2-benzisothiazol-3-ones (**293**) ^[83CB1708]. Aryl-4-phenylhydrazono-1,4-dihydro-2*H*-3,1-benzothiazines (**294**) on thermolysis yield 1-aryl-3-phenylimino-2,3-dihydro-2,1-benzisothiazoles (**295**) ^[84JHC1625]. Benzothiete undergoes cycloaddition on heating with nitrosobenzene to form 2-phenyl-4*H*-3,1,2-benzoxathiazine, which on oxidation with peracetic acid leads to 2-phenyl-2,3-dihydro-1,2-benzisothiazole 1,1-dioxide (Scheme 33) ^[86TL5703]. The oxidation of 1,3-benzothiazin-4(*H*)-ones (**296**) or 4-aryl-2*H*-1,3-benzothiazines (**297**) with sodium periodate results in ring contraction to give 1,2-benzisothiazole-3(2*H*)-one 1-oxides (**298**) and 3-aryl-1,2-benzisothiazoles (**299**), respectively ^[88T2985]. Similar oxidative ring contractions occur with 6,7-dimethoxy-2-aryl-3,4-dihydro-2*H*-1,3-benzothiazines (**300**) (*R*¹ = *R*² = H, *R*³ = Ar), the *N*-substituted derivatives (**300**) (*R*² = H, *R*³ = Ph), and the *N*-substituted 4-phenyl isomers (**300**) (*R*² = Ph, *R*³ = H) to give the 1,2-benzisothiazole (**301**), 2-substituted 1,2-benzisothiazolidine 1-oxides (**302**), (*R*² = H), and their 3-phenyl analogs (**302**) (*R*² = Ph), respectively ^[89T2731].



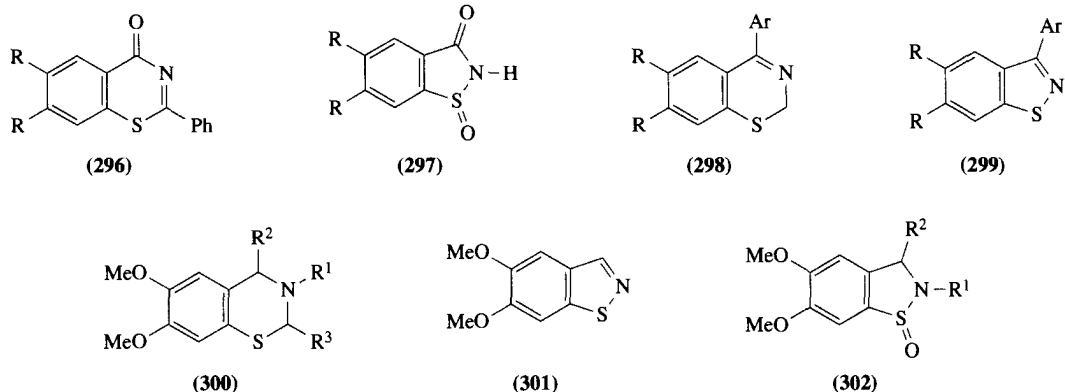
Scheme 31



Scheme 32

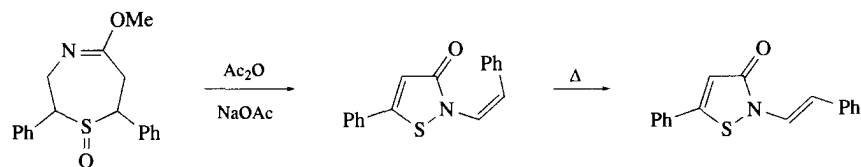


Scheme 33



3.05.10.4 From Seven-membered Heterocycles

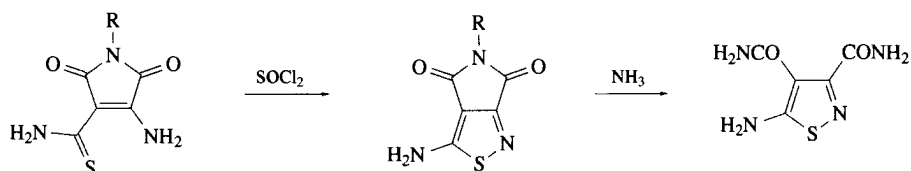
The Pummerer reaction on dihydro- and tetrahydrothiazepines results in ring contraction to isothiazolin-3-one derivatives. For example, 2,7-diphenyl-5-methoxy-2,3-dihydro-1,4-thiazepine 1-oxide affords quantitatively 5-phenyl-(*Z*)-*N*-styrylisothiazolin-3-one, which on heating isomerizes to the (*E*) isomer (Scheme 34) <87JOC5239>.



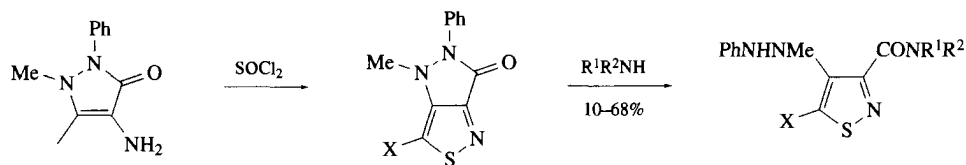
Scheme 34

3.05.10.5 From Fused Heterocyclic Systems

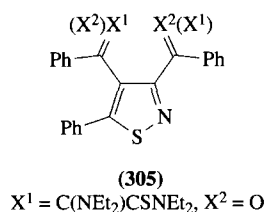
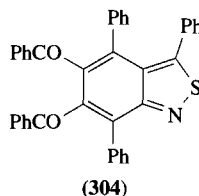
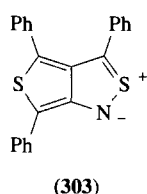
2-Amino-3-thiocarbonylmaleimides cyclize on oxidation to afford the 5-aminoisothiazole 3,4-dicarboximide. Reaction with ammonia gives the 3,4-biscarboxamide (Scheme 35) <88S449>. The amino pyrazole with thionyl chloride gives pyrazolo[4,3-*c*]isothiazoles, which with alkyl amines undergo ring opening to produce 3,4-disubstituted isothiazoles (Scheme 36) <86JHC1773>. Similar reactions with 5-amino-6-methyl-4(3*H*)-pyrimidinone and 1,3-disubstituted 5-amino-6-methyluracils also produce 4-aminoisothiazole-3-carboxamide derivatives <87T3917>. The cycloaddition product of the thieno[3,4-*c*]isothiazole (303) with dibenzoylthyne loses sulfur to yield 3,4,7-triphenyl-5,6-dibenzoyl-2,1-benzisothiazole (304). The reaction with bis(diethylamino)ethyne gives a mixture of isothiazoles (305) via an initial reaction with oxygen <86LA1796>.



Scheme 35



Scheme 36



3.05.11 COMPARISON OF THE VARIOUS SYNTHETIC ROUTES AVAILABLE

A variety of strategies have been developed for the synthesis of the isothiazole ring system, and the route selected will depend on the substituents required and the availability of starting materials. The most useful and general method remains the formation of the S—N bond by oxidative cyclization of a suitable S—C—C—N unit because such compounds are readily available. Depending on the choice of starting material the route is applicable to the synthesis of isothiazoles, isothiazolin-3-ones, their dihydro analogs, or isothiazolium salts as well as 1,2-benzisothiazoles and 2,1-benzisothiazoles and their derivatives (see Section 3.05.9.1.1).

The C—C bond formation of isothiazolidine 1,1-dioxides from the *N,O*-dimesylates of 2-amino alcohols (see Section 3.05.9.1.3) is an improvement over earlier routes using thermal or base-catalysed cyclization of halo- or tosyloxysulfonamides, halosulfonylalkylamines, or alkyl-haloalkanesulfonamides, as the starting material is readily available. Also, the method allows isothiazolidines to be prepared with substituents in the *N*, 3, and 4-positions with the possibility of retaining any chiral centers present (91S859). However, the scope of this route has not been fully explored.

Several novel methods for the synthesis of isothiazoles have been described which may be of more general use. Oxime dithioacetals on reaction with thionyl chloride cyclize to give in good yields 5-methylthiothiazoles, which previously have been prepared by thiolate substitution on the ring (89JOC1088) (see Section 3.05.9.1.1). The cyclization of 2-(hydroxyimino)alkyl arenecarbodithioates with tosyl isocyanate gives in 43–73% yields the 3-substituted 5-arylisothiazoles from readily available materials, but heating in a sealed tube is required. The *N,N*-dialkyldithiocarbamate and trithiocarbonate derivatives cyclize under milder conditions but lead to the formation of the bis(4-isothiazolyl) disulfides (84CL1691, 87S349) (see Section 3.05.9.1.1). The *N*-alkylsulfonylamidines of 2-keto acids cyclize to produce 3-dialkylamino-4-hydroxy-2-isothiazoline 1,1-dioxides, which may be converted to the 3-dialkylaminoisothiazole 1,1-dioxides (92T3227) (see Section 3.05.9.1.3). The condensation of substituted methane sulfonamides with diethyl oxalate gives the 4-hydroxy-isothiazolin-3-ones, which on nucleophilic substitution leads to other derivatives (83JOC763, 84JOC2212) (see Section 3.05.9.2.2). A new synthesis of 4-unsubstituted isothiazoles from 1-alkyne aldehydes or ketones, hydroxyamine-*O*-sulfonic acid, and sodium hydrosulfide has the advantage that the one-pot reaction is carried out in water and the yields are comparable to other more laborious routes (89H2997) (see Section 3.05.9.3). The cyclization of readily available 3-amino-3-thioacrylonitriles with chloramine gives good yields of 3-amino 5-substituted aminoisothiazole-4-carboxylic acid derivatives, which previously have been prepared through oxidative cyclization of relatively inaccessible thiocarbamoylacetamidines (88JHC759) (see Section 3.05.9.2). The reaction of oxime tosylates with thiols with an adjacent reactive methylene group, originally described in 1979, has been further extended and is a useful route to a range of substituted 4-amino or 4-hydroxy isothiazoles (79LA1534, 86CPB701, 87JHC243, 92TL6523) (see Section 3.05.9.2.2).

The most general routes to 1,2-benzisothiazoles start from suitable 2-acyl or 2-carboxylic acid derivatives of benzenethiols. A minor improvement in the synthesis of 1,2-benzothiazoles from oximes of 2-acyl benzenethiols is the use of acetic anhydride in pyridine (88CJC1405) (see Section 3.05.9.1.1). The advantage of using the thermolysis of 2-(benzylsulfinyl)benzamide or treatment of the corresponding *t*-butylsulfinyl compound with trichloroacetic acid for the preparation of 1,2-benzisothiazolin-3-ones is that the conditions are milder than those previously reported for the cyclization (92TL153) (see Section 3.05.9.1.1).

Various routes are used for the synthesis of 1,2-benzisothiazole 1,1-dioxides, and recent advances are the cyclization of *N*-acyl-benzenesulfonamides using two equivalents of LDA, and a one-pot procedure in which *ortho*-lithiated *N,N*-diphenylbenzenesulfonamides are reacted with nitriles (92JOC5328, 89S394) (see Sections 3.05.9.1.3 and 3.05.9.2.2).

Earlier work to prepare substituted saccharins by *ortho*-lithiation and carbonation of sulfonamides is limited by the availability of starting materials and poor yields (71JOC1843). An

improvement recently described is a two-step process via *ortho*-lithiation of readily available *N,N*-diethylbenzamides <91TL7179> (see Section 3.05.9.1.1). The synthesis of nitrosaccharins and 4-alkyl- or 4-arylsaccharins via aminolysis of 2-chlorosulfonylbenzoate esters avoids the oxidation step involved in the synthesis from 2-toluenesulfonamides <86JHC1253, 91BMC733> (see Section 3.05.9.2.1).

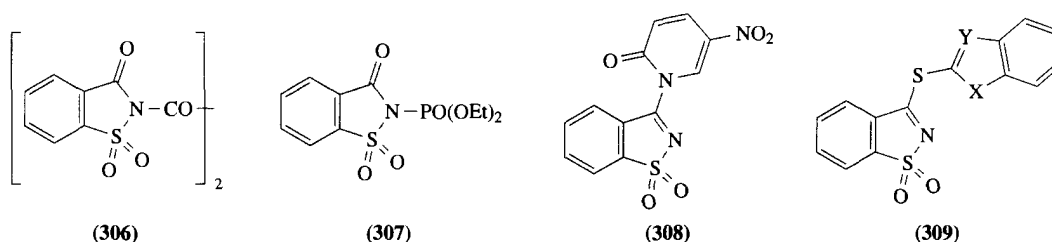
The reaction of 2-toluidines with thionyl chloride, or preferably *N*-sulfinylmethanesulfonamide as there are fewer side reactions, continues to be the main method of preparing 2,1-benzisothiazoles because of the availability of starting materials (for examples, see Section 3.05.9.2.1).

3.05.12 IMPORTANT COMPOUNDS AND APPLICATIONS

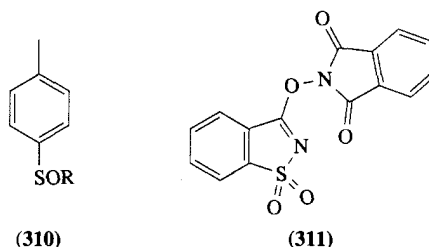
3.05.12.1 Chemical Applications

The use of isothiazole derivatives as fluorinating agents, oxidizing agents, and chiral auxiliaries are covered in Sections 3.05.6.3.4 and 3.05.6.4.2. *N*-Bromosaccharin is an excellent brominating agent for both benzylic and α -carbonyl positions <82JOC1588>. The chlorination and bromination of aromatic compounds using *N*-halosaccharin in a pyridinium poly(hydrogen fluoride) system has been reported <92SC2513>.

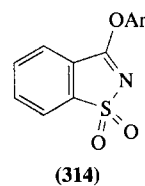
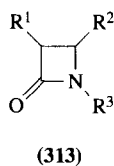
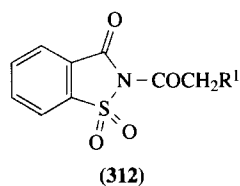
The reactive condensing agents 2,2'-oxalydi(2-sulfobenzimide) (**306**) <90CPB2583, 91CPB3030>, diethyl 2-(3-oxo-2,3-dihydro-1,2-benzisulfonazolyl)phosphonate (**307**) <85CL123>, 3-(5-nitro-1,2-dihydro-1-pyridyl-2-one)-1,2-benzisothiazole 1,1-dioxide (**308**) <84BCJ781>, and 3-(benzothiazol-2-ylthio)- and 3-(benzoxazol-2-ylthio)-1,2-benzisothiazole 1,1-dioxides (**309**) (X = S, O) <82S933> have been developed for the synthesis of amides, esters, and thioesters, and in some cases nitriles and lactones.



The reaction of 4-toluenesulfinic acid (**310**) (R = OH) with alcohols and thiols in the presence of 3-(phthalimidoxy)-1,2-benzisothiazole 1,1-dioxide (**311**) is a convenient synthesis of sulfinates (**310**) (R = OR¹) and thiosulfinates (**310**) (R = SR¹) <82CPB1646>. With Grignard reagents (RMgX), direct C-sulfinylation takes place to give the sulfoxide (**310**) <83BCJ349>. Thiosaccharin reacts with alkyl halides to produce 3-alkylthio-1,2-benzisothiazole 1,1-dioxides, which are synthetic equivalents for alkane thiols, as with piperidine the alkane thiol is released <83BCJ949>.



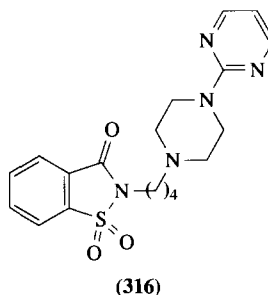
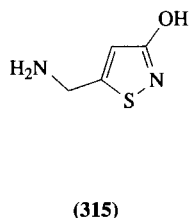
The reaction of 2-acylsaccharins (**312**) with imines (R²CH=NR³) is a useful synthesis of β -lactams (**313**) <84SC353>. Phenols are converted into the arene (ArH) by catalytic hydrogenolysis of the 3-aryloxy derivatives (**314**), which are prepared from 3-chloro-1,2-benzisothiazole 1,1-dioxide <90TL5789>. An efficient phosphorylating agent for the synthesis of nucleoside 3'-phosphodiester is obtained by from 3-chloro-1,2-benzisothiazole 1,1-dioxide and 5-chloro-8-quinolyl phosphate <84CPB1650>. *N*-(2-Nitrobenzenesulfonyl)saccharin is useful for the protection of amino groups in peptides <85S512>.



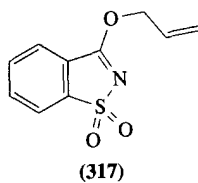
3.05.12.2 Biological and Industrial Applications

Saccharin, which is used as a sweetening agent, is the most important and best known isothiazole. It is 500 times as sweet as sugar in dilute solution, but leaves a bitter, metallic aftertaste. There are numerous reviews and publications on the history and development of saccharin (e.g., see Mitchell and Pearson <91MI 305-02>), analytical methods (e.g., see Zubair and Hassan <84MI 305-02>), and the long running saga of its claimed carcinogenic potential <90MI 305-02, 91MI 305-02, 92MI 305-02>. For the present work, discussion will be limited to some of the attempts to relate molecular properties to sweetness, still an unresolved problem. The current view is that sweetness depends critically on the relationship in a molecule of a hydrogen bond donor (AH) (or electrophilic center) and acceptor (B) (or nucleophilic center), and a hydrophobic centre (γ) situated some 550 pm away from the AHB groups. In the case of saccharin, AH corresponds to NH, B is generally considered to be the SO₂ oxygen atoms, although the role of the C=O group is also important, and γ the aromatic ring. Stereochemical requirements have been predicted using molecular mechanics, and other parameters such as hydrophobicity have also been considered <85MI 305-02, 88MI 305-01>. Substitution at the nitrogen atom destroys the AHB system and results in tasteless or bitter-tasting substances. It also appears that substitution at positions 4, 5, or 7 will remove any sweet taste, possibly because access to a specific receptor is blocked. Sweetness can be retained with nonbulky substituents (e.g., Me, F, OH, or NH₂) in the 6 position. Attempts to relate sweetness to variations in the C=O bond length for various sweet and bitter saccharin derivatives have not been successful <92AX(B)269>, although further work looking at other bond lengths is in progress, and electron density studies from x-ray crystallography are also being investigated <91AX(B)905>. Raman spectroscopy has been used to examine the role of water in hydrogen bonding and sweetness, where the relationship between hydrogen bonding to the AHB center, and the hindered mobility of water round the γ center, may be relevant <90JST(237)327>.

Examples of other applications of isothiazoles are given in CHEC-I <84CHEC-I(6)131>. Thiomuscimol (**315**), which exists as a zwitterion, is active on the central nervous system as a potent agonist of γ -aminobutyrate (GABA) receptors, and molecular mechanics has been used to investigate these interactions <85EJM447, 87MI 305-03>. Ipsapirone (**316**) is a nonbenzodiazepine anxiolytic serotonin (5-HT) receptor agonist.



The antifungal properties of isothiazolones (**25**) have been exploited, and these compounds (marketed under the name Kathon) are used as biocides and preservatives, with applications as diverse as cooling-tower water, lipstick, paints, cutting oils, and shampoos. There are numerous descriptions and patents in the literature, and a very wide range of analytical procedures has been employed to study both detection levels and stability of the formulations <89JC317, 92MI 305-03>. There have been some concerns about the safety of these compounds when used in cosmetics. Probenazole (**317**) is an antifungal agent used to treat rice blast fungus, and its mode of action has been investigated by molecular graphics <87MI 305-04>.



Saccharin and its sodium salts are used as components of curing agents for adhesives for acrylates on metal films. Surface-enhanced Raman spectroscopy has been used to show that the saccharin molecules migrate to the metal surface, so that they must be directly involved in the binding process <90L721>. There are numerous patents on azo dyes based on 3-azo-substituted 2,1-benzisothiazoles.

3.06

Thiazoles

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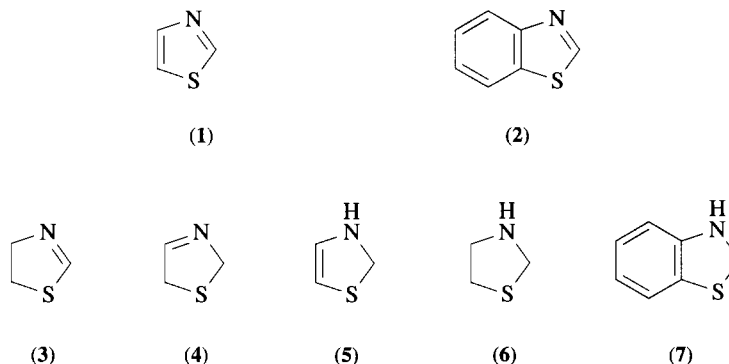
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3.06.1 INTRODUCTION

The following structures will be treated in this chapter:



In addition, oxo, thioxo, and amino compounds are considered in the corresponding subsections.

3.06.2 THEORETICAL METHODS

The electron distribution in thiazole and the resultant electrostatic environment have been investigated in detail by means of *ab initio* computational studies $\langle 92JA2313 \rangle$. The sharing of a significant amount of charge between the sulfur p_z orbitals and those of the adjacent carbon atoms C_2 and C_5 indicates participation of these orbitals in $S-C_2$ and $S-C_5$ π -bonding. Likewise, the N_3-C_4 bond also have large $2p_z$ overlap populations. These results are in agreement with a significant degree of conjugation for the thiazole ring. The gross orbital population measures the total charge assigned by the population analysis to an individual atomic orbital. As a result of π -bonding the outermost sulfur p_z orbital losses roughly 1/5 to 1/4 of an electron to the rest of the ring thus producing a net positive charge on the sulfur atom. The net atomic charges of thiazole have been calculated by both semiempirical $\langle 93JCC75 \rangle$ and *ab initio* $\langle 92JA2313 \rangle$ methods.

Thiazole has also been studied by several LCAO-MO based computations at lower levels of theory $\langle 89JST(53)269 \rangle$ as well as by spin-coupled computations $\langle 89JCS(P2)263 \rangle$. These calculations provide a resonance energy for thiazole of 34 kJ mol^{-1} showing a marked similarity between the spin-coupled orbitals of thiazole and those of thiophene. Whereas five of the orbitals are very localized, with one on each atom, the sixth orbital, which is centered on the sulfur atom, is significantly delocalized onto the neighboring carbon atoms, in a similar way to thiophene.

Based on semiempirical SCF MO calculations, the ionization potentials of thiazole and several benzothiazole derivatives obtained by photoelectron spectroscopy, have been assigned to molecular orbitals $\langle 93JST(296)115 \rangle$.

PPP (LCI-SCF-MO) calculations applied to mono bromothiazoles made it possible to predict the allowed transitions in the usual region of the UV spectrum (see Section 3.06.3.3). Successful correlations were obtained when the experimental absorption bands were compared with the results of the PPP calculations $\langle 84H(22)1077 \rangle$.

A variety of computational methods have been compared in the prediction of bond lengths, bond angles, and the heat of formation of thiazole $\langle 93JCC75 \rangle$. Among these methods are the semiempirical techniques AM1, PM3, and MNDO, and the thermochemical basis sets of Benson.

Unfortunately, since a true experimental value for the heat of formation of thiazole is not known, it is not possible to evaluate the accuracy of the calculated values. However a close practical estimation of an experimental ΔH_f° for thiazole can be obtained (see Section 3.06.4). Dewar's AM1 semiempirical MO method has also been used by Bean $\langle 93JOC7336 \rangle$ to calculate the heats of formation and charges in the 4- and 5-substituted-2-methyl thiazoles and their benzyl-like anions. This study afforded also proton and hydride ion affinities of the benzyl-like anion and cation of 2-methylthiazoles (see Section 3.06.7.3.2).

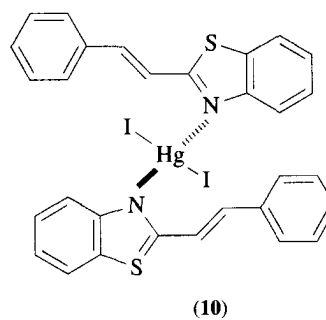
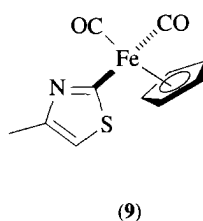
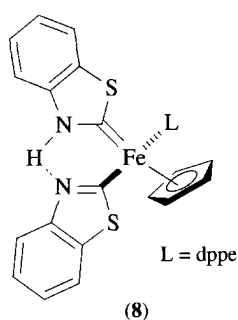
Theoretical methods have also been used for studying the reactivity of some thiazole derivatives. Thus, quantum chemical calculations by the CNDO/2 method have been carried out for 2-methylthiazole and 2-phenylthiazole as well as their protonated forms and complexes with $AlCl_3$. Information regarding the orientation of the electrophilic substitution of the non-protonated and

protonated forms of 2-phenylthiazole were thus obtained <85CS266>. The catalytic effect of thiazolium salts in the benzoin condensation has been studied by means of MNDO calculations <88JOC4433>. The same type of calculations were used to explain the chemical behavior of 4-substituted thiazolidinedithiones <90JCS(P1)2459>. Steric parameters for quantitative structure-activity relationship studies, were calculated for 2- and 4-substituted thiazoles utilizing the AM1 method <95TL6159>.

3.06.3 EXPERIMENTAL STRUCTURAL METHODS

3.06.3.1 X-ray Diffraction

Since 1983 a large number of structures of thiazole derivatives have been determined by x-ray analysis. The structures of complexes with metal atoms were also obtained: mixed copper(I) complexes with 1,3-thiazolidine-2-thione and triarylphosphines have been found to be dimeric with the thione ligand bridging two metal atoms <91ICA(184)161, 91POL935>. Monomeric complexes between 1,3-thiazolidine-2-thione and copper(I) have been characterized <91ICA(186)199>. The structures of 2-benzothiazolyl and 4-methyl-2-thiazolyl complexes of cyclopentadienyliron(II) (**8**) and (**9**) have been established <92JCS(D)1009>. A crystallographic study of the *trans*-2-styrylbenzothiazole complex with mercury(I) iodide (**10**) showed that the organic moiety of this complex is only roughly planar presumably because of the free rotation of the aromatic ring as well as packing forces <93POL2235>. The crystal structure of an organic ion-radical salt (3,3'-diethyl-4,4'-dimethyl-2,2'-thiazolocyanine-[TCNQ]₂) has been studied by x-ray diffraction <94MI 306-01>.

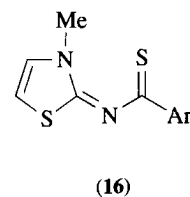
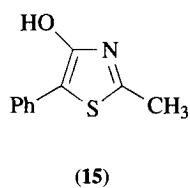
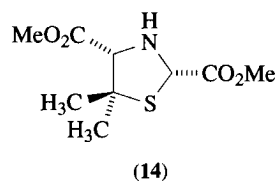
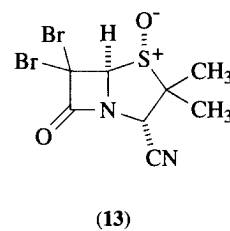
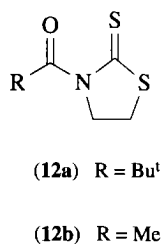
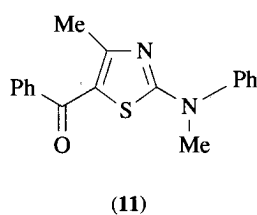


The conformational preferences of 2-amino-5-acylthiazoles were established by a crystallographic analysis of (**11**) <88JCS(P1)2209> as it will be discussed later (see Section 3.06.4.3). A similar study showed a remarkable difference in the conformation of 3-acyl-thiazolidin-2-thiones (**12a**) and (**12b**); thus the twist angle about the C(O)—N bond in (**12a**) was found to be 20.1°, whereas that of (**12b**) showed a value of 74.3°, an extremely large value for this class of compounds <93AG(E)1083>. Crystallographic studies by x-ray diffraction showed two dominant conformations in the solid state for the thiazolidine ring in the fused bicyclic penam derivative (**13**) <91CJC578>. X-ray crystallography was used to confirm the predicted conformation by computational methods for thiazolidine (**14**) and the predominant tautomeric hydroxy form of 4-hydroxythiazoles, such as (**15**), which were previously assigned <86AKZ688> by NMR studies (see Section 3.06.4.4). In a similar way the tautomerism of 2-aminobenzothiazoles has been investigated by x-ray structural analysis <94JCS(P2)615>. An x-ray analysis of *N*-(2-thiazolylidene)thioamide (**16**) has revealed a short intermolecular S(1)...S(2) contact of 2.9 Å. It was postulated that the development of opposite charges on the sulfur atoms plays an important role in the short S—S contact <94H(37)1933>.

The crystal structure of a lithiated thiazole showed the carbene character of the compound (see Section 3.06.5.7.1) <95AG(E)487>.

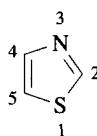
3.06.3.2 Microwave Spectroscopy

Microwave spectral analysis of thiazole in the gas-phase was carried out to determine bond lengths and bond angles <71JST(8)225>. The results are listed in Tables 1 and 2. These experimental values were compared with those obtained from theoretical calculations (see Section 3.06.2) by



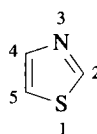
semiempirical and *ab initio* methods <93JCC75>. The ³³S nuclear quadrupole coupling of thiazole-³³S can be studied by Fourier transform microwave spectroscopy. In this study the rotational spectrum of thiazole has been reinvestigated <93ZN(A)1219>.

Table 1 Bond lengths (Å) of thiazole.



Bond	Bond length (Å)	Bond	Bond length (Å)
S ₁ —C ₂	1.7239 ± 0.0009	C ₅ —S ₁	1.7130 ± 0.0003
C ₂ —N ₃	1.3042 ± 0.0011	C ₂ —H ₂	1.0767 ± 0.0018
N ₃ —C ₄	1.3721 ± 0.0002	C ₄ —H ₄	1.0798 ± 0.0001
C ₄ —C ₅	1.3670 ± 0.0004	C ₅ —H ₅	1.0765 ± 0.0002

Table 2 Bond angles (°) of thiazole.



Angle	Bond angle (°)	Angle	Bond angle (°)
S ₁ —C ₂ —N ₃	115.18 ± 0.01	N ₃ —C ₂ —H ₂	123.56 ± 0.50
C ₂ —N ₃ —C ₄	110.12 ± 0.02	N ₃ —C ₄ —H ₄	119.35 ± 0.01
N ₃ —C ₄ —C ₅	115.81 ± 0.01	C ₅ —C ₄ —H ₄	124.84 ± 0.01
C ₄ —C ₅ —S ₁	109.57 ± 0.01	C ₄ —C ₅ —H ₅	129.03 ± 0.03
C ₅ —S ₁ —C ₂	89.33 ± 0.03	S ₁ —C ₅ —H ₅	121.40 ± 0.03
S ₁ —C ₂ —H ₂	121.26 ± 0.50		

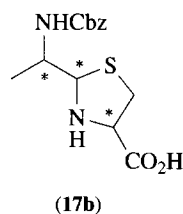
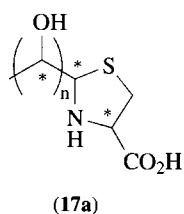
3.06.3.3 UV Spectroscopy

The UV absorption spectra of thiazole and bromothiazoles show two broad absorption bands, both corresponding to $\pi \rightarrow \pi^*$ transitions. These experimental results are in good agreement with those predicted by PPP (LCI-SF-MO) calculations <84H(22)1077>.

Similar studies carried out with 2-aryl- and 2-hetarylbenzothiazoles in different solvents and at various pH values showed a similar behavior for these compounds (<93DP293, 93MI 306-02, 94M209>). Also in this case two absorption maxima resulting from singlet $\pi \rightarrow \pi^*$ transitions were observed. The transitions energies obtained by means of PPP-SCF-CI quantum chemical calculations were in good agreement with the experimental values.

UV-visible spectra have been used in studies of the amino-imino tautomerism of differentially substituted 2-aminothiazoles and 2-aminobenzothiazoles (<92JHC1461, 94JCS(P2)615>). The spectra were recorded in different solvents and in the presence of variable amounts of salts in order to change medium polarity.

The CD spectra of 2-substituted thiazolidine-4-carboxylic acids have been studied. The spectra of 2-polyhydroxyalkyl derivatives (**17a**) appeared dominated by Cotton effects at 237–247 nm, 217–221 nm, and 198–203 nm due to the excitation of thiazolidine chromophore (<87CCA185, 90SC2235>). It was found that the chirality of the heterocyclic chromophore, and not the configuration of the substituent at the C-2, was responsible for the signs and magnitudes of the effects. The CD spectra, measured in the far and near UV spectral region of 2-(1'-(*N*-benzyloxycarbonyl-amino)-ethyl)thiazolidine-4-carboxylic acid (**17b**), confirmed these observations (<90SC2235, 92TA1401>).



The electron donor-acceptor molecular complexes between iodine and thiazole, benzothiazole, and some derivatives have been studied in several organic solvents by UV spectroscopy (<87CJC468>). In all cases, the presence of the thiazole ring produces a displacement of the λ_{max} iodine band at 512 nm towards shorter wavelengths and a decrease of its absorbance. Moreover, a sharp isosbestic point near 470 nm was observed for all iodine-thiazole complexes. 2-Aryl and 2-hetarylbenzothiazoles showed fluorescence, the maxima of emission being between 350 nm and 395 nm. Both substituent and solvent effects on the spectra were observed (<93MI 306-02>). The photophysical properties of bis(benzothiazolylidene)squaraine dyes have also been studied (<93JPC13625>).

3.06.3.4 Photoelectron Spectroscopy

The He^I photoelectron spectra of thiazole, benzothiazole, and naphtho[1,2-*d*]thiazoles have been reported (<93JST(296)115>). This study confirms most of earlier results (<84CHEC-I(4)240>). The assignments of ionization potentials to molecular orbitals have been made on the basis of semiempirical SCF MO calculations.

An important consideration is the fact that, relative to thiazole, the nitrogen lone-pair orbital n_N of benzothiazole is slightly destabilized, while the corresponding sulfur orbital n_S is destabilized to a larger extent (1.4 eV).

The photoelectron spectroscopic properties of several *N*-methylthiazoline-2-thiones have also been studied (<95JOC2330>).

3.06.3.5 IR and Raman Spectroscopy

Some derivatives of both thiazole and benzothiazole have been studied by IR spectroscopy. In particular, an extensive study has been carried out with thiazole-2-carboxylic acids and the corresponding carboxylate ions (<88MI 306-01>). The infrared spectra of 2,3-disubstituted 1,3-thiazolidin-4-ones have been studied and the majority of the absorption bands assigned (<93PS(78)223>). The tautomerism of thiazoles substituted in 2- and 4-position by amino, thio, and hydroxy groups was examined by infrared spectroscopy (<85JPR251>) (see Section 3.06.4.4).

The conformational preferences (see Section 3.06.4.3) of 2-(*N,N*-disubstituted amino)thiazoles (**11**) bearing a 4-substituent and a 5-acyl group were established by high resolution infrared spectroscopy (<88JCS(P1)2209>). The conformation was confirmed by x-ray crystallography (see Section

3.06.3.1). Raman spectroscopy has been used in the spectral analysis of several benzothiazolines <77HCA215> and some benzothiazolium photochromic styryl dyes <93SA(A)1055>. Gold (III) chloride complexes of the type of LAuCl_3 (L = thiazole) have been studied by low frequency Raman and infrared spectroscopy <93MI 306-03>.

3.06.3.6 NMR Spectroscopy

3.06.3.6.1 Proton Spectra

Thiazole exhibits a ^1H NMR spectrum of first order. Table 3 lists the relevant chemical shifts for which a relationship exists with the calculated π -electron densities on the respective carbon atoms (to which the protons are bonded). Simple correlations were observed in other cases. For instance, a satisfactory linear relationship between the experimental δ values and the calculated π -electron densities was found for bromothiazoles <84H(22)1077>. Correlations between the experimental δ values of some substituted thiazoles and the σ_p Hammet constants have been also reported <85SUL17>.

Table 3 Chemical shifts (δ) of thiazole.

<i>Solvent</i>	H_2	H_4	H_5	<i>Solvent</i>	H_2	H_4	H_5
CDCl_3	8.88	7.98	7.41	C_6D_6	8.68	7.83	7.19

The conformation of 2-substituted 1,3-thiazolidines was investigated by NMR spectroscopy <74JA1465> (see Section 3.06.4.3). The effect of restricted rotation about the $\text{C(S)}\text{—N}$ bond in thiazole-2-thiocarboxamides can be observed by ^1H NMR spectroscopy <85SUL17>. A considerable difference was found between the ring conformational equilibria for diastereomers of 2-substituted 1,3-thiazolidine-4-carboxylic acids depending on the mutual orientation of the alkyl substituent at C-2 and the carboxylic group at C-4 <92TA1401>. 5,5-Dimethyl-2-thiazoline-4-carboxylates with a substituent at the C-2 showed no equivalence between the groups at the C-5 giving rise to an ABX system. In addition these compounds showed a concentration dependence for this splitting pattern <83JCED351>. Hydroxy- and thiothiazoles substituted with aryl groups at the 3-position have also been subjected to conformational studies using ^1H NMR spectroscopy either by comparison of their proton NMR spectra using deuterated chloroform and quinoline as solvents <83MI 306-01>, or by recording the spectra in the presence of a chiral auxiliary <92T7157>. Chiral lanthanide shifts reagents served to study the preferred conformation of 5-substituted-4-thiazolidinones <93MI 306-04>.

3.06.3.6.2 Carbon-13 Spectra

The ^{13}C NMR spectra of a large number of benzothiazoles, including 2-amino and 2-methyl-benzothiazoles differentially substituted in the benzene ring were determined <79JOC1136>. The obtained δ values were successfully correlated with simple Hammett constants; Swain–Lupton and Taft–DSP treatments were also applied. In a similar way linear dependencies with high correlation coefficients have been obtained between the total charges, calculated in the sp basis, and ^{13}C chemical shifts for thiazoles <85CS266>. A number of 2,3-substituted 1,3-thiazolidin-4-ones have been studied by ^{13}C NMR spectroscopy. In this study the variations in the chemical shifts were examined and the influence of S-oxidation was investigated <93MRC348>.

Carbon-13 and ^1H NMR spectroscopy have been employed for conformational studies of some thiazolidinone derivatives <83MI 306-01, 92T7157> as discussed in Section 3.06.3.6.1. A similar study was carried out with penicillin sulfoxide derivatives <91CJC578>.

Nuclear Overhauser enhancements (NOE) were used to measure the nuclear relaxation rates of ^{13}C as a function of temperatures for neat thiazole <84MP1411>. A study of the spin-spin coupling between ^{13}C nuclei in five-membered heteroaromatic ring systems showed the high aromaticity of thiazole <94MRC62>.

3.06.3.6.3 Nitrogen-15 Spectra

Thiazole shows a ^{15}N chemical shift of 57.00 ppm relative to nitromethane when the spectrum is registered in pure liquid. The shielding of nitrogen remains practically unchanged in the fused ring of benzothiazole ($\delta^{15}\text{N}$ of benzothiazole: 61.00 ppm, acetone). Nitrogen-15 spectroscopy has been used in the characterization of neutral methanate complexes (ML_2) between Zn^{II} and 2-thiazoline or benzothiazole derivatives <91G365>.

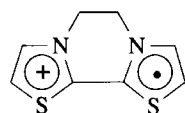
3.06.3.7 Mass Spectrometry

The mass spectra of thiazoles are characterized by fragments formed by cleavage of the 1,2 and 3,4 bonds. It has been well established that thiazole fragments upon electron impact by two major routes involving loss of ethyne or hydrogen cyanide <75ICA(12)127>.

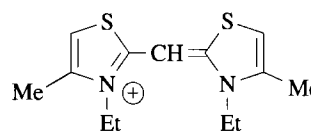
The more common fragmentation is that in which HCN is eliminated and a thiirenium radical cation is formed. Similar fragmentations patterns were observed for 2-aminobenzothiazoles <83IJM503>, 2-hetarylbenzothiazoles <88JHC145>, and thiazoles substituted in 2- and 4-position <85JPR251>. Some derivatives of thiazolidine have also been studied by electron impact mass spectrometry <88OMS(23)2493>. These studies included 2,4-thiazolidinediones substituted in position three and five <91MI 306-01, 91MI 306-02, 92MI 306-01>. The chemical stability of thiazole-2-nitrosimines has been confirmed by mass spectrometry on the basis of the high intensity of $\text{M}^{+\bullet}$, this sometimes being the base peak <94AP(327)581>.

3.06.3.8 ESR Spectrometry

A stable radical cation of the dimethylene bridged 2,2'-bithiazolium salt (**18**) could be observed by ESR spectroscopy after hydrolysis of the PF_6^- salt of (**18**) at -0.29 eV in acetonitrile <90TL1539>. The ESR spectra of an organic ion-radical salt have been measured <93MI 306-05>. The salt consists of 3,3'-diethyl-4,4'-dimethyl-2,2'-thiazolo cyanine (**19**) and two TCNQ molecules. The structure of the salt has been confirmed by x-ray analysis <94MI 306-01>.

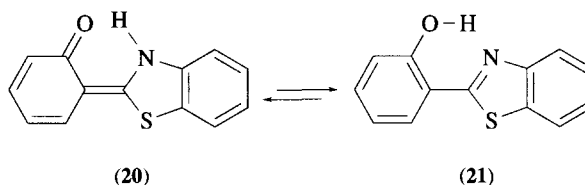


(18)



(19)

Time-resolved electron paramagnetic resonance served to detect the short-lived triplet state of the keto tautomer (**20**) of 2-(2-hydroxyphenyl)benzothiazole (**21**) generated by excited state intramolecular proton transfer <92CC641>.



(1)

3.06.4 THERMODYNAMIC ASPECTS

3.06.4.1 Intermolecular Forces

3.06.4.1.1 Melting and boiling points

The normal boiling points of pure thiazole and benzothiazole are 116.8°C and 231.0°C , respectively. At 34 mm Hg benzothiazole boils at 131.0°C ; the normal melting point of pure benzothiazole is 2°C .

Thiazole presents attraction forces which lead to co-operative motions. The importance of the reorientation of the permanent electrical dipole moment of thiazole (1.6 D) for the molecular motion has been explored by measuring nuclear relaxation rates of ^{13}C and ^{14}N <84MP1411>.

3.06.4.1.2 Solubility

Racemic materials such as DL-thiazolidine-4-carboxylic acid can be optically resolved by preferential crystallization. Infrared spectrum, solubility, and ternary solubility diagram indicated that DL-thiazolidine-4-carboxylic acid is a conglomerate. The appropriate conditions for the optical resolution of that conglomerate are predictable by the free energy of critical nucleation in super-saturated solutions <87BCJ3277>. More efficient optical resolutions can be achieved by adding a co-solute such as glycine. However, the best results are obtained by replacing crystallization using L-amino acids as optically active co-solutes <92BCJ267>. The chromatographic parameters of some substituted 1,5-thiazolidine-4-ones have been determined by HPLC <94IJC(B)590>.

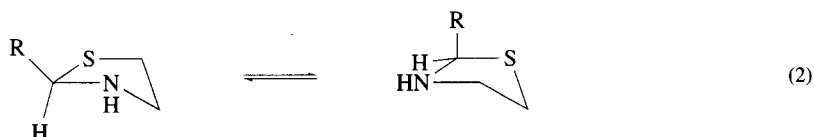
3.06.4.2 Aromaticity and Stability

A true experimental value for the heat of formation of unsubstituted thiazole is not known. However, a close estimation of an experimental ΔH_f° for thiazole can be obtained by using the experimental ΔH_f° for 4-methylthiazole and the enthalpic additivity value for the methyl substituent from Benson's method. This method gives a value of ΔH_f° (thiazole) = 36.78 kcal mol $^{-1}$ which has been compared with those calculated through several computational methods (see Section 3.06.2).

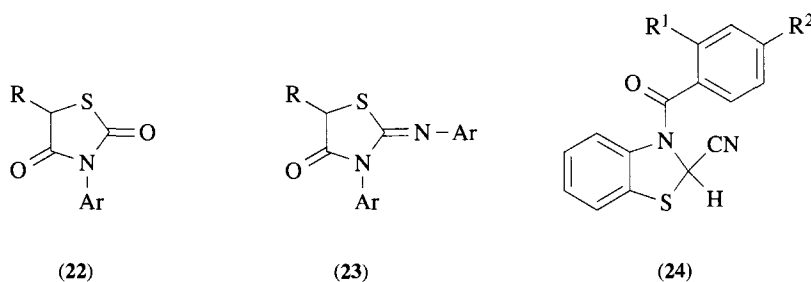
Semiempirical methods assign a resonance energy for thiazole of 36.78 kcal mol $^{-1}$ (see Section 3.06.2), pointing out a marked similarity with thiophene. The aromatic character of thiazole is also demonstrated by its reactivity towards electrophilic substitutions (see Section 3.06.5).

3.06.4.3 Conformations

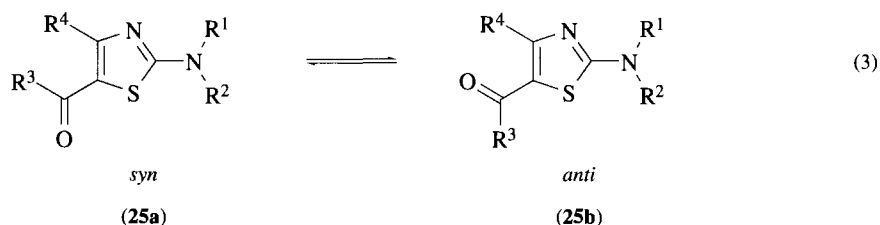
Conformational analysis of 1,3-thiazolidines and other thiazole derivatives has been carried out by NMR methods (see Section 3.06.3.6.1). Thus, the analysis of the coupling constants of the ^1H NMR spectra <74JA1465> permitted to postulate envelopes with either C-4 or C-5 as the flap atom and with the 2-substituent *anti* to the flap as the predominant conformations (Equation (2)).



Comparison of the ^1H NMR spectra of (22) and (23) in different solvents show the presence of rotational isomers resulting from the restricted rotation about the aryl C—N bond <83MI 306-01>. Similarly, the analysis of the NMR spectra of sterically hindered *N*-aryl substituted-2-thioxo-4-thiazolidinones registered in the presence of a chiral auxiliary, showed that these compounds form enantiomers by partial rotation around the C—N bond <92T7157>. Conformational analysis of Reissert compounds (24) using high resolution variable temperature NMR spectroscopy indicated that the major conformer is the *Z* amide (*Z*: *E* ratio 79:21) in CDCl_3 at 213 K whilst in $\text{C}_6\text{D}_5\text{CD}_3$ at 213 K a *Z*: *E* ratio of 57:43 was observed <93JOC2851>.



The conformations of 3-substituted-2-benzothiazolinones have been studied by UV and IR spectroscopy and the quantum chemistry semiempirical method AM1 <93MI 306-06, 93MI 306-07>. 5-Acyl-2-(*N,N*-disubstituted amino)thiazoles unsubstituted or with a phenyl group at the 4-position, in solution exist predominantly as the carbonyl *O,S-syn* rotamers (**25a**). On the other hand, a *t*-butyl group in the same position induces the *O,S-anti* arrangement (**25b**) (Equation (3)); with the 4-methyl derivatives both forms are present <87JCS(P2)2305, 88JCS(P1)2209>.



The conformation in solution of the important thiazole-containing hexapeptides Patellamides B and C (see Section 3.06.11) have been determined by NMR spectroscopy and molecular dynamics <95JOC3944>.

3.06.4.4 Tautomerism

3.06.4.4.1 Substituted thiazoles

Thiazoles and their derivatives bearing amino, hydroxy, or thio groups in the 2-position can exist in at least two tautomeric forms.

In general, whereas 2-amino substituted thiazoles are present in the aromatic form, the hydroxy and thio derivatives exist in the oxo and thioxo forms, respectively. The predominant tautomeric form may be determined by spectroscopic methods and confirmed by means of HMO calculations <84CHEC-I(4)240>. For 2-aminothiazoles and 2-aminobenzothiazoles the tautomeric equilibrium can be expected to shift towards the imino form when electron withdrawing substituents are bonded to the thiazole ring or the exocyclic nitrogen. The tautomeric constants of the equilibrium amine-imine were determined by measuring pK_{BH}^+ values <82JCS(P2)535>. The effect of the solvent and/or additives can be of importance. In fact, the tautomeric equilibrium in toluene or carbon tetrachloride is shifted towards the imino form by adding small amounts of tetrabutylammonium bromide <92JHC1461> or of dimethyl sulfoxide <94JCS(P2)615>. In the case of 2-hydrazinobenzothiazoles, the structure of both amino and imino tautomers have been proved by acetylation and formylation <86MI 306-01>.

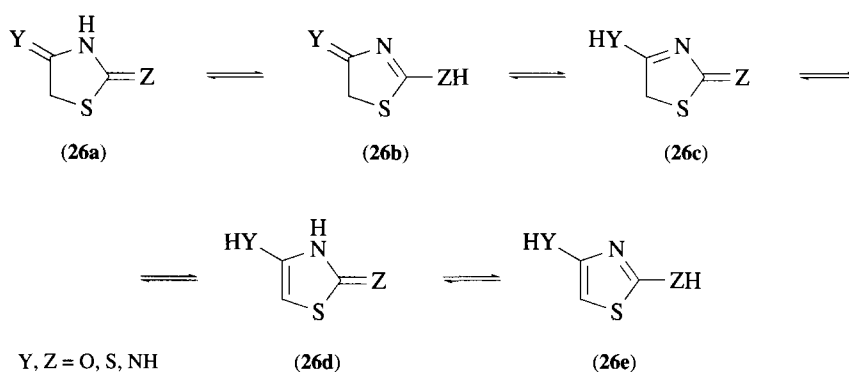
Thiazoles substituted in the 4-position by a hydroxyl function occur preferentially as the aromatic form, as has been demonstrated by x-ray analysis <86AKZ688> and NMR studies <86AKZ685>.

Substituted thiazoles at C-2 or C-4 with hydroxy, thio, and amino groups can be represented by five tautomeric forms (**26a-e**) (Scheme 1). However, form (**26e**) has never been observed <85JPR251>. The aminothiazoles exist predominantly in the amino form when the substituent is in position two (**26b**, Z = NH). On the other hand, when the substituent is in position four the amino form is preferred, although there are exceptions to this rule (for instance, in the case Y = Z = NHCOMe). The hydroxy and thio derivatives predominantly exist in the oxo and thioxo forms (**26a**, Y, Z = O, S). The main evidence of these arguments came from the ^{13}C NMR spectra of the thioxo derivatives and from the IR spectra of the oxo and amino derivatives.

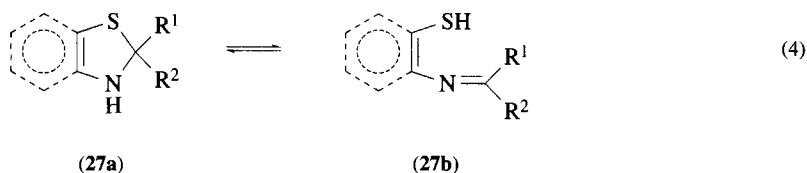
The tautomer population of thiazolidine-2,5-dithiones has been studied by theoretical calculations with the aim of explaining the reactivity of these compounds <90JCS(P1)2459>. Semiempirical and *ab initio* calculations carried out on rhodanine (2-thioxo-4-thiazolidinone) indicated (**26a**) as the most stable form. Further confirmation of these results emerged from the comparison of the calculated vibrational spectra with experimental IR data <94MI 306-02>.

3.06.4.4.2 Ring-chain tautomerism

The ring-chain tautomerism of 1,3-thiazolidines and 1,3-benzothiazolines can be considered as a reversible intramolecular addition to the C=N bond. The system highly prefers the ring form (**27a**) and only in some cases the open-chain tautomer (**27b**) can be detected (Equation (4)).



Scheme 1



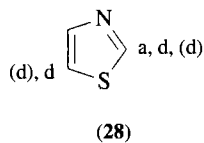
The presence of the open-chain form can be proved indirectly by several ways such as the formation of metal chelates $\langle 87RRC151 \rangle$, hydrolysis $\langle 79JA420 \rangle$, or C-2 epimerization $\langle 87JHC1629, 89JHC589 \rangle$. Direct evidence of the presence of the open-chain tautomer has been obtained by NMR studies $\langle 90T6545 \rangle$.

3.06.5 REACTIVITY OF FULLY CONJUGATED RINGS

3.06.5.1 General Survey of Reactivity

3.06.5.1.1 Neutral thiazoles

Thiazole (**28**) may be considered to be derived from benzene by replacing a CH group with a nitrogen atom and a CH=CH group with a sulfur atom. Hence, the chemistry of thiazole shows similarities to those of five- and six-membered aromatic rings. The closest system is thiophene. The donor-acceptor concept which has been successfully applied to 1,3-diazoles $\langle 92H(33)1129 \rangle$ can be extended to thiazole (**28**) in order to predict both reactivity and regioselectivity.



The reactive centers are described by using Begtrup's notation $\langle 92H(33)1129 \rangle$: a and d represent an acceptor or donor center, respectively, as the result of π -electron delocalization; (d) represents a donor center created after deprotonation. Thus electrophiles attack thiazoles preferentially at C-5, then at C-4; electron releasing groups are required to allow electrophilic substitution reactions to go readily (see Section 3.06.5.4). Nucleophilic attacks to give displacement products are favored in thiazoles possessing a leaving group at the 2-position. As an example, 2-chlorothiazole is about 100 times more reactive than 2-chloropyridine in nucleophilic displacement processes, and 2-chlorobenzo-thiazole is still more reactive (see Section 3.06.7.9). Both thiazoles and their benzo derivatives are deprotonated preferentially at C-2 by strong bases (see Section 3.06.5.7). The resulting organo-metallic derivatives react with electrophiles in the normal manner (see Section 3.06.7.10).

3.06.5.1.2 Thiazolium ions

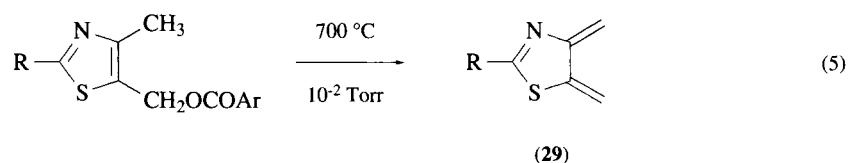
Thiazoles can be quaternized at nitrogen by reaction with a range of alkylating agents. These salts can form an ylide by deprotonation at C-2. This thiazolium 2-ylide is markedly stable because of the ability of sulfur to stabilize an adjacent carbanion. The reaction is of considerable importance due to the occurrence of thiazolium-2-ylides as intermediates in classical biochemical (thiamine action) and chemical (Stetter reaction) processes (see Section 3.06.12). Desilylation at C-2 can lead to a thiazolium 2-ylide as well. Thus, the formation of this type of intermediate has been formulated as a key step along the reaction pathway involving a 2-trialkylsilylthiazole and C-electrophiles (Dondoni reaction, see Section 3.06.12.12). Thiazolium salts are also susceptible to be oxidized by a variety of oxidants (see Section 3.06.5.4.8).

3.06.5.1.3 Thiazolones, thiazolethiones, thiazolimines

The main characteristic of these compounds is their tautomerism (see Section 3.06.4.4). Therefore, their reactivity strongly depends on the electron displacement in the molecules. Whereas the attack of electrophiles occurs at the β -position to the nitrogen or sulfur atom, the attack of nucleophiles takes place at the α -position, mainly at C-2. Nucleophiles can also act as bases by removing a hydrogen atom from the heterocyclic ring.

3.06.5.2 Thermal and Photochemical Reactions

The flash pyrolysis of the *p*-chlorobenzoate esters leads to the thiazole-4,5-xilylenes (**29**) (Equation (5)) <90TL1487>.

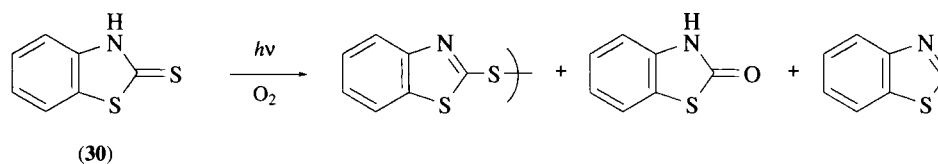


The photo-rearrangement of substituted thiazoles into isomeric thiazoles and isothiazoles seems to proceed through tricyclic sulfonium cations, as indicated by deuterium-labeling studies <78JCS(P1)685>.

Irradiation of mesoionic 2-alkyl-4-thiazolones gives highly strained thiirans <77JCS(P1)1107>. Similarly, triphenylthiazolium-4-olate in the presence of Bu_3P leads to the quinolinone via desulfuration to an azetinone, isomerization of the latter to a ketene and intramolecular cyclization <88JCS(P1)189>.

Photolysis of 4-amino-*N*-methylthiazolium salts gives enamino nitriles by isomerization and hydration of the hitherto unknown quasi-aromatic 2-imino-2-dihydroazete intermediates.

The photoreactivity of benzothiazolethione (**30**) has been studied in several solvents in the presence of oxygen with and without methylene blue as a sensitizer. Disulfide, 2-oxo-derivative, benzothiazole, and elemental sulfur were the main products <87ZN(B)1153>.



Scheme 2

3.06.5.3 Electrophilic Attack at Nitrogen

3.06.5.3.1 Introduction

Because of its aza-aromatic character the thiazole ring is little inclined to react with π -acceptors. Comparing thiazole and pyridine, it appears that a positive charge (partial or total) is less stabilized

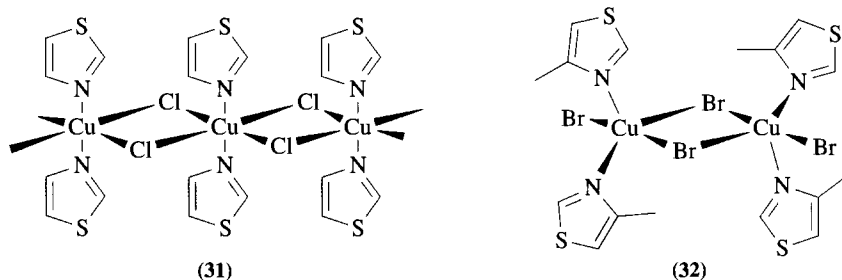
in the thiazole than pyridine ring as a consequence of the higher aromatic character of the latter. On the other hand, when thiazole is compared with other 1,3-azoles such as oxazole, the former delocalizes better a positive charge at the atoms of the cycle. This can be explained by the different electronegativity of sulfur and oxygen.

3.06.5.3.2 Basicity of thiazole

The basicity of thiazoles is well-documented <84CHEC-I(4)240>, and a number of pK_a values of some representative thiazoles can be found there as well as in the references cited therein.

3.06.5.3.3 Metal ions

A large number of metal complexes with thiazole, benzothiazole, or alkyl derivatives are known. Since the sulfur atom is less nucleophilic than nitrogen, the latter atom is expected to be the dominant donor. The coordination by the heterocyclic nitrogen atom has been confirmed through crystallographic analyses of the complexes (see Section 3.06.3). Among the most studied complexes are those formed with copper(II) salts <94CCR91>. The stoichiometry of the complexes are variable depending on the preparation conditions. The 1:4 (metal–ligand) complexes have tetragonally distorted octahedral structures, and the 1:2 (metal–ligand) complexes have polymeric halogen bridged structures (31) with terminal ligands and tetragonal (4 + 2) coordination at the metal. Reaction between anhydrous copper(II) bromide and 4-methylthiazole in aqueous methanol yields (32) a centrosymmetric dimeric complex which has tetragonal-pyramidal coordination at the metal.



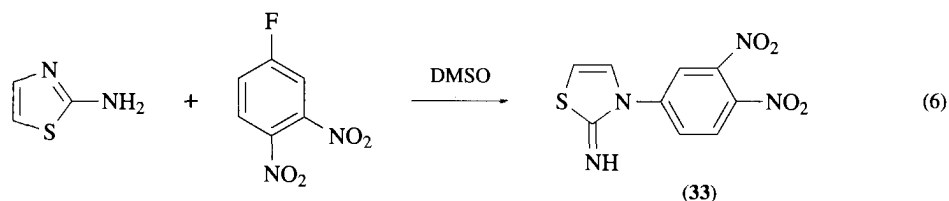
Complexes with Zn^{II} , Co^{II} , Ni^{II} , and Hg^{II} are also formed and in general they are of type ML_2X_2 (X = halogen atom). These complexes have tetrahedral or octahedral structures.

3.06.5.3.4 Alkyl halides

The alkylation of the nitrogen atom of thiazoles and benzothiazoles by alkyl halides proceeds readily to give the corresponding thiazolium salts in good yields. The same reaction occurs with α -bromoketones and α -bromoesters <86JHC1889>. The dependence of the rate of this reaction on the substituents of the heterocyclic ring has been extensively studied <84CHEC-I(4)240>.

In the case of substituted thiazoles (or benzothiazoles) with a hydroxy, thio, or amino group, alkylation at the endocyclic nitrogen or at the exocyclic heteroatom can equally occur. 2-Hydroxythiazoles and 2-hydroxybenzothiazoles give predominantly the corresponding *N*-alkylated compounds <88JHC1601, 89JHC1245>. When the reaction is carried out in the presence of silver carbonate the *O*-alkylated compound is obtained as major product <87G281>.

The regioselectivity of the alkylation is much less defined for the 2-amino derivatives. Under neutral conditions alkylation takes place preferentially at the endocyclic nitrogen atom, but under basic conditions the product alkylated at the exocyclic nitrogen predominates <86MI 306-02>. 2-Aminothiazoles also react as nucleophiles with some aryl halides (Equation (6)). In the absence of steric hindrance, the aza nitrogen is a more effective nucleophilic site than the exocyclic amino nitrogen <81JOC3178>. The structure of the imino compound (33) has been confirmed by x-ray crystallographic analysis.



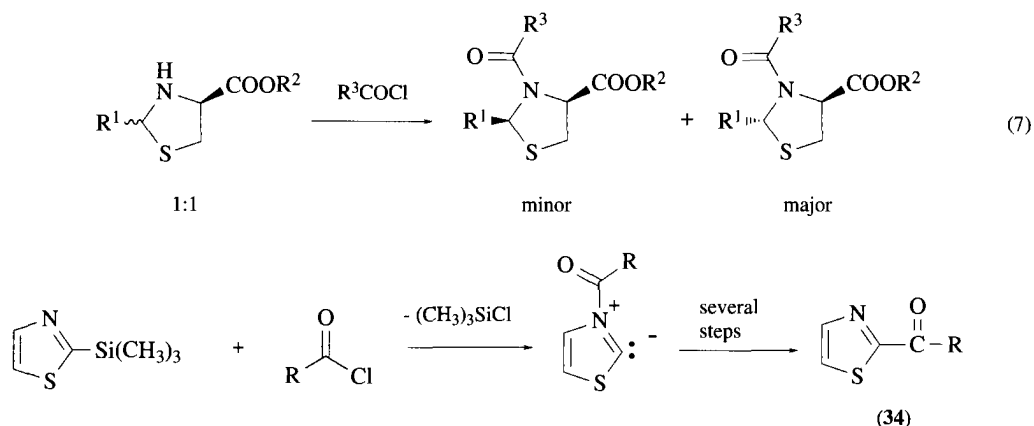
The quaternary salts of 2,2'-(polymethylenedithio)dibenzothiazoles can be prepared with methyl iodide or dimethyl sulfate. Other alkylating agents like ethyl iodide, allyl iodide, and benzyl bromide are unsuccessful in their quaternization, the reaction rate depending on the length of the polymethylene chain <90MI 306-01>.

The quaternization of substituted benzothiazoles depends dramatically on steric and electronic effects of substituents <90MI 306-02, 90MI 306-03>.

3.06.5.3.5 Acyl halides

Thiazoles can be quaternized at nitrogen by the action of acyl halides. Treatment of thiazole with acyl chloride produces *N*-acyl-1,3-thiazolium chloride <84TL3633>.

Acylation at the nitrogen atom of chiral disubstituted thiazolidines gives preferentially the *trans* isomer (Equation (7)) <87CL1361>. In the case of 2-(trimethylsilyl)thiazole <83TL2901> the thiazolium salt may not form since the acylation of nitrogen and desilylation at C-2 very likely occurs concertedly giving rise directly to a *N*-acylthiazolium 2-ylide which then evolves to the 2-acylthiazole (34) by a multi-step process (Scheme 3). This hypothesis is supported by a mechanistic study of the reaction of the same silylated thiazole with aldehydes (see Section 3.06.12.2) <93JOC3196>.



Scheme 3

3.06.5.3.6 Peroxy acids

The oxidation of thiazoles by peroxy acids leads to the corresponding *N*-oxides. Peracetic, *m*-chloroperbenzoic, permaleic, and trifluoroperacetic acid have been employed for this reaction. Chemical yields range from 4% to 50%, the more basic thiazoles producing higher yields. Thus, thiazole, 4,5-dimethylthiazole, and 2-phenylthiazole can be oxidized in moderate to good yields. However, neither 4-chloro-2-phenylthiazole nor 5-chloro-2-phenylthiazole could be oxidized. The *N*-oxidation leads to an enhancement of the acidity of the protons of the ring. In thiazole-*N*-oxides the 2-position is more active towards electrophiles owing to the delocalization of the negative charge of the oxygen atom.

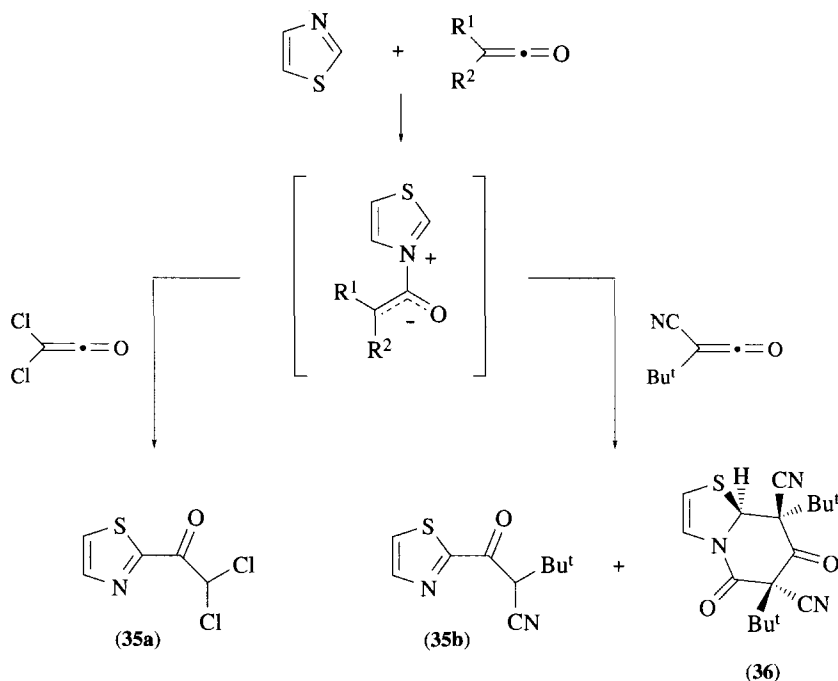
Although earlier warnings concerning the instability of thiazole-*N*-oxides have been reported, Begtrup and Hansen <92ACS372> have found that these compounds are stable for months when stored in a cool and dry atmosphere.

3.06.5.3.7 Other reactions

In addition to those described above, there are also various unsaturated electrophiles which attack the nitrogen atom of the thiazole ring. Substituted benzothiazoles bearing an amino, hydroxy, or thio group at C-2 react with acrylonitrile and related compounds (i.e., acrylamide, methyl acrylate, acrylic acid) under base conditions to give the corresponding alkylated products. Reactions occur at both the endocyclic nitrogen atom and the exocyclic functional group. Studies on the regioselectivity of these reaction have been carried out for 2-aminobenzothiazoles <86KGS986, 87MI 306-01> and 2-thiobenzothiazoles <86JHC1629, 86KGS554, 86KGS688>. The addition of 2-hydroxybenzothiazole to acrylonitrile in the presence of triethylamine gives the corresponding *N*-alkylated product <91MI 306-03>. Also 1,3-thiazoles undergo aluminum chloride-catalyzed additions of α,β -unsaturated esters and nitriles. The nature and distribution of the resulting adducts depend on the substituent at C-2 of the heterocyclic ring and on the nucleophile employed as a quencher of the reaction mixture <82JOC3844>.

2-Thiobenzothiazole reacts with formaldehyde to give the corresponding *N*-hydroxymethyl derivative <84KGS40>. 2-Hydroxybenzothiazole reacts with dichlorocarbene to give 1:1 or 3:1 adducts depending on the reaction conditions <90IJC(B)280>.

Thiazole adds *t*-butylcyanoketene and dichloroketene to give a zwitterion wherein *N*-thiazolium and enolate moieties are linked by carbon–nitrogen bond. This intermediate leads to the corresponding 2-acylthiazole (35). The reaction with *t*-butyldicyanoketene leads also to the 2:1 cyclic adduct (36) (Scheme 4) <84JOC590>. The same reactions have been observed with 4- and 5-methylthiazoles.



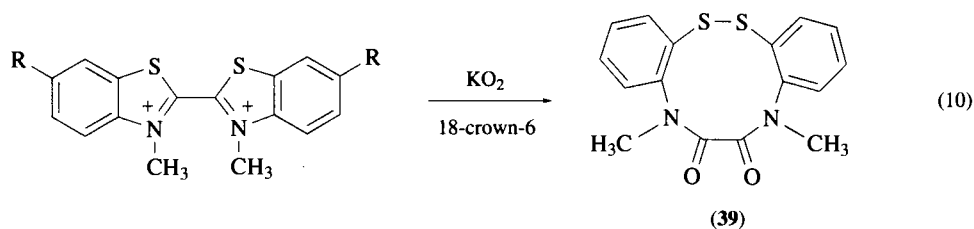
Scheme 4

3.06.5.4 Electrophilic Attack at Carbon

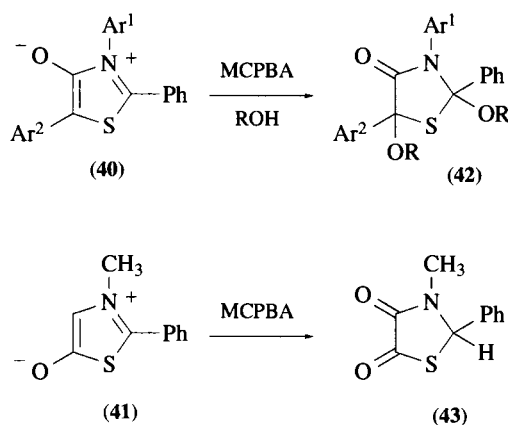
3.06.5.4.1 Reactivity and orientation

It is well known that in thiazole, like in pyridine, the nitrogen atom deactivates the ring towards electrophilic attack. In addition, since most electrophilic substitution reactions occur in an acid medium, the heterocycle undergoes further deactivation as a result of the protonation. As a consequence, thiazoles require electron-releasing groups to allow electrophilic substitution reactions to go readily. The C-5 is the most favored position while substitution at C-4 only takes place if the latter position is already occupied. The electrophilic substitution at C-2 does not occur at all.

Electron-deficient 3,3'-dimethyl-2,2'-bithiazolium or bibenzothiazolium salts react with KO_2 to give the ten-membered 1,2,5,8-dithiadiazine-6,7-dione (**39**) in moderate yield (Equation (10)) <92TL6983>.



Reaction of mesoionic thiazoles (40) and (41) with *m*-chloroperbenzoic acid (MCPBA) affords thiazolidine-4-ones (42) and thiazolidine-4,5-diones (43), respectively, accompanied by several minor products of further degradation (Scheme 5) <80JOC4850>.



Scheme 5

3.06.5.4.6 Other reactions

Nitrosation of 2-(dimethylamino)thiazoles under acid conditions gives 5-nitroso-derivatives <88JCS(P1)2209>.

3.06.5.5 Electrophilic Attack at Sulfur

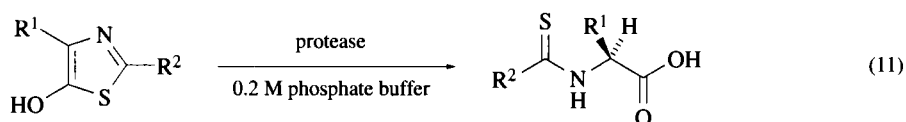
The *S*-oxidation of thiazoles to sulfoxides or sulfones has not been reported. Under base conditions both thiazoles and benzothiazoles are resistant to the action of $\text{PhI}(\text{OAc})_2$ <88IJC(B)929>. Raney Nickel promotes desulfuration of thiazoles, probably through an initial coordination of the sulfur at nickel, affording carbonyl compounds <84CHEC-I(4)240>.

3.06.5.6 Nucleophilic Attack at Carbon

The most favored position in the thiazole ring for a nucleophilic attack is at C-2. On the other hand, the 5-position is less reactive and the 4-position is not reactive at all unless strong electron-withdrawing substituents are present at C-5. Obviously the reactivity of C-2 towards nucleophiles is enhanced in thiazolium salts.

3.06.5.6.1 Hydroxide ion and other O-nucleophiles

Thiazoles and benzothiazoles are quite inert in the presence of hydroxide and alkoxide ions. However, two proteases were found to catalyze the enantioselective hydrolysis of several 5-hydroxythiazoles to give α -amino acids <93JOC3252> (Equation (11)).



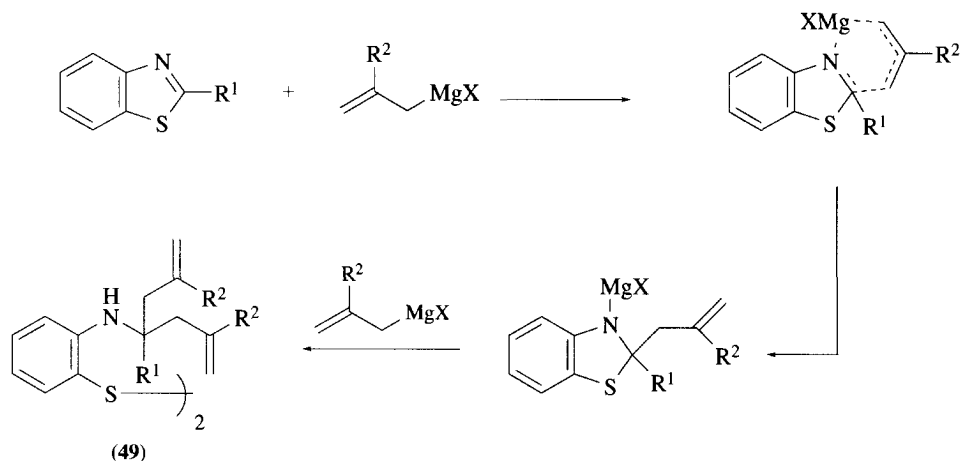
$$\begin{array}{ccccc}
 \begin{array}{c} \text{R}^1 \\ | \\ \text{R}^2 \text{---} \text{C} \text{---} \text{N}^+ \\ | \quad \diagup \\ \text{R}^3 \quad \text{S} \quad \text{H} \end{array} & + \text{OH}^- & \xrightleftharpoons{k_1} & \begin{array}{c} \text{R}^1 \\ | \\ \text{R}^2 \text{---} \text{C} \text{---} \text{N} \\ | \quad \diagup \quad | \\ \text{R}^3 \quad \text{S} \quad \text{H} \quad \text{OH} \end{array} & \xrightleftharpoons{k_2} & \begin{array}{c} \text{R}^1 \\ | \\ \text{R}^2 \text{---} \text{C} \text{---} \text{N} \text{---} \text{C} \text{---} \text{H} \\ | \quad \diagup \quad || \\ \text{R}^3 \quad \text{SH} \quad \text{O} \end{array} + \text{H}^+ \\
 (44) & & & (45) & & (46) \\
 & & & \parallel \quad k_3 & & \parallel \quad k_4 \\
 & & & \begin{array}{c} \text{H} \quad \text{R}^1 \\ \diagdown \quad / \\ \text{R}^2 \text{---} \text{C} \text{---} \text{N}^+ \\ | \quad \diagup \\ \text{R}^3 \quad \text{S} \quad \text{OH} \end{array} & & \begin{array}{c} \text{R}^1 \\ | \\ \text{R}^2 \text{---} \text{C} \text{---} \text{N} \text{---} \text{C} \text{---} \text{H} \\ | \quad \diagup \quad || \\ \text{R}^3 \quad \text{S}^- \quad \text{O} \end{array} + 2\text{H}^+ \\
 & & & (48) & & (47)
 \end{array}$$

Table 4 Rate constants for the hydrolysis of 3-benzyl-5-(2-hydroxyethyl)-4-methylthiazolium bromide at 25°C.

Source: <92JCS(P2)1551>.

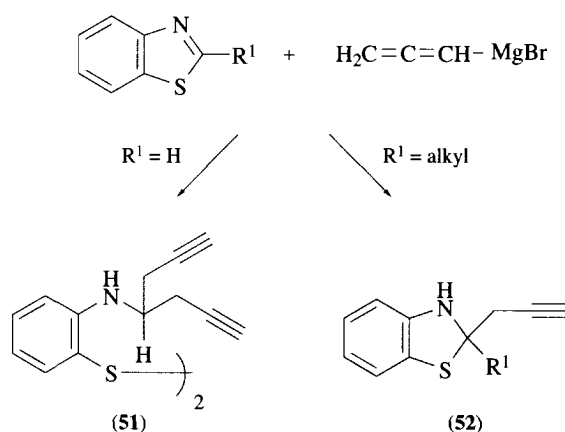
Reaction of organolithium and organomagnesium compounds with thiazoles and benzothiazoles give rise, in some cases, to the corresponding metalated compounds (see Section 3.06.5.7). However, some allylic organometallic reagents add to thiazoles and benzothiazoles to yield adducts which can evolve to ring opened products ^[84TL2047]. The addition of allylmagnesium halides to benzothiazoles affords the disulfide (**49**). A possible mechanism of the reaction is outlined in Scheme 7.

$$\text{benzothiazole} + \text{Bu}_3\text{SnCH}_2\text{CH=CH}_2 \xrightarrow[\text{Et}_3\text{N}]{\text{ClCO}_2\text{R}} \text{benzothiazol-2-ylidene-1-(CO}_2\text{R)-3-propenyl-2,3-dihydro-1H-indene} \quad (12)$$



Scheme 7

In a similar way to allylic Grignard reagents, allenyl magnesium bromide reacts with benzothiazole to give 2,2'-dithio-*N*-dipropargylmethyl dianiline (**51**). It is noteworthy that with 2-alkylthiazoles the propargylbenzothiazoline (**52**) is the product of the reaction (Scheme 8) <86S638>.

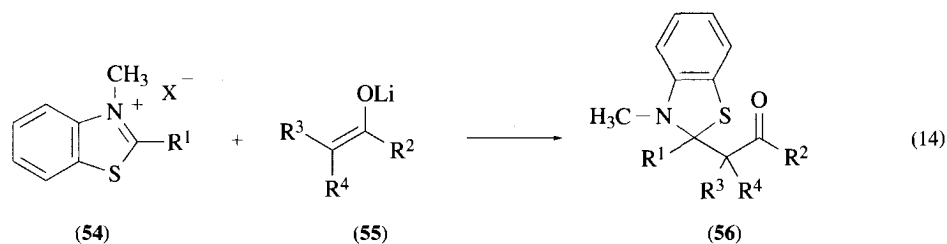


Scheme 8

Direct ethynylation of thiazole and benzothiazole can be achieved by reaction with bis(tri-butylstannyl)acetylene (**53**) (Equation (13)). Also in this case the presence of a chloroformate is needed for the progress of the reaction <94SL557>.



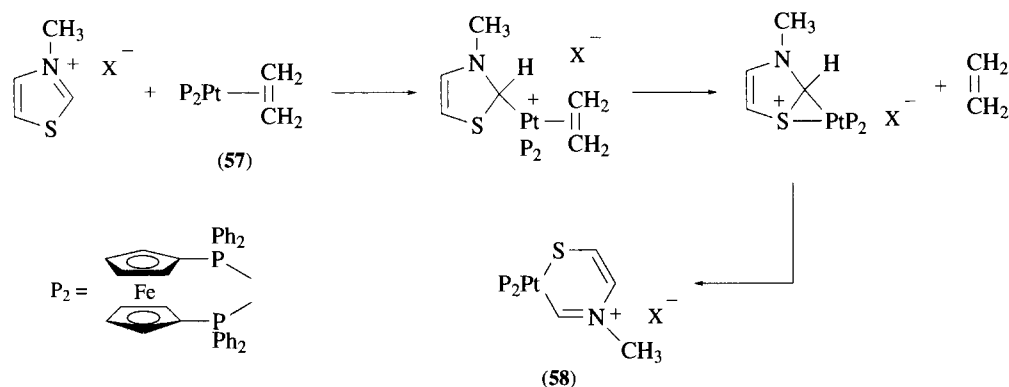
N-Methylbenzothiazolium salts (**54**) undergo addition of lithium enolates (**55**) derived either from ketones or esters to give benzothiazolines (**56**) in good yields (Equation (14)) <89BCJ3389>.



Similarly, *N*-acylthiazolium salts generated *in situ* from thiazoles and acyl chlorides react with silyl enol ethers to give *N*-acyl-2-substituted-4-thiazolines <84TL3633>.

3.06.5.6.3 Other reactions

The reaction between *N*-methylthiazolium iodide or tetrafluoroborate with 1,1-bis(diphenylphosphino)ferrocene- η^2 -ethene-platinum (**57**) leads to the formation of a ring expanded adduct (**58**) by formal C—S insertion <94JA5180>. A mechanism for the ring-opening process based on an initial nucleophilic attack on C-2 of the thiazolium ring is shown in Scheme 9.



Scheme 9

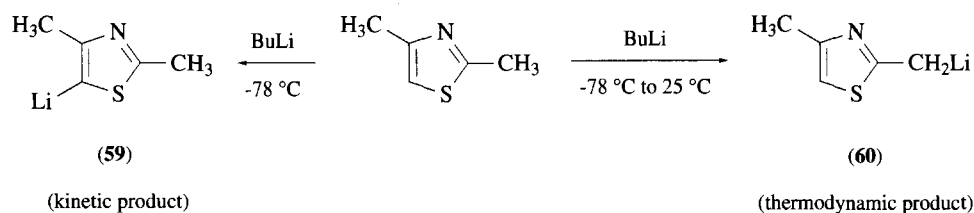
3.06.5.7 Nucleophilic Attack at Hydrogen Linked to Carbon (Deprotonation)

3.06.5.7.1 Metalation at a ring carbon atom

The acidities of thiazole ($pK_a \sim 28.3$) and benzothiazole ($pK_a \sim 28.9$) have been measured in THF at -60°C by deprotonation at C-2 using lithium tetramethylpiperidine <85CJC3505>.

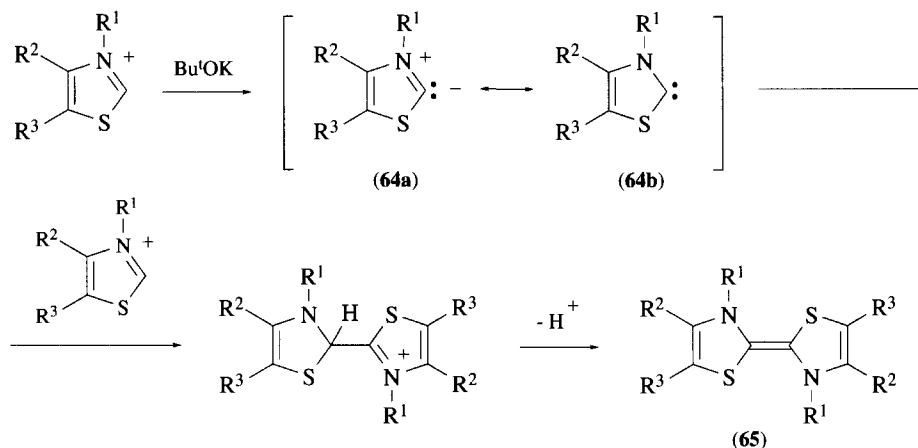
The treatment of both thiazole and benzothiazole with an appropriate base such as butyl- or phenyllithium leads to the exclusive deprotonation at C-2. The progress of the lithiation can be followed by deuteration of the reaction mixture. These studies indicate that the lithium-hydrogen exchange occurs instantaneously <88BCJ3637>. When the 2-position is blocked, deprotonation occurs selectively at C-5. However if the substituent at C-2 is an alkyl group, the kinetic acidities of the protons at the α -position and at the 5-position are similar (see Section 3.06.7.3). The reaction of 2,4-dimethylthiazole with butyllithium at -78°C yields as major product the 5-lithio derivative (**59**) but if the reaction is carried out at higher temperature the thermodynamically more stable 2-lithiomethyl derivative (**60**) is obtained (Scheme 10). The metalation at these two positions is also dependent on the strength and bulk of the base employed <74JOC1192>. In fact, deprotonation can also be achieved by lithium diisopropylamide. This base, however, is commonly preferred for selective deprotonations at the 5-position.

The crystal structure of a dimer of 4-*t*-butyl-2-lithiothiazole incorporating two molecules of



Scheme 10

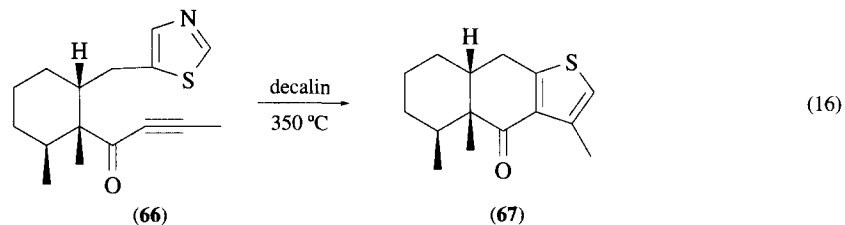
undergoes addition rather than insertion reactions. Bordwell and Satish <91JA985> also concluded that dimerization of (64) in non-hydroxylic solvents occurs by an addition-elimination mechanism involving the ylide form (64a) rather than single carbene intermediates (64b) (Scheme 12).



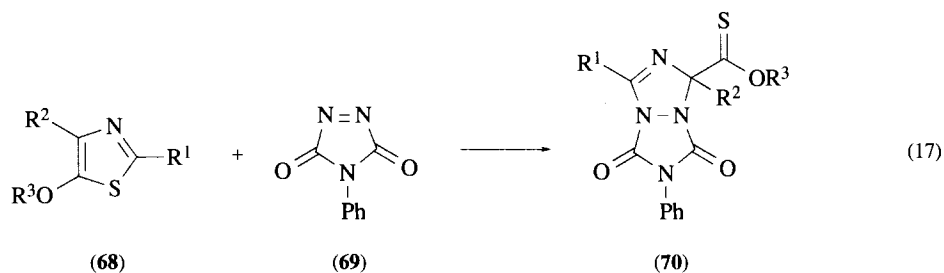
Scheme 12

3.06.5.8 Cyclic Transition State Reactions with a Second Molecule

Thiazoles have a low reactivity in cycloaddition reactions due to their high aromatic character. However, it has been possible to achieve intramolecular Diels–Alder reactions in some cases. The reaction of the acetylenic thiazole (66) in decalin at 350 °C affords, after loss of acetonitrile, the thiophene derivative (67) in 75% yield (Equation (16)). The reaction is also applicable to other thiazoles although with some limitations <88T3327>.



5-Alkoxythiazoles (68) give an abnormal Diels–Alder reaction with highly reactive dienophiles such as 4-phenyl-3*H*-1,2,4-triazole-3,5(4*H*)-dione (PTAD), diethyl azodicarboxylate (dead), or diethyl oxomalonate. As an example, the reaction of (68) with PTAD (69) is illustrated in Equation (17). The product of the reaction (70) is the formal [3 + 2] cycloadduct between (69) and the corresponding nitrile ylide derived by the opening of thiazole ring system. For this abnormal Diels–Alder reaction of thiazoles a stepwise mechanism has been proposed <92BCJ3315>.



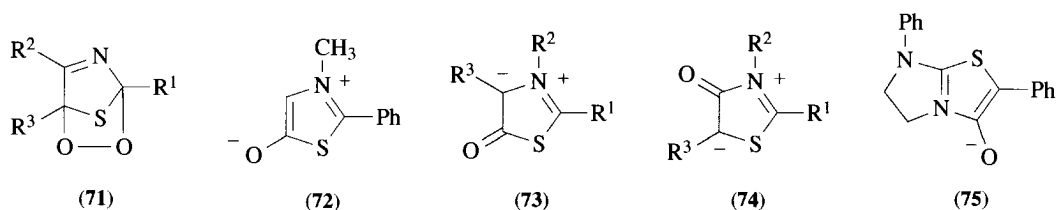
Singlet oxygen adds in a [4 + 2] fashion to thiazole nucleus disrupting the aromaticity of the ring.

The resulting thioozonide (**71**) decomposes in methanol to give an amide and a 1,2-dicarbonyl compound <83JOC2302, 84TL2935>.

A similar reaction occurs with the mesoionic compound (**72**). Decomposition of the cycloadduct gives rise to carbonyl sulfide (COS) and *N*-formyl-*N*-methylbenzamide in 12% yield together with *N*-methylbenzamide and the corresponding thioamides <79T229>.

Mesoionic thiazoles represent masked ylides which can undergo cycloaddition reactions. 1,3-Thiazolium-5-olate (**73**) and thioisomünchnone (**74**) can be considered as an azomethine ylide dipole and a thiocarbonyl ylide dipole, respectively. The cycloaddition chemistry of these compounds have been studied and their utility for the synthesis of heterocycles demonstrated <94S993>.

Thioisomünchnones (**74**) have also been employed in intramolecular cycloaddition reactions. The rate of cycloaddition is strongly influenced by the electronic nature of the 2-, 3-, and 5-substituents <89JOC1077>. Mesoionic imidazo[2,1-*b*]thiazolium-4-olate (**75**) undergoes 1,3-dipolar cycloaddition with aromatic aldehydes to give thiiranes via ring-opening of the initial 1:1-cycloadduct or alkenes by spontaneous desulfuration subsequent to the cycloadduct opening <93TL2999>. The reactivity and regioselectivity of the 1,3-dipolar cycloaddition reactions of 1,3-thiazolium-4-olate systems with isocyanates have been rationalized by MNDO and AM1 calculations <92T4193>.



3.06.6 REACTIVITY OF NONCONJUGATED RINGS

3.06.6.1 Isomers of Aromatic Derivatives

Thiazoles substituted in positions 2, 4, or 5 by hydroxy, thio, or amino groups are in tautomeric equilibrium with the corresponding oxo, thioxo, or imino thiazolines as discussed in Section 3.06.4.

The reactivity of this class of compounds is discussed either in Section 3.06.5, whether the transformation occurs at the aromatic ring level or in Section 3.06.7, when the protomeric group (hydroxy, thio, or amino) is responsible for the reactivity. Thiazoles substituted by two of these groups also present prototropic tautomerism although with some restrictions (see Section 3.06.4). The reactivity of those compounds is discussed in Section 3.06.5 and Section 3.06.7, in a similar fashion to the monosubstituted derivatives.

3.06.6.2 Dihydro Derivatives

3.06.6.2.1 Tautomerism

Thiazolines substituted with one hydroxy, thio, or amino group in a position that represents an enol, enethiol, or enamine function, respectively, are in tautomeric equilibrium with the corresponding oxo, thioxo, or imino thiazolidines.

3.06.6.2.2 Aromatization

2-Thiazolines and 3-thiazolines are easily aromatized to the corresponding thiazoles by the action of oxidants such as nickel peroxide <94TL1379>, 2,3-dichloro-5,6-dicyano-1,4-dibenzoquinone, or *t*-butyl perbenzoate via the Kharasch–Sosnovsky reaction <94TL2481, 94TL6803>. The aromatization of 2-allyl-4-thiazolines and benzothiazolines to the corresponding thiazoles and benzothiazoles by oxidation with basic aqueous potassium ferricyanide has been described <94JOC1319>. 4,5-Dihydro-

5-methylenethiazoles can be easily isomerized into 5-methylthiazoles by treatment of a benzene solution with Amberlist or with dbu at room temperature or at 50°C, respectively, for a few hours <93JOC1349>.

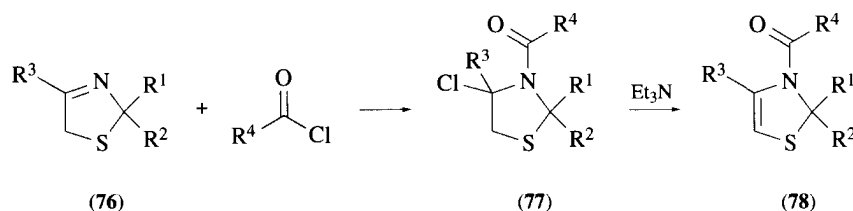
3.06.6.2.3 Electrophilic attack at nitrogen

(i) Alkyl halides

2-Thiazolines are readily alkylated at the nitrogen atom when treated with alkyl chlorides, yielding *N*-alkyl-2-thiazolinium salts. Prolonged reaction at temperatures above 120°C resulted in decreased yield of alkylated product and in formation of 1,3-dialkylated ureas via ring degradation <79AHC(25)83>.

(ii) Acyl halides

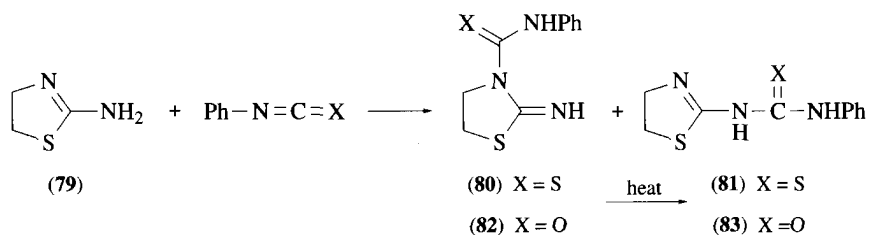
The reaction of 3-thiazolines (**76**) with acid chlorides in dichloromethane leads to *N*-acyl-4-chloro-3-thiazolidines (**77**) which are easily dehydrohalogenated by triethylamine to give the corresponding *N*-acyl-4-thiazolines (**78**) (Scheme 13) <91PS(61)173>. 5,5-Dimethyl-3-thiazoline is also acetylated by acyl chlorides to give *N*-acyl-4-chloro-5,5-dimethyl thiazolidine <87CZ149>. 1-Ethoxy-5,5-dimethyl-2-thiazoline reacts with acyl and thioacyl chlorides to yield *N*-(thio)acyl-5,5-dimethyl-2-thiazolidinone <82JPR1005>. In a similar fashion 2-thiothiazoline is acylated at nitrogen by methyl monoesters in the presence of dcc and catalytic amounts of dmap and dmap · HCl <94JOC5453>.



Scheme 13

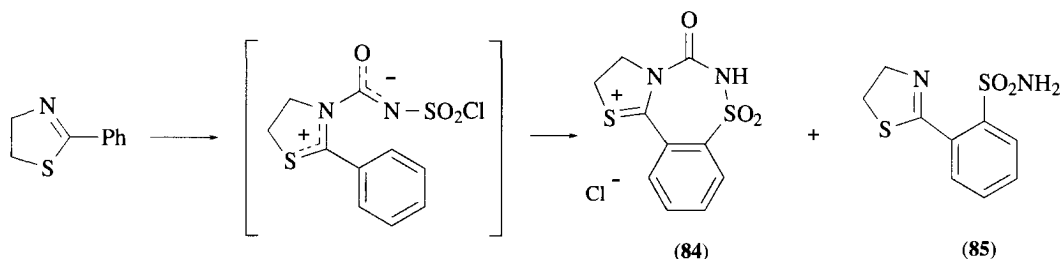
(iii) Other electrophiles

Phenylisothiocyanate and phenylisocyanate adds to 2-amino-2-thiazoline (**79**) to give the corresponding adducts <86JOC1910>. The reaction of (**79**) with phenyl isothiocyanate resulted in almost exclusive formation of thiocarbamilide (**80**), only a small amount of thiourea (**81**) being obtained. Similarly, the reaction of (**79**) with phenyl isocyanate at 0–5°C affords (**82**) along with small amounts of (**83**). However, when the reaction is carried out at ambient temperature the urea derivative (**83**) becomes the major product. Both (**80**) and (**82**) are converted to (**81**) and (**83**), respectively, when heated neat or in solution (Scheme 14).



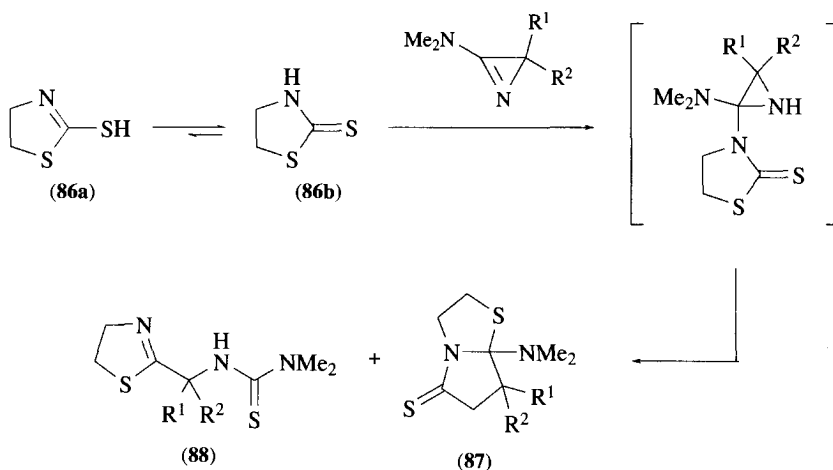
Scheme 14

2-Alkylthiazolines undergo cyclization reaction with chlorosulfonyl isocyanate in the presence of triethylamine to give thiadiazines and thiazolidine fused thiadiazines <93SC121>. In the case of the reaction between 2-phenyl-2-thiazolines the two products **(84)** and **(85)** shown in Scheme 15 are formed. The latter should arise from the former by the action of water.



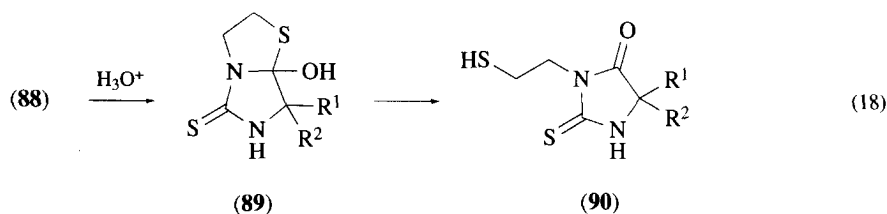
Scheme 15

2-Thio-2-thiazoline (**(86a)**), which is in tautomeric equilibrium with **(86b)**, reacts with 3-(dimethyl-amino)-2*H*-azirines in acetonitrile at ambient temperature giving rise to a mixture of imidazo[4,3-*b*]thiazole (**(87)**) and the thiazoline substituted dimethylthiourea (**(88)**) (Scheme 16) <86HCA2013>. When the reaction is carried out in isopropanol as a solvent, the thiourea derivative (**(88)**) is the only product. In polar solvents or under dimethylamine catalysis, compound **(87)** isomerizes to **(88)**.



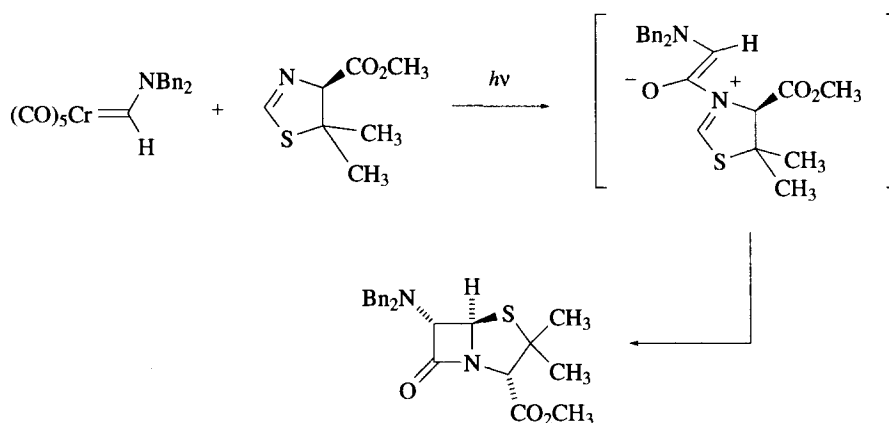
Scheme 16

The thiazoline bearing thiourea (**(88)**) undergoes intramolecular cyclization to give the imidazol[4,3-*b*]thiazole (**(89)**) which leads to the 2-thiohydantoin (**(90)**) (Equation (18)).



Optically active thiazolines give rise to β -lactams through the photolysis of chromium alkoxy-carbene complexes (Scheme 17). This reaction proceeds with very high stereoselectivity <94JOC4967>.

5,5-Dimethyl-3-thiazoline reacts with PdCl_4^{2-} , PdCl_6^{2-} , CuCl_2 , and CoCl_2 to give the corresponding complexes ML_2Cl_2 and $\text{L}(\text{Cl})\text{PdCl}_2\text{Pd}(\text{Cl})\text{L}$ <92ZN(B)1343>.

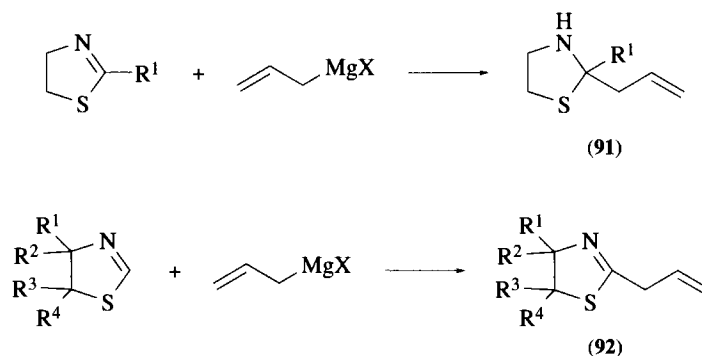


Scheme 17

3.06.6.2.4 Nucleophilic attack at carbon

(i) Carbanions

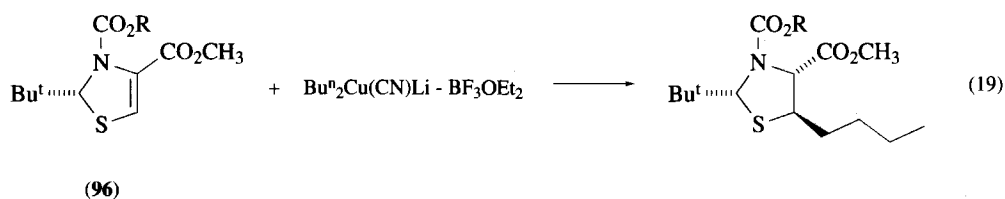
Allyl magnesium halides adds to both 2-substituted $\langle 87\text{BSF}837 \rangle$ and 4,5-disubstituted 2-thiazolines $\langle 87\text{JOM}(335)283, 91\text{JOM}(406)57 \rangle$ to give the corresponding 2-allylthiazolidines (**91**) and 2-allyl-2-thiazolines (**92**), respectively (Scheme 18). On the other hand, addition of allyl and propargyl Grignard derivatives to 1,3-thiazol-5(4*H*)-thiones (**93**) occurs chemoselectively at C-5 to give (**94**). By contrast, the addition to the $\text{C}=\text{S}$ bond of (**93**) by methyl, ethyl, and isopropyl magnesium halides leads to 2-thiazolines (**95**) (Scheme 19) $\langle 86\text{HCA}773 \rangle$. Treatment of 2-thiazolines with butyllithium leads to an equilibrium mixture of the C-2 anion and the open-chain β -isocyano thiolate $\langle 93\text{H}(36)473 \rangle$.

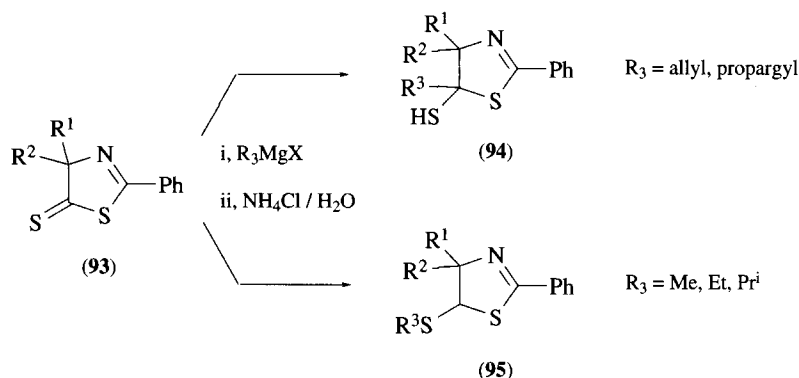


Scheme 18

A variety of C-nucleophiles can be added to 3-thiazolines to give the corresponding substituted thiazolidines $\langle 83\text{TL}4503 \rangle$. Among those nucleophiles are organolithium compounds, Grignard reagents, nitronates, and silyl and lithium enol ethers.

Cuprate additions with BF_3 activation have been carried out with enantiopure 4-thiazolines (**96**) (Equation (19)). Although the reaction takes place with a poor yield an excellent diastereoselectivity is achieved $\langle 91\text{JCS}(P1)2291 \rangle$.



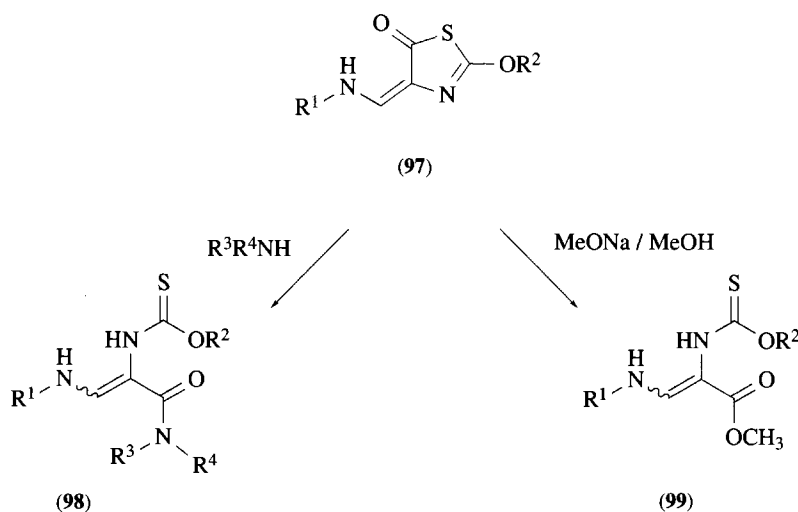


Scheme 19

(ii) Other nucleophiles

Treatment of 4,4-disubstituted thiazolidine-2,5-dithiones with hydroxylamine hydrochloride and pyridine in refluxing ethanol afforded thiohydroxamic acids <92T7091>.

Several *N*-nucleophiles react with thiazolones (**97**) leading to dehydro amino acid derivatives (**98**) <94JHC199>. Similarly the reaction with sodium methoxyde affords the corresponding dehydro amino ester (**99**) (Scheme 20).

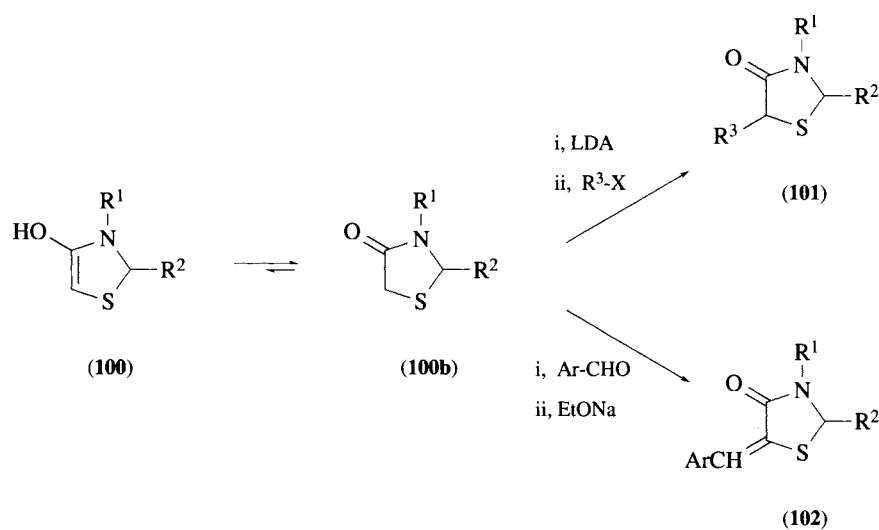


Scheme 20

A study on the hydrolysis of benzothiazolines to give the corresponding aldehydes or ketones have been carried out by Chikashita and co-workers <89BCJ1215>. The hydrolysis can be achieved with several reagents such as $AgNO_3$, $HgCl_2$, NBS, $MeOSO_2F/K_2CO_3$, or Chloramine T <85H(23)295>.

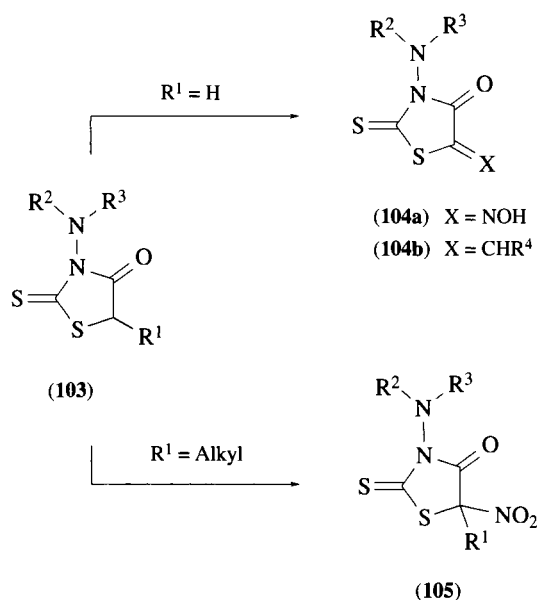
3.06.6.2.5 Other reactions

Alkylation of the predominant keto tautomer of 4-hydroxythiazoles can be achieved with LDA and alkyl halides <85CJC3313>. Compound (**100b**) reacts with aromatic aldehydes under basic conditions to give the corresponding arylidene derivatives (**102**) (Scheme 21) <87M1 306-02>.



Scheme 21

The reaction can be accelerated by adsorbing the aldehydes on potassium fluoride on alumina and irradiating with microwaves $\langle 93PS(79)33 \rangle$. 3-Aminorhodanines (103) are converted to the 5-hydroxyimino derivatives (104a) under nitrosating or nitrating conditions $\langle 93AP(326)871 \rangle$ and to the 5-methylene derivatives (104b) by condensation with aldehydes $\langle 95JHC1019 \rangle$. When the reactions are carried out with C-5 substituted rhodanines, 5-nitroderivatives (105) are formed (Scheme 22) $\langle 93AP(326)875 \rangle$.



Scheme 22

4,4-Disubstituted 1,3-thiazol-5(4H)-thiones undergo cyclosubstitution reactions with acetylene carboxylates or acetylene carbonitriles to yield 1,4-dithiafulvenes $\langle 86HCA419 \rangle$.

2,5-Dihydro thiazoles have been applied as the imine components in the synthesis of oligopeptides based on the Ugi four components condensation (4CC) reaction $\langle 94S619 \rangle$.

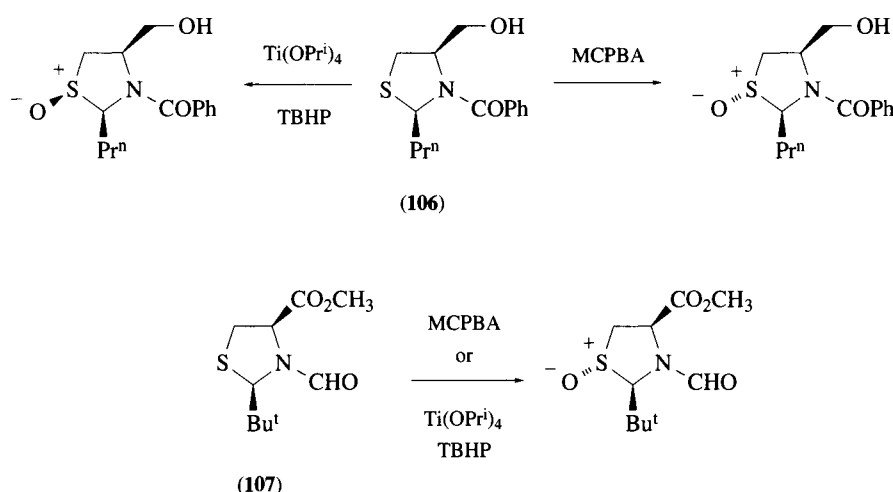
3.06.6.3 Tetrahydro Derivatives

3.06.6.3.1 Tautomerism

1,3-Thiazolidines substituted with imino, oxo, or thioxo groups are in tautomeric equilibrium with the corresponding dihydro derivatives. In addition, 1,3-thiazolidines can be in equilibrium with the open-chain form depending on the nature of the substituents <84CHEC-I(4)273>. Evidence for the existence of this equilibrium comes from the configurational instability at C-2 <91T7029, 94JHC77>.

3.06.6.3.2 Electrophilic attack at sulfur

The oxidation of thiazolidines at the sulfur atom is carried out by several oxidizing reagents, the most commonly used being hydrogen peroxide, peracids like *m*-chloroperbenzoic acid (MCPBA), and peroxides like *t*-butylhydroperoxide (TBHP). A study of the stereocontrolled *S*-oxidation of chiral thiazolidines has been reported <86TL3391>. Both the substituents and the oxidation conditions influence the stereochemical course of the reaction. While oxidation of the 2,4-disubstituted thiazolidine (**106**) with MCPBA affords exclusively the *trans*-sulfoxide, the use of Ti(OPr^{*i*})₄/tbhp as oxidizing system leads to the *cis*-sulfoxide as the major product. However, when a bulky substituent is present at C-2, the *trans*-isomer is obtained in all cases (Scheme 23). The excellent selectivity of this reaction has been exploited in the preparation of interesting intermediates for the synthesis of enantiomerically pure α -amino acids <91JCS(P1)2291>.



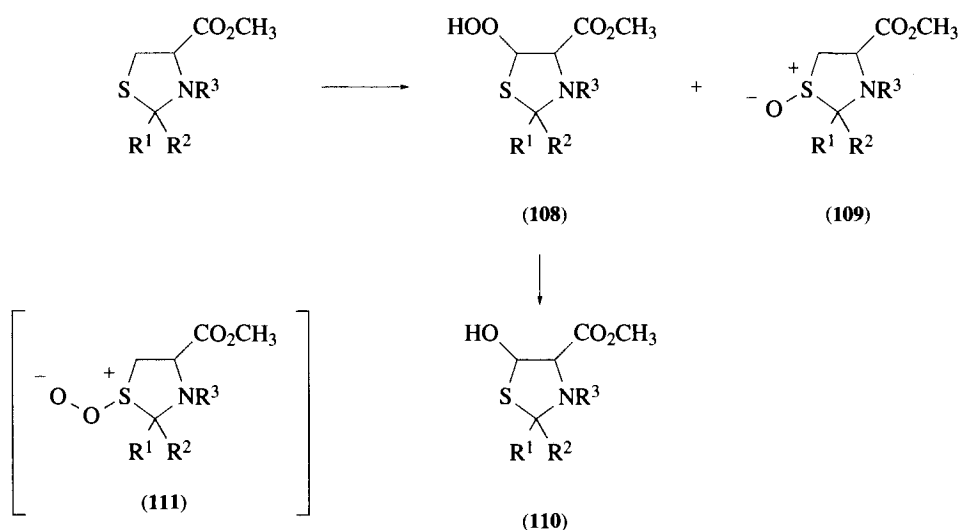
Scheme 23

The reaction of 1,3-thiazolidines with singlet oxygen leads to the hydroperoxide (**108**) or to the sulfoxide (**109**) in variable ratios depending on the reaction conditions and the substituents. The hydroperoxide (**108**) is transformed into the 5-hydroxythiazolidine (**110**) <91JA2696>. In all cases the reaction takes place through the primary intermediate (**111**) (Scheme 24).

4-Oxo-1,3-thiazolidines are also amenable to oxidation by the action of sodium periodate <90OPP544>, hydrogen peroxide, MCPBA, and tbhp to give the corresponding sulfoxides <85CJC3313>. More oxidized compounds are obtained with the use of potassium permanganate in a mixed phase system of CH₂Cl₂/H₂O containing benzyltriethylammonium chloride and benzoic acid as additives <94TL6143>.

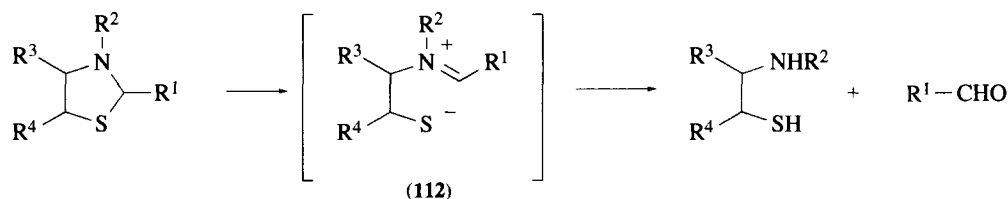
3.06.6.3.3 Ring opening

Thiazolidines undergo hydrolysis to aldehyde and amino thiol under acid or basic aqueous conditions. The mechanism of the reaction of some model compounds has been investigated by kinetic measurements under different conditions <91JA3071>. It has been concluded that the reaction involves C—S bond breaking and proceeds by the formation of an iminium thiolate zwitterion



Scheme 24

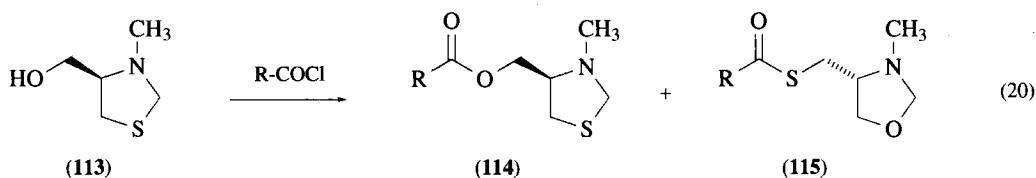
intermediate (112). The main reason for the mechanistic studies of thiazolidine ring opening arose from the presence of this moiety in penicillin derivatives. In this context the thiazolidine ring-opening reactions of penicilloyl esters and amides have also been studied (Scheme 25) <91JCS(P1)1219>.



Scheme 25

The hydrolysis of thiazolidines to aldehydes is conveniently carried out under neutral conditions by the assistance of metal ions such as Hg^{II} or Cu^{II} <93JOC275>. Unlike the above hydrolysis under acid or base conditions, the synthetic value of this important transformation has been demonstrated (see Section 3.06.12). Open-chain compounds are obtained when thiazolidines are treated with tris(trimethylsilyl)silane in a reaction in which the thiazolidine derivatives act as a source of α -aminoalkyl radicals <91TL2857, 91TL6265>.

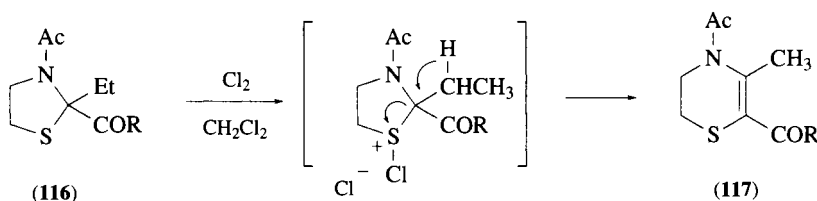
Acylation of thiazolidine (113) shows competition between *O*-acylation and ring opening to give (114) or (115) depending on the bulkiness of the acyl group (Equation (20)) <85TL869>.



3.06.6.3.4 Other reactions

Treatment of 1,3-thiazolidines (116) with chlorine affords dihydro-1,4-thiazines (117) through the ring opening of a unisolable chlorosulfonium salt (Scheme 26) <93JHC1105>.

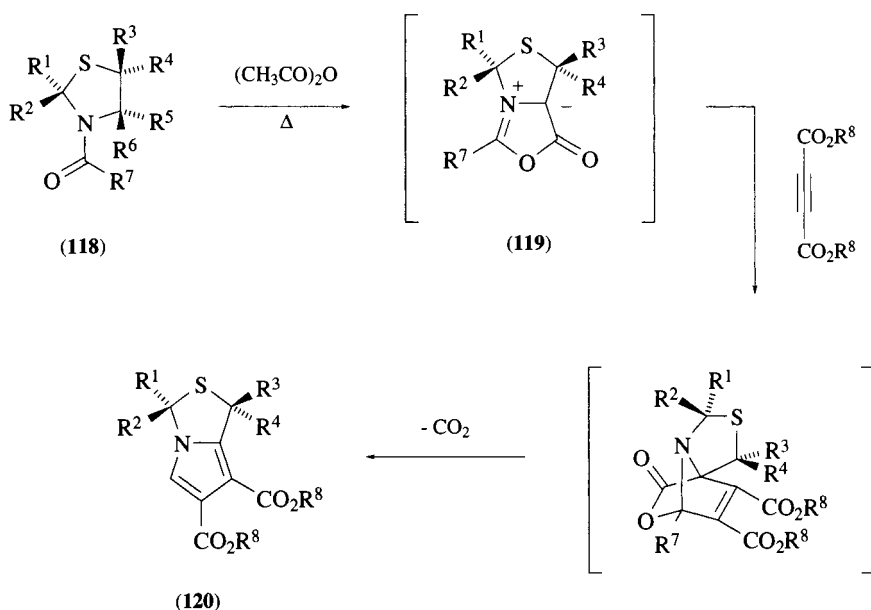
Mesoionic intermediates (119) generated *in situ* from 2-substituted-3-acyl-1,3-thiazolidine-4-carboxylic acids (118) give [3 + 2] cycloaddition reactions with acetylene dicarboxylates to afford



Scheme 26

pyrrolo[1,2-*c*]thiazoles (**120**) <94MI189>. Similarly, the reaction with imines leads to imidazo[1,5-*c*]thiazole derivatives (Scheme 27) <95T9385>.

1,3-Thiazolidines react with carbon monoxide in the presence of catalytic amounts of chloro (1,5-cyclooctadiene)rhodium(I) dimer and potassium iodide to give 2-thiazolidinones <94JA5662>.



Scheme 27

3.06.7 REACTIVITY OF SUBSTITUENTS ATTACHED TO RING CARBON ATOMS

3.06.7.1 General Survey

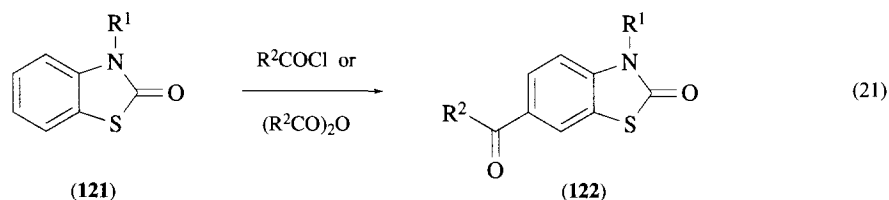
An analysis, based on the donor-acceptor concept concerning the general reactivity of the thiazole ring, shows that the 2-position is electron-deficient while the 5-position is electron-rich and the 4-position is neutral <92ACS372, 92H(33)1129>. In consequence, the reactivity of the substituents linked to carbon atoms of the thiazole ring depends on their position in the heterocyclic nucleus. As an example, 2-alkylthiazoles are more easily deprotonated in α -position than 5-alkyl derivatives; 2-halothiazoles are more reactive towards nucleophilic displacement than 4- or 5-halothiazoles. In general, the different π -electron delocalization exhibited by the thiazole ring makes the 2-position the most reactive.

3.06.7.2 Fused Benzenoid Rings

General guidelines on the reactivity of the benzene nucleus in benzothiazole has been described previously in the first edition of *Comprehensive Heterocyclic Chemistry* (CHEC-1) <84CHEC-1(4)274>.

Treatment of benzothiazole with an excess of chlorosulfonic acid and then thionyl chloride affords a 4:1 mixture of the 4- and 7-sulfonyl chlorides, respectively. Chlorosulfonic acid alone fails to react with benzothiazole. This is probably due to the formation of the 4-sulfonic acid where an intramolecular hydrogen bond inhibits the formation of the chlorinated derivative <92PS(73)107>. Interestingly, when the same reaction is carried out with 2-methylbenzothiazole the major product is the 6-sulfonyl chloride.

2-(3*H*)-Benzothiazolones (**121**) undergo Friedel–Crafts acylation through the reaction with acyl chlorides or anhydrides in the presence of a large excess (7–11 equivalents) of the AlCl_3 –DMF reagent (Equation (21)). The same 6-acyl-2-(3*H*)-benzothiazolones (**122**) are obtained from (**121**) and anhydrides in the presence of polyphosphoric acid <94JOC1574>.



3.06.7.3 Alkyl Groups

3.06.7.3.1 Reactions similar to those of toluene

Bromination with *N*-bromosuccinimide of 2-alkylthiazoles affords α -dibromothiazoles in good yields. The hydrolysis of these compounds leads to 2-acylthiazoles <91T2851>. The same reaction can be utilized to obtain 2-(bromomethyl)benzothiazole from 2-methylbenzothiazoles <91JMC108>.

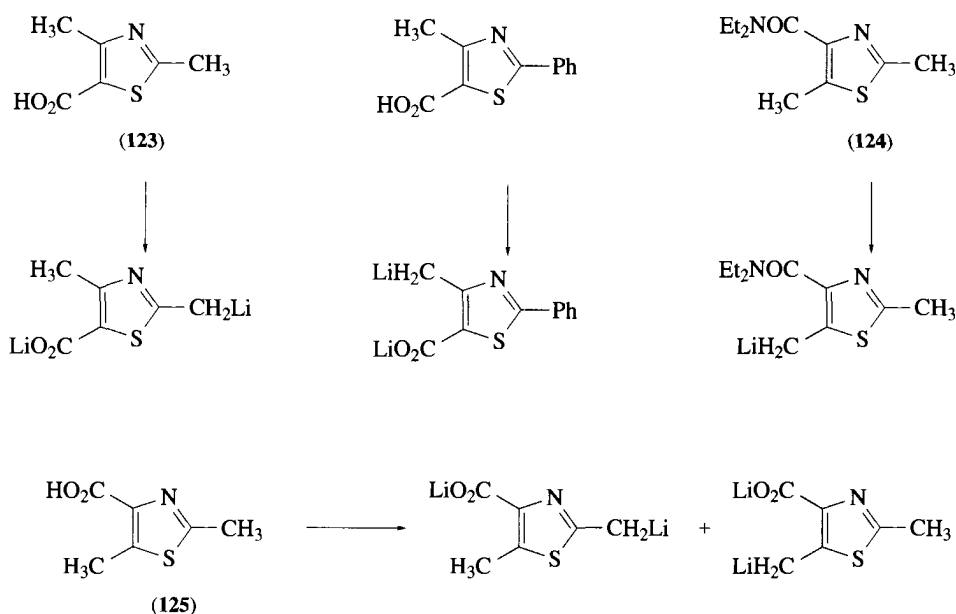
3.06.7.3.2 Alkylthiazoles: reactions involving essentially complete anion formation

Deprotonation at -78°C of 2-methyl-4-alkylthiazoles with butyllithium proceeds at the 2-methyl group. On the other hand, in the case of 2-methyl-4-arylthiazoles, deprotonation takes place predominantly at C-5 <74JOC1192>. However at elevated temperatures only the lithiomethyl anion is obtained, thus demonstrating the higher thermodynamic acidity of the 2-methyl group protons (see Section 3.06.5.7.1).

2,4-Dimethylthiazole carboxylic acid (**123**) can be metalated at the 2-methyl group in a regioselective way affording the corresponding dianion. When the 2-position is blocked (e.g., by a phenyl group) 4- or 5-methyl groups can be lithiated <87TL3585>. Metalation of 2,5-dimethyl derivatives (**125**) is not regioselective but occurs in varying proportions at both methyl groups under a variety of conditions <91JCS(P1)2417>. In contrast diethylamide (**124**) affords exclusively the metalated compounds at the 5-methyl group (Scheme 28).

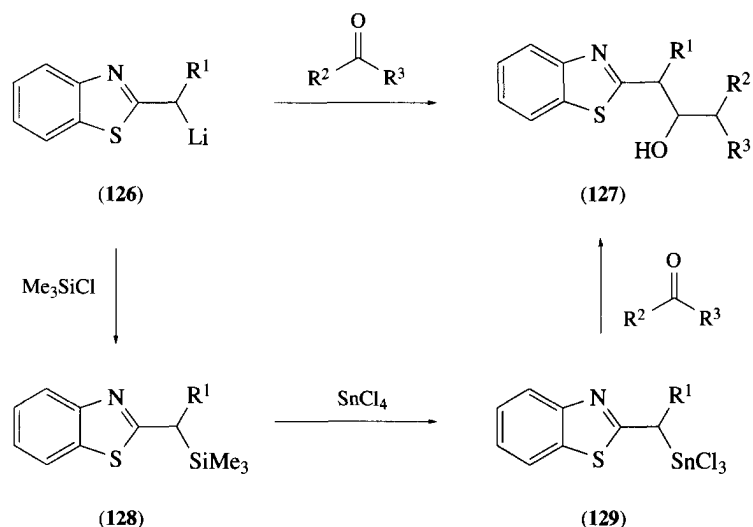
An extensive study on the metalation of 2-methylbenzothiazole ($\text{p}K_{\text{HA}}^+ = 27.6$) has been reported <85JOM(293)265>. Both butyllithium and phenyllithium, in the presence of linear or cyclic ethers at -78°C , afford 2-benzothiazolylmethylolithium in almost quantitative yield.

In a similar way 2-alkyl-2-thiazolines can be metalated at the 2-alkyl group by using butyllithium or lithium diisopropylamide in tetrahydrofuran as a solvent <92TL3801>. 2-Alkylolithium-thiazoles and benzothiazoles react with electrophiles to give the corresponding adducts. It has been reported that the reaction of 2-lithiomethylthiazoles and 2-lithiomethylthiazolines with α -oxoketene dithioacetals <90T4295> and the reaction of 2-lithiomethylbenzothiazoles (**126**) with aldehydes and ketones affords, after hydrolytic work-up, the β -hydroxybenzothiazoles (**127**) in good yields <86S375> (Scheme 29). Similar reactions can be achieved with other organic polar functions like carboxylic esters nitriles and acyl chlorides <91JHC1541>. Treatment of (**126**) with trimethylsilyl chloride according to the Corey's procedure <78TL5> affords trimethylsilylalkylbenzothiazoles (**128**) which are unreactive towards aldehydes. Only when the carbonyl compounds are activated with a Lewis acid are compounds (**127**) obtained <87T1937>. An instantaneous reaction takes place between (**128**) and tin(IV) chloride to give 2-trichlorostannylalkylbenzothiazoles (**129**). In contrast to (**128**) organotin derivatives (**129**) react with carbonyl compounds to give (**127**) with good diastereoselectivities and chemical yields. 2-Lithiomethylbenzothiazoles (**126**) also react with epoxides affording γ -hydroxy-



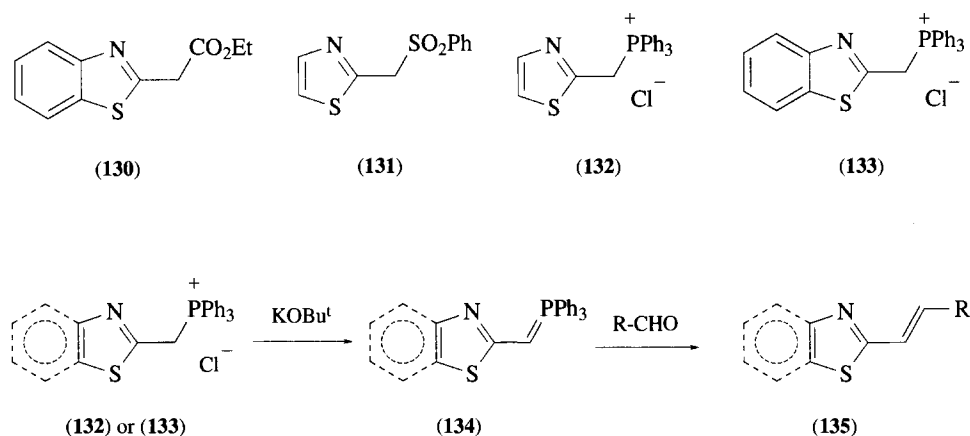
Scheme 28

alkyl-benzothiazoles <90T8169>. It is also possible to metalate 2-chloromethylbenzothiazole which couples with carbonyl compounds leading to oxiranes <92TL7953>.



Scheme 29

The presence of an electron-withdrawing group can facilitate the formation of the α -anion in 2-alkylthiazoles and benzothiazoles. Thus, ethyl 2-benzothiazolyl acetate (130) undergoes α -deprotonation with sodium hydride at 0°C <89JHC1519>. The presence of a phenylsulfonyl group also allows the easy generation of the corresponding α -anion <94UP 306-01>. Triphenylphosphonium salts (132) and (133) derived from 2-methylthiazole and 2-methylbenzothiazole, respectively, are readily available in multigram scale <88T2021>. Deprotonation of those compounds affords the corresponding semi-stabilized phosphoranes (134) which can be employed in classical Wittig condensations with aldehydes to obtain 2-alkenylthiazoles (135) mainly or exclusively as *E*-isomers (Scheme 30) <88T2021, 93S277>.



Scheme 30

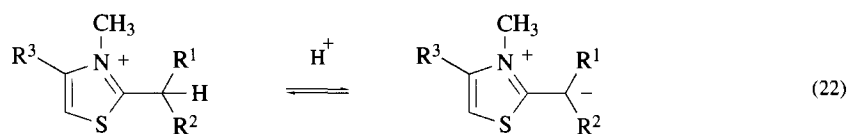
3.06.7.3.3 Alkylthiazoles: reactions involving traces of reactive anions

The addition of Grignard reagents to alkylbenzothiazoles promotes a Claisen-type self-condensation reaction presumably through the formation of an intermediate carbanion $\langle 84\text{TL}2051 \rangle$.

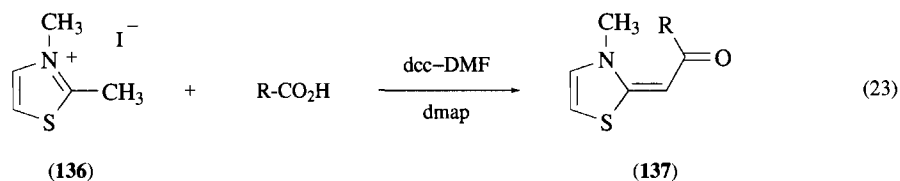
2-Alkylbenzothiazoles condensate with α,β -unsaturated ketones or nitriles in dichloromethane-aqueous sodium hydroxide in the presence of a phase transfer catalyst $\langle 87\text{MI } 306-03 \rangle$. 2-Methylbenzothiazole can be efficiently condensed with aromatic aldehydes by using KF- or $\text{CsF-Al}_2\text{O}_3$ base system in dimethylformamide $\langle 94\text{S}973 \rangle$.

3.06.7.3.4 C-Alkylthiazolium ions

The acidity of the protons attached to a 2-alkyl group is enhanced in 2-alkylthiazolium cations. A study based on spectrophotometric titrations has allowed $\text{p}K_{\text{HA}^+}$ values to be calculated for some 2-alkylthiazolium cations in both DMSO and aqueous solutions (Equation (22)) $\langle 90\text{JA}792 \rangle$.



The values of $\text{p}K_{\text{HA}^+}$ are in the range of 8.5–14.8 in DMSO. The acidities in aqueous solutions were within ± 1 unit of that in DMSO. The use of bases such as 4-dimethylaminopyridine (dmap) results in convenient condensation reactions of 2,3-dimethylthiazolium iodide (136) with carboxylic acids to obtain 2-acylmethylidene-3-methylthiazolines (137) in moderate to good yields (Equation (23)) $\langle 89\text{S}50 \rangle$.



Triethylamine has also been employed as a base to induce the formation of an α -anion in 2-methylalkylthiazolium ions. The resulting anionic species have been made to react with 1,2-dicarbonyls in an extension of the Westphal condensation $\langle 86\text{JHC}1889, 94\text{JOC}8294 \rangle$.

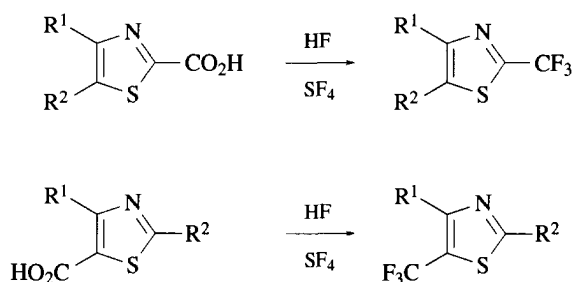
3.06.7.4 Other C-Linked Substituents

3.06.7.4.1 Aryl groups

As discussed in Section 3.06.5.3.2, 2-phenylthiazole undergoes electrophilic substitution at the heteroaromatic ring. However, bromination in sulfuric acid in the presence of silver sulfate introduces bromine into the *para*-position of the benzene ring <85CS295>. This is caused by the protonation of the thiazole ring and the ensuing deactivation. A similar behavior is observed in the nitration of 2-phenylthiazole with nitric acid in sulfuric acid. Also in this case the electrophilic substitution is directed towards the *para*-position (the ratio of the *o* : *m* : *p*-isomers being 3 : 8 : 89).

3.06.7.4.2 Carboxylic acids

The chemistry of thiazole carboxylic acids is well-documented in CHEC-I <84CHEC-I(4)240>. Thus, thiazole carboxylic acids show a standard reactivity for the carboxyl functionality; they form acid chlorides with thionyl chlorides, esters with alcohols in a variety of conditions, amides with ammonia, etc. The resulting acid derivatives also exhibit a standard reactivity depending on the functionalization. In addition, thiazole carboxylic acids decarboxylate in acidic aqueous solutions. The rate constants observed for the process suggest either a unimolecular decarboxyprotonation or a bimolecular protodecarboxylation depending on the proton activity <91JCS(P2)349>. Thiazole carboxylic acids react with sulfur tetrafluoride and hydrogen fluoride to give trifluoromethylated thiazoles <91JFC(55)173>. This reaction needs special conditions and equipment <91JFC(55)169> and works with both 2- and 5-thiazole carboxylic acids (Scheme 31).



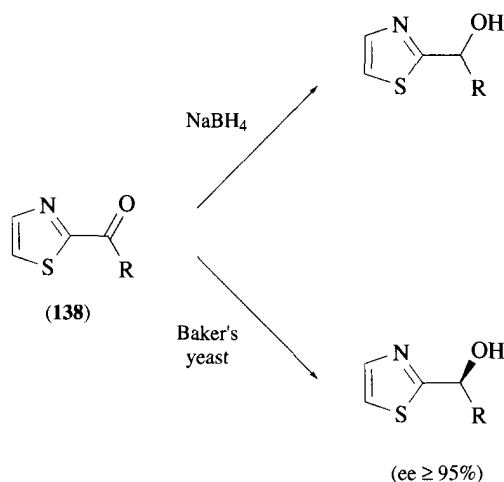
Scheme 31

3.06.7.4.3 Aldehydes and ketones

Thiazole carboxaldehydes show the standard reactivity of aromatic aldehydes. For instance, they are easily reduced with sodium borohydride <88T2021>, react with hydroxylamine hydrochloride to give oximes <87S998>, and undergo nucleophilic addition of organometallics such as Grignard reagents <94TL5293>.

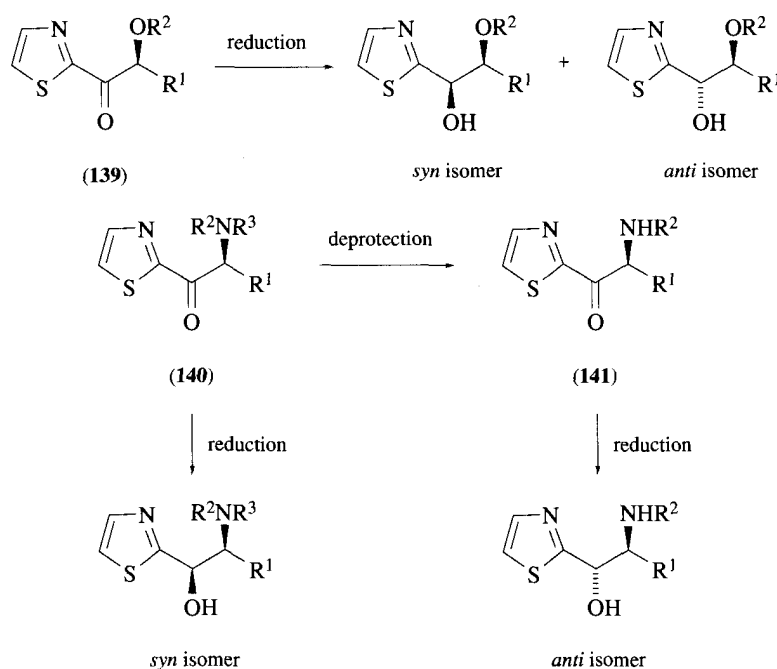
Thiazolyl ketones also exhibit a reactivity typical of the carbonyl group. By virtue of the synthetic equivalence of the thiazole ring to the formyl group, 2-thiazolyl ketones are useful intermediates in a variety of synthetic methodologies (see Section 3.06.12.1). 2-Thiazolyl ketones (**138**) can be reduced by chemical and enzymatic methods to give the corresponding thiazolyl carbinols in high yields <88FES1119, 88G211>. The reduction of 2-acylthiazoles (**138**) can be also carried out in a diastereoselective way when a chiral group is in α -position to the carbonyl function (Scheme 32).

For 2-thiazolyl- α -alkoxy ketones (**139**) the reduction with various hydride releasing reagents (L-selectride, K-selectride, dibal-H, zinc, or sodium borohydride) gives predominantly the *syn* isomer <89JOC702, 92S201>; the *anti* isomer is obtained in some cases by the proper choice of the reducing agent <89JOC702, 93T2939>. Similar results are obtained with 2-thiazolyl- α -amino ketones <88CC10, 91CC1576, 92TL7259>. Moreover, in this case tunable stereoselective reduction leading to the *syn* or *anti* amino alcohol can be achieved through a double or single protection respectively of the amino group (Scheme 33). This behavior can be rationalized by assuming an external hydride delivery to



Scheme 32

the less hindered face of the carbonyl existing in a non-chelated conformation **A** (Felkin-Ahn-Houk model) for (**140**) and in a chelated conformation **B** (Cram chelate model) for (**141**) (Figure 1).



Scheme 33

The reduction can be carried out in a distereoselective manner also when the chiral group is in β -position to the carbonyl. Moreover, a reversal of the sense of the diastereoselectivity can be achieved by the use of diisobutylaluminum hydride (dibal-H) or tetramethylammonium triacetoxyborohydride ($\text{Me}_4\text{NBH}(\text{OAc})_3$) to give 1,3-*syn* or 1,3-*anti* diols, respectively (Scheme 34) <93S903>.

2-Acetylthiazole undergoes aldol condensation with aldehydes to give β -alkoxy-2-acylthiazoles <89TL6063, 91JOC5294>. The use of lithium *t*-butoxide for the *in situ* generation of the lithium enolate of 2-acetylthiazole is crucial for the reaction. The generation of other enolates (e.g., zinc enolate) leads to a lack of reproducibility of the aldol reaction <91JCS(P1)2691>.

Treatment of 2-bromoacetylthiazole (**142**) with triphenylphosphine affords the phosphonium salt which on treatment with aqueous sodium hydroxide gives the stabilized [(2-thiazolyl-carbonyl)methylene]triphenylphosphorane (**143**) (Scheme 35) <91TL3247, 94JA3324>. This compound

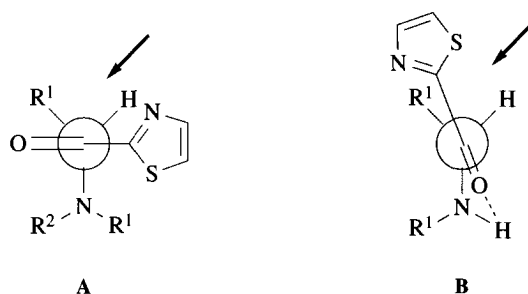
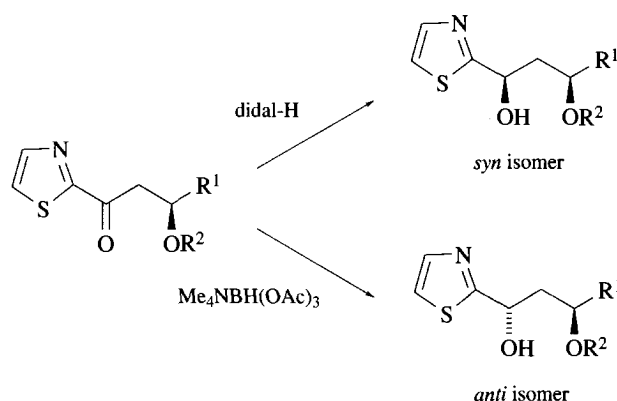
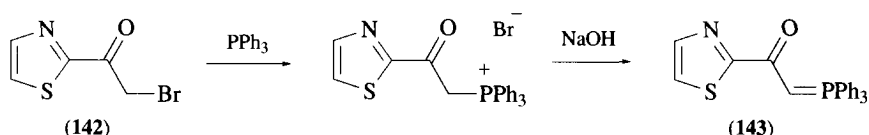


Figure 1 Conformation of thiazolyl aminoketones and sites of hydride addition to the C=O bond (see arrows).



Scheme 34

has been employed as an equivalent of the pyruvate unit in the synthesis of ulosonic acids (see Section 3.06.12.1).



Scheme 35

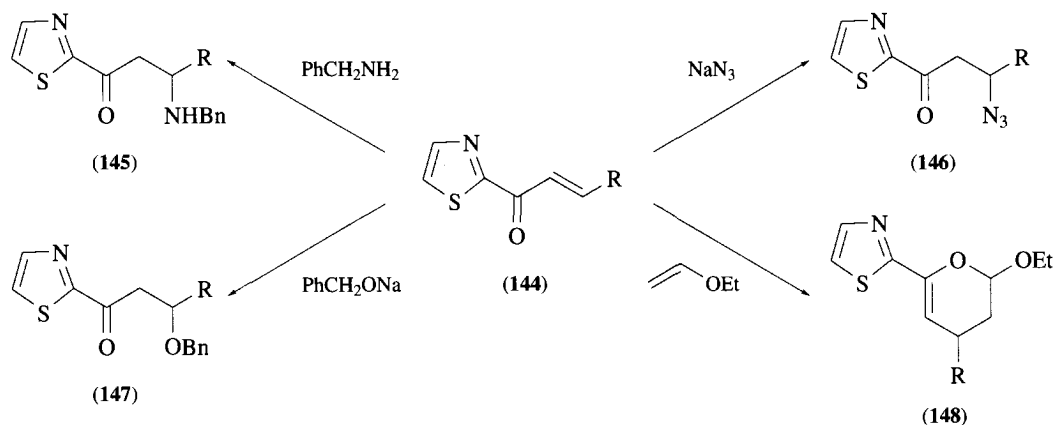
Organometallics reagents such as Grignard compounds add to thiazolyl ketones to give thiazolyl carbinols <91JMC2176>. Nitrogen-nucleophiles like benzylamine or sodium azide react with 2-thiazolyl- α,β -enones (**144**) affording β -amino-2-acetylthiazoles (**145**) <93SL256, 94TA2209> and β -azido-2-acetylthiazoles (**146**), respectively. Similarly oxygen-nucleophiles like sodium benzyolate react with (**144**) to afford the corresponding β -alkoxy-2-acetylthiazoles (**147**) <91TL3247, 94JA3324>. Compounds (**144**) can also act as heterodienes in cycloaddition reaction with ethyl vinyl ether to give 6-thiazolyl 3,4-dihydro-2H-pyran derivatives (**148**) as shown in Scheme 36 <94CC1963>.

2-Acylthiazoles can be quaternized with alkylating agents to give 2-acylthiazolium salts which proved to be efficient catalysts in the *O*-acylation of aromatic hydroxylamines <91CC1127>.

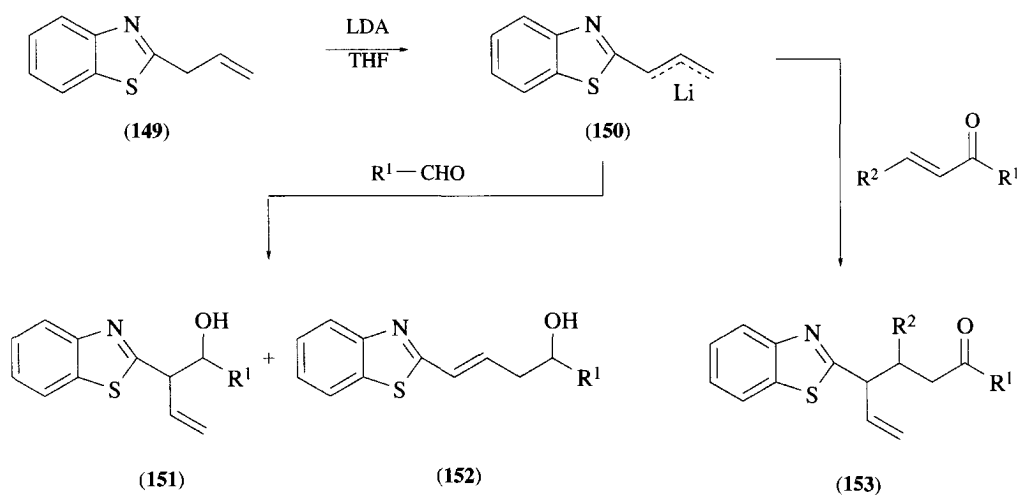
3.06.7.4.4 Vinyl and allyl groups

2-Allylbenzothiazoles (**149**) can be metalated with LDA in THF at -78°C to form stabilized allylic carbanions. The obtained 2-allyllithiobenzothiazole reacts with aldehydes to give α - or γ -regioisomers depending on the reaction conditions, particularly the reaction temperature and time <87TL6385>. The organometallic derivative (**150**) also reacts with α,β -unsaturated carbonyl compounds to afford predominantly the α -regioisomer. (**153**) (Scheme 37) <90G297>.

2-Allylbenzothiazoles isomerize to vinylthiazoles upon treatment with bases. The *E/Z* diastereo-



Scheme 36



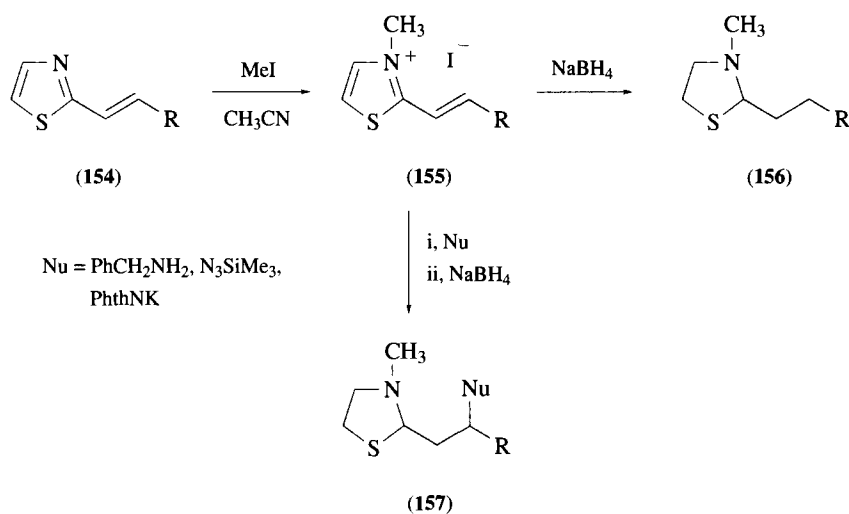
Scheme 37

selectivity of the resulting alkenes depends on the employed base ^{<91T3365>}. 2-Vinyl thiazoles undergo electrophilic additions such as epoxidation with *tbhp* or peracids ^{<91UP 306-01>} and *cis*-hydroxylation using catalytic osmium tetroxide with *N*-morpholine oxide as a reoxidant ^{<91CC1576, 93T2939>}.

Nucleophilic additions to vinyl thiazoles are also possible. However, the electron-withdrawing character of the 2-thiazolyl group is not sufficient to make 2-alkenylthiazoles (154) good Michael-type acceptors. Activation by quaternization of the heterocyclic ring overcomes this problem. The resulting *N*-methyl 2-alkenylthiazolium salts (155) add smoothly the hydride ion to give thiazolidines (156) ^{<90T6167, 93S277>} and undergo 1,4-conjugate addition of nitrogen nucleophiles to give, after quenching *in situ* with sodium borohydride, thiazolidines (157) bearing the nucleophile fragment in the alkyl side-chain (Scheme 38).

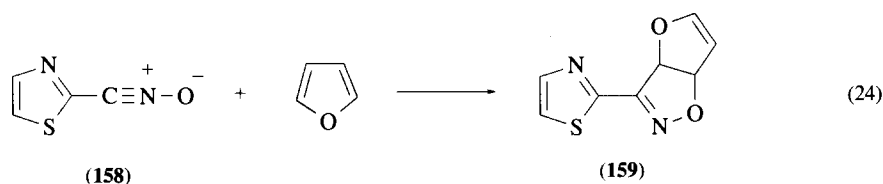
3.06.7.4.5 Other substituents

Halomethylthiazoles are quite reactive compounds which have been employed in several synthetic processes. For instance, 2-chloromethylthiazole is a key intermediate in the preparation of the thiazole bearing phosphorane (134) of considerable synthetic utility (see Section 3.06.12.1). 2-Iodomethyl-2-thiazolines give elimination reactions under basic conditions to afford unusual 5-methylene-2-thiazolines ^{<89TL4435>}. A similar reaction takes place when 5-acetoxymethyl thiazoles undergo thermal elimination of acetic acid to give 5-methylene-2-thiazolines, too ^{<94TL5293>}. Thia-



Scheme 38

zole-2-carbonitrile *N*-oxide (**158**) undergoes 1,3-dipolar cycloaddition with furan to give furo-isoxazolidine (**159**) as the only isomer (Equation (24)) <88T3215>.



Imino derivatives have been used in the construction of oxazole derivatives <92TL6523> and in the coupling reactions with carbonyl compounds <91T4465>.

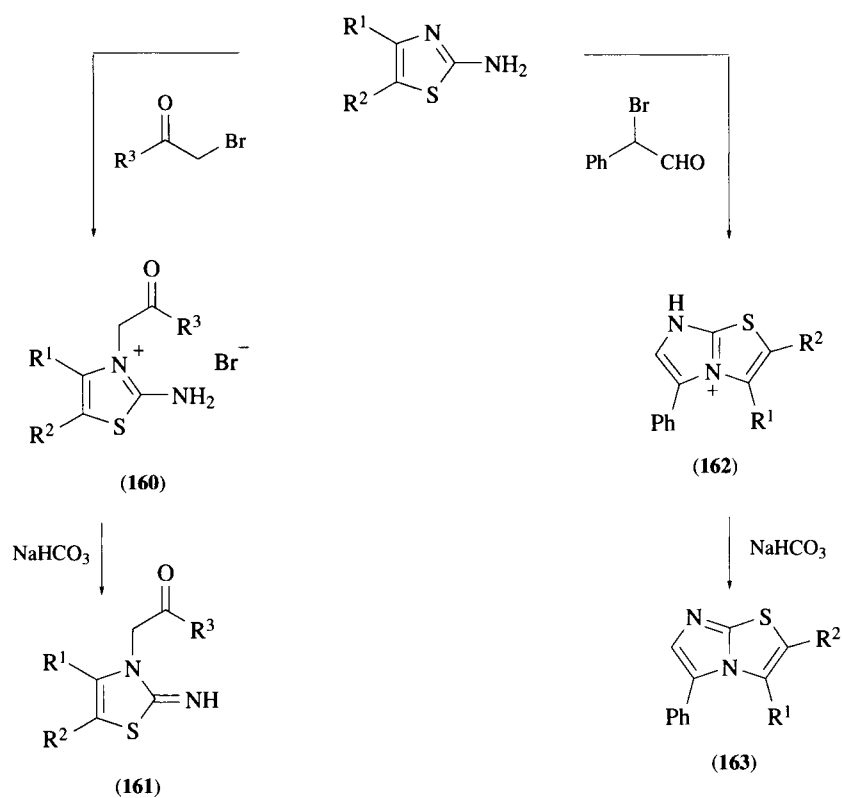
3.06.7.5 Aminothiazoles

3.06.7.5.1 Reactions with electrophiles (except nitrous acid)

As discussed in Section 3.06.5 aminothiazoles react with alkyl halides to give mainly the product of alkylation at the endocyclic nitrogen when the reaction is conducted in the absence of strong bases; with acyl and sulfonyl halides, the exocyclic nitrogen becomes the main nucleophilic site. The reaction of 2-aminothiazoles with heterocyclic or aromatic aldehydes show ample differences depending on the various amine-aldehyde pairs <91S621>. In general the azomethine derivatives are obtained by a suitable procedure which has to be followed in each case. The increase of the amine/aldehyde ratio leads to bis-amines as the major products of the reaction.

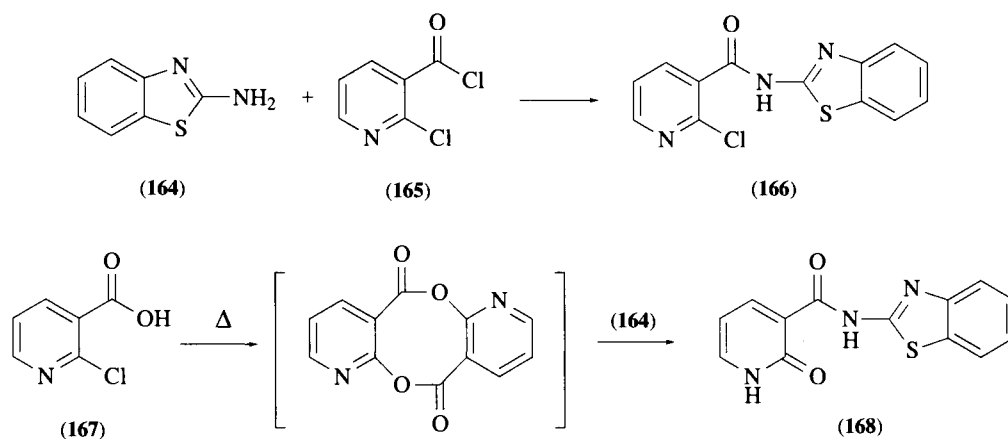
The reaction of 2-aminothiazole and 2-aminobenzothiazole with 2-benzoyl-2-bromoacetate has been employed in the preparation of several fused imidazole systems <89JHC1875>. α -Bromo ketones attack the ring nitrogen of 2-aminothiazoles to give the salts (**160**). The same type of reaction takes place with ethylbromoacetate (Scheme 39). Basification of (**160**) affords the imines (**161**) which are intermediates in the synthesis of imidazo[2,1-*b*]thiazoles <89JCS(P1)643>. On the other hand, when an α -bromo aldehyde is made to react with 2-aminothiazoles, the salt (**162**) is formed directly leading to (**163**) after basification.

2-Aminobenzothiazoles (**164**) react with 2-chloronicotinoyl chloride (**165**) to give the corresponding 2-chloronicotinamides (**166**). When 2-chloronicotinic acid (**167**) is used the amide (**168**) is obtained (Scheme 40). This behavior can be explained by the low reactivity of 2-chloronicotinic



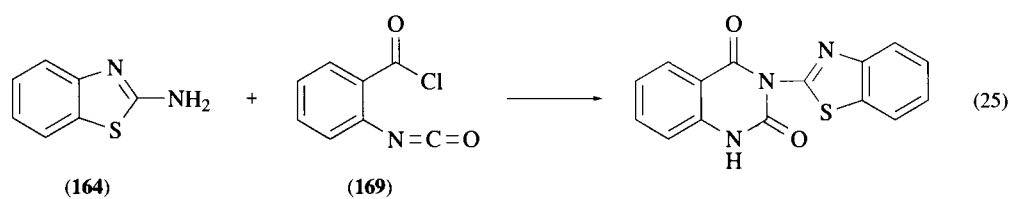
Scheme 39

acid which allows the formation of a dimer as a reactive intermediate resulting from the thermal degradation of (167) <86H(24)87>.



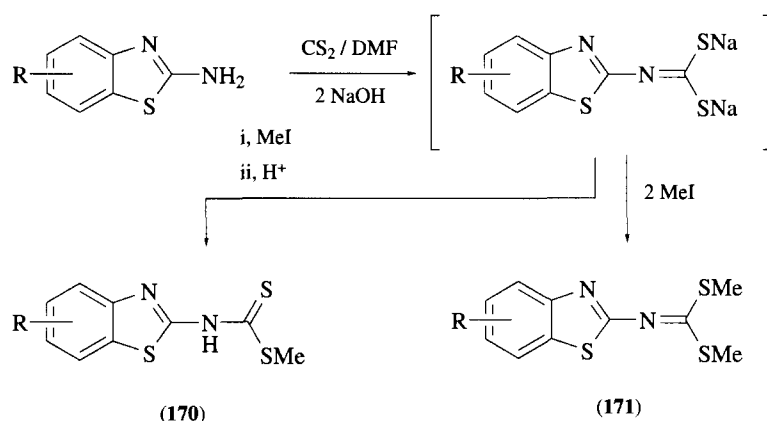
Scheme 40

2-Aminobenzothiazole (164) also reacts with ambident electrophilic reagents such as 2-isocyanatobenzoyl chloride (169) to give the corresponding adducts (Equation (25)) <84S520>.



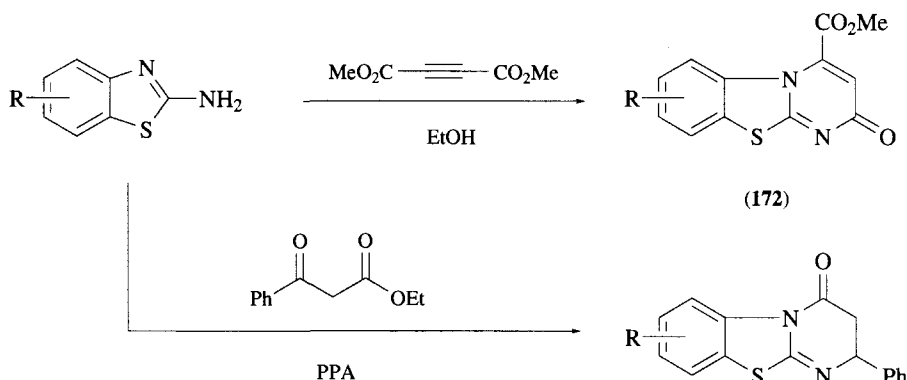
Although the reaction of aminothiazoles and aminothiazolines with isocyanates and isothiocyanates has been described, a reinvestigation of this reaction showed that initial attack occurs at the endocyclic nitrogen (kinetic control). The resulting adduct may then undergo intramolecular rearrangement and/or dissociate to the starting materials which recombine by reaction at the exocyclic nitrogen (thermodynamic control) <86JOC1910>. The reaction of 2-arylaminothiazoline hydrochlorides with isocyanates and isothiocyanates leads to ureas and thioureas respectively as the result of the attack to the endocyclic nitrogen. However, in both cases no *endo*-nitrogen to *exo*-nitrogen rearrangement is observed under thermal conditions <93H(35)1237>.

2-Aminobenzothiazoles appeared unreactive toward carbon disulfide under base conditions (triethylamine or pyridine). Nevertheless, when a superbasic medium consisting of sodium hydroxide in an aprotic polar solvent, such as DMF, is used, a very fast reaction takes place. The resulting dithiocarbamic acid derivatives can be transformed into dithiocarbamates (170) or dithiocarbonimidates (171) by addition of one or two equivalents of methyl iodide, respectively (Scheme 41) <82S590>.



Scheme 41

N-Formylation of 2-aminobenzothiazoles is achieved by treatment with *N*-phenyl formamide and two equivalents of benzenesulfonyl chloride in pyridine as a solvent <88CCC311>. Condensation of 2-aminobenzothiazole with dimethylacetylenedicarboxylate in ethanol affords pyrimido-benzothiazolones (172). Similar heterocyclic systems are obtained when 2-aminobenzothiazoles are treated with ethylbenzoyl acetate in polyphosphoric acid (Scheme 42) <88JHC949>.



Scheme 42

2-Aminothiazole reacts with diazaminium perchlorates to yield 1,3,5-triazinium perchlorates <94JHC535>. 2-Aminothiazole also reacts with hetaryl nitroso compounds to give the corresponding azo compounds <88JHC1663>.

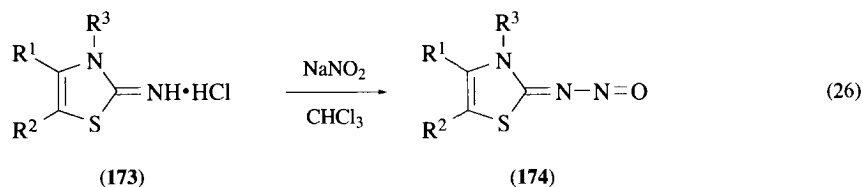
The reaction of 2-aminobenzothiazole with propylene glycol in methanol at room temperature causes the opening of the heterocyclic ring affording *o*-aminothiophenols <93ZOR209>. A similar

ring-opening arises from the treatment of 4,7-dimethylbenzothiazoles with potassium hydroxide in ethyleneglycol <93SC663>. 2-Aminothiazole can also act as a suitable nucleophile in Mitsunobu reactions when the exocyclic nitrogen is protected as a carbamate <95TL6463>.

3.06.7.5.2 Reactions with nitrous acid: diazotization

2-Aminothiazole is easily diazotized in a concentrated solution of nitric and phosphoric acid. A large-scale procedure for the diazotization of 2-aminothiazole and its conversion to 2-bromothiazole has been reported <B-92M 306-02>. The synthesis of 2-halothiazoles can be easily achieved from 2-aminothiazole by (i) diazotization and (ii) treatment with CuCl, CuBr, or NaI <85JHC1621>. When the diazonium salt derived from 2-aminothiazole is treated with sodium azide the 2-azido derivative in equilibrium with its tetrazole cyclization product are obtained <92BMC1603>.

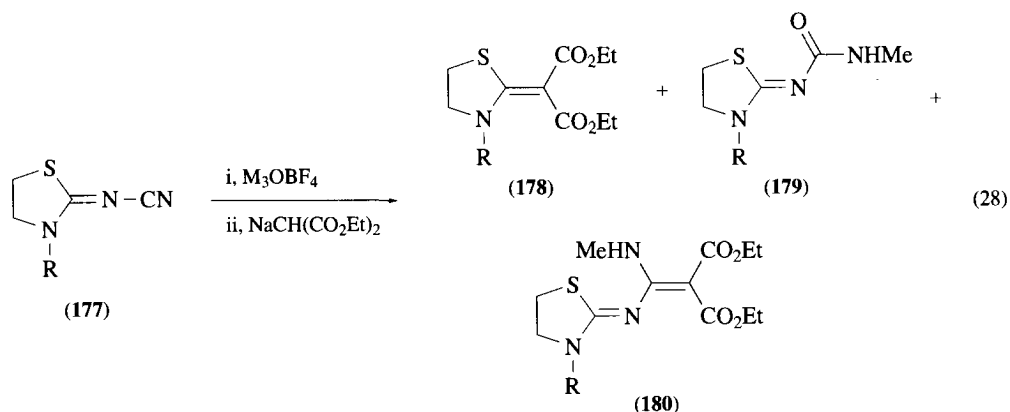
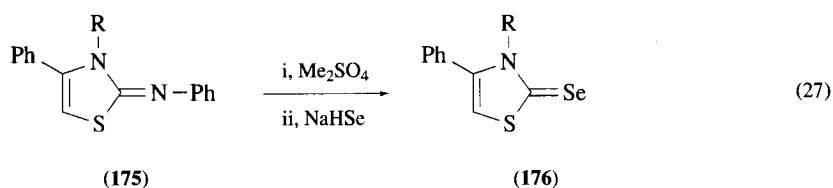
Treatment of the imino compounds (173) with sodium nitrite in chloroform affords nitrosimines (174) (Equation (26)) <94AP(327)581>. Compounds (174) are rapidly degraded to give 2-thiazolones through the photolytic cleavage of the N—NO bond and extrusion of N₂ <94AP(327)359>.



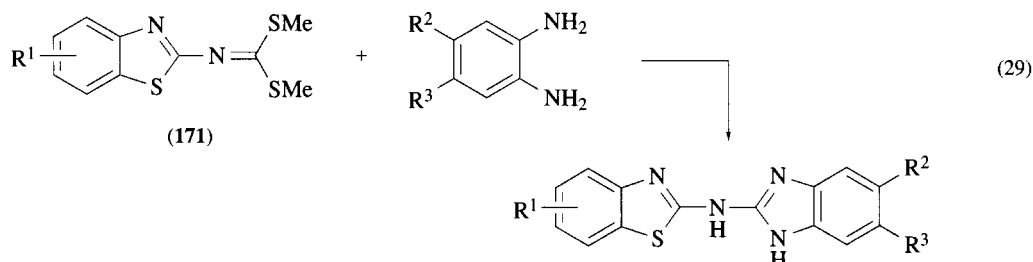
A study of the diazotization mechanism of 2-aminothiazole has shown that 2-aminothiazole is protonated at the endocyclic nitrogen and then attacked by the NO⁺ ion, the final status of the process being an equilibrium between the protonated form and the diazonium salt <89HCA800>.

3.06.7.6 Other N-Linked Substituents

Methylation of iminothiazolines (175) followed by reaction with NaHSe gives 2-selenoxothiazolines (176) (Equation (27)) <84PJC447>. 3-Alkyl-2-(N-cyanoimino)thiazolidines (177) are methylated with trimethyloxonium tetrafluoroborate; the resulting nitrilium salts react with sodium diethyl malonate to afford methylenethiazolidines (178) and urea derivatives (179) along with the iminothiazolidines (180) (Equation (28)) <93H(36)55>.

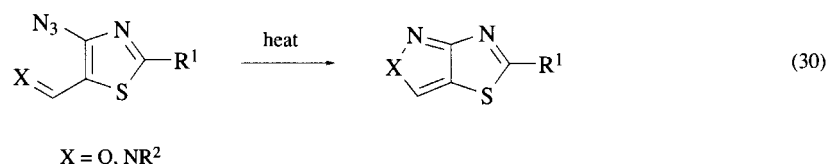


Dithiocarbamates (**171**) react with dinucleophiles such as 1,2-phenylenediamines to give bis-heterocyclic compounds (Equation (29)) linked by an amino bridge <82S1066>.

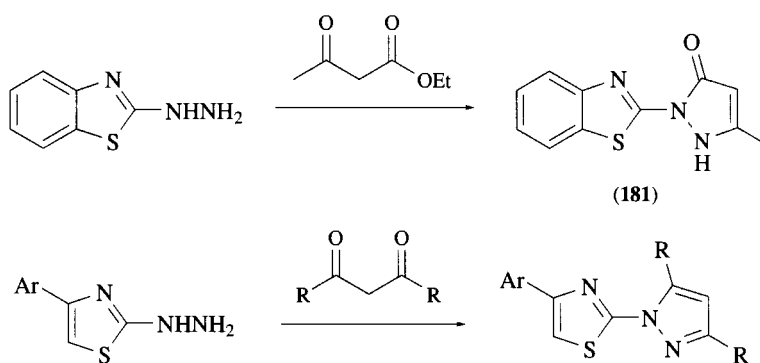


The reaction can be extended to other dinucleophiles like aliphatic diamines, diaminopyridines, diaminopyrimidines <85S867>, 2-aminothiophenol, or 2-aminophenol <87S368>. Isocyanatothiazoles are highly reactive compounds which upon treatment with nucleophiles afford the corresponding adducts <91JHC1003>. These adducts can be elaborated to further functionalized compounds <91JHC1013>.

Heating of 4-azidothiazoles having an imino or aldehyde group at the 5-position affords fused pyrazolo- and isoxazolo[3,4-*d*]thiazoles (Equation (30)). When an alkenyl group is in 5-position of the thiazole ring, 4*H*-pyrrolo[2,3-*d*]thiazoles are obtained <92JCS(P1)973>.

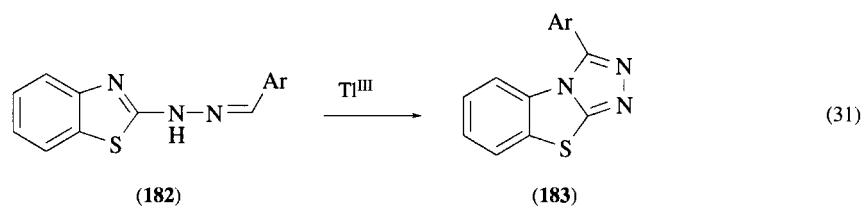


Condensation of 2-hydrazinobenzothiazoles with a variety of electrophiles leads to interesting intermediates in the synthesis of useful heterocycles <88BCJ1339>. In particular, the reaction of 2-hydrazinobenzothiazole with ethyl acetoacetate gives the corresponding pyrazolone (Scheme 43). An identical reaction takes place with 2-hydrazinobenzothiazoles and 1,3-dicarbonyl compounds to give pyrazoles <88JHC543>.



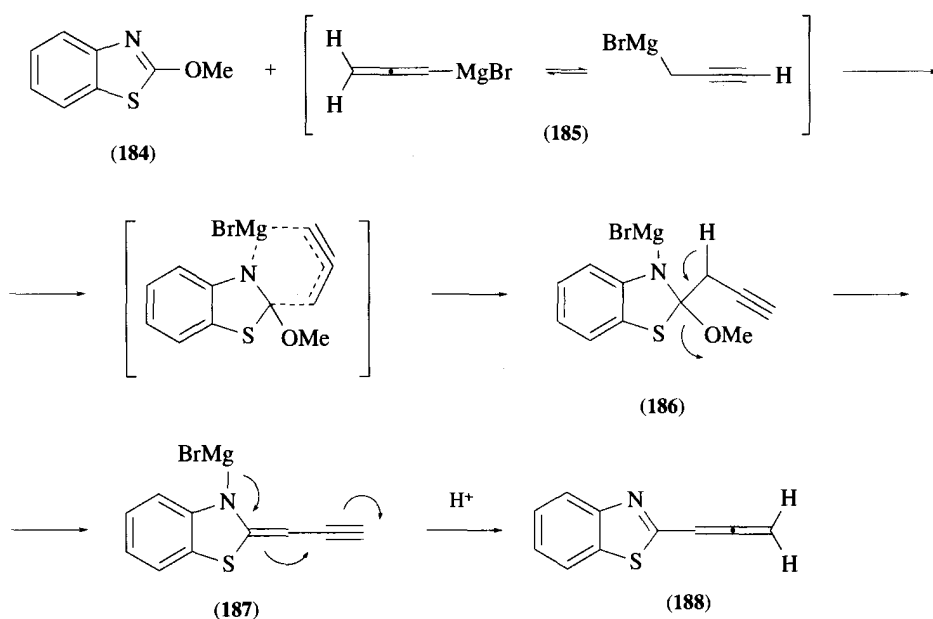
Scheme 43

2-Benzothiazolyhydrazones (**182**) can be oxidized with thallium(III) salts to afford triazolo [3,4-*b*]benzothiazoles (**183**) by intramolecular cyclization (Equation (31)) <94SC2627>.



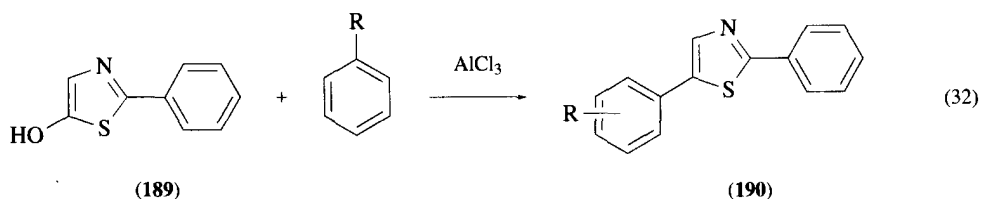
3.06.7.7 O-Linked Substituents

The tautomerism of hydroxythiazoles has been discussed in Section 3.06.4.4. The reactivity of hydroxythiazoles is well-documented in CHEC-I <84CHEC-I(4)285>. 2-Methoxy benzothiazole (**184**) has been found to react with allenylmagnesium bromide (**185**) to produce 2-allenylbenzothiazole (**188**), the formation of which can be rationalized in terms of a S_Ei' mechanism involving the attack of the allenic form of the Grignard reagent followed by the elimination of methanol and isomerization of the intermediate (**187**) (Scheme 44) <86S638>.



Scheme 44

5-Hydroxythiazol (**189**) reacts with aromatic compounds in the presence of catalytic aluminum trichloride to afford 5-arylthiazoles (**190**) (Equation (32)) <87RRC1175>.



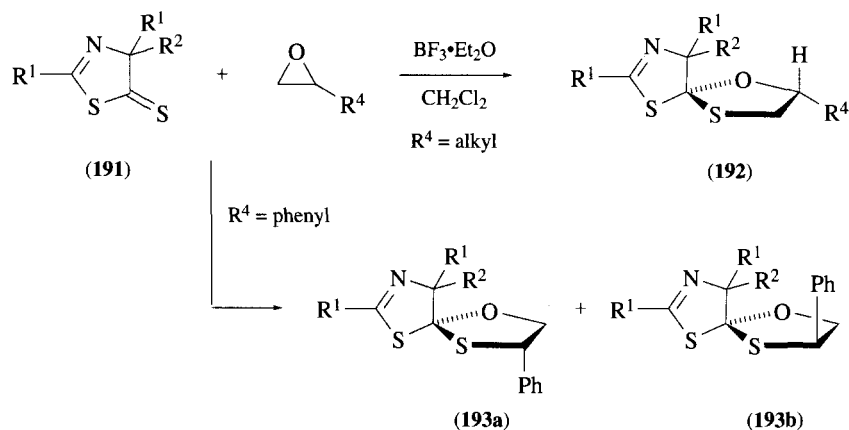
3.06.7.8 S-Linked Substituents

3.06.7.8.1 Thiones

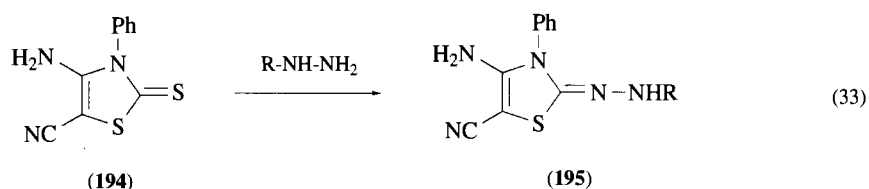
The reaction of 1,3-thiazole-5-(4*H*)-thiones (**191**) with alkyl oxiranes in the presence of catalytic boron trifluoride etherate gives rise exclusively to spiroderivatives (**192**) in good yields (Scheme 45) <90HCA2287>.

On the other hand, the reaction of (**191**) with phenyl oxirane affords a mixture of the spiro-derivative isomers (**193a**) and (**193b**).

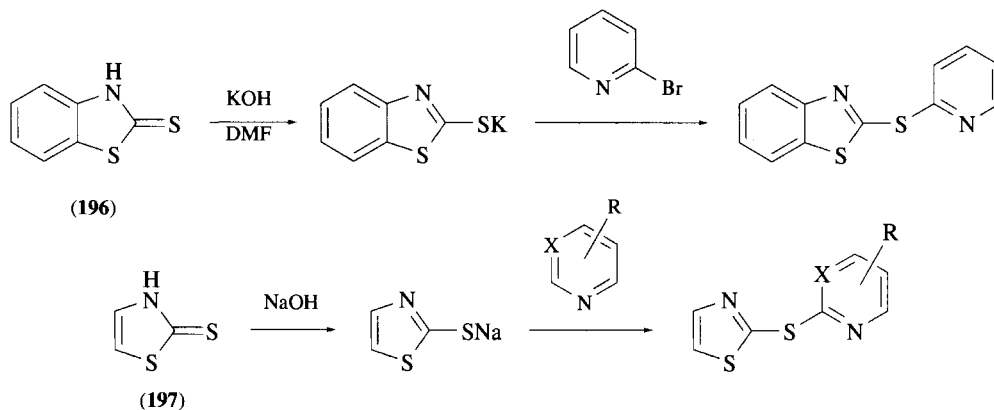
Thione (**194**) reacts with hydrazine hydrate and phenylhydrazine to give the hydrazone derivatives (**195**) (Equation (33)) <94JCR(S)126>.



Scheme 45



2-Thiobenzothiazole (**196**) reacts with alkyl halides $\langle 89\text{KGS1289} \rangle$ and α -haloketones $\langle 89\text{IZV158} \rangle$ in a basic medium to give the corresponding *S*-alkyl derivatives. In fact, the action of bases on (**196**) generates an anion which can act as a nucleophile. As an example, the potassium salt of (**196**) gives rise to substitution reactions in a pyridine nucleus $\langle 87\text{H}(26)427 \rangle$. Analogously, the sodium salt of 2-mercaptothiazole (**197**) reacts with 2-chloropyridine, pyrimidines, and pyrazines to give the corresponding products of substitution reaction (Scheme 46) $\langle 93\text{CPB1258} \rangle$.

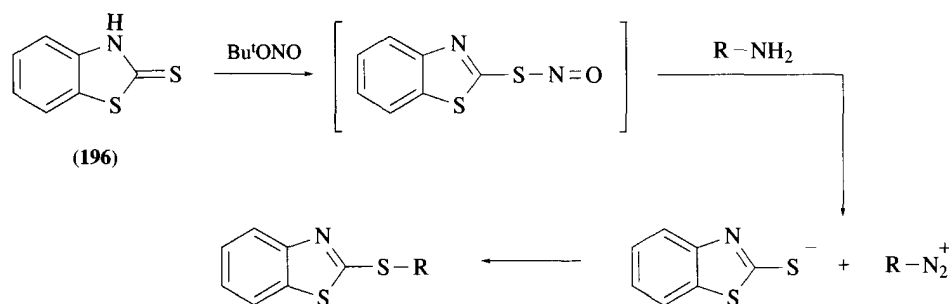


Scheme 46

Nucleophilic attack of the sulfur atom can also occur in the absence of bases. Compound (**196**) reacts with primary amines in the presence of *t*-butyl nitrite to afford the *S*-alkylated products by the mechanism outlined in Scheme 47 $\langle 84\text{TL2675} \rangle$. In this reaction 2-thiobenzothiazole acts as an efficient nitroso transfer reagent.

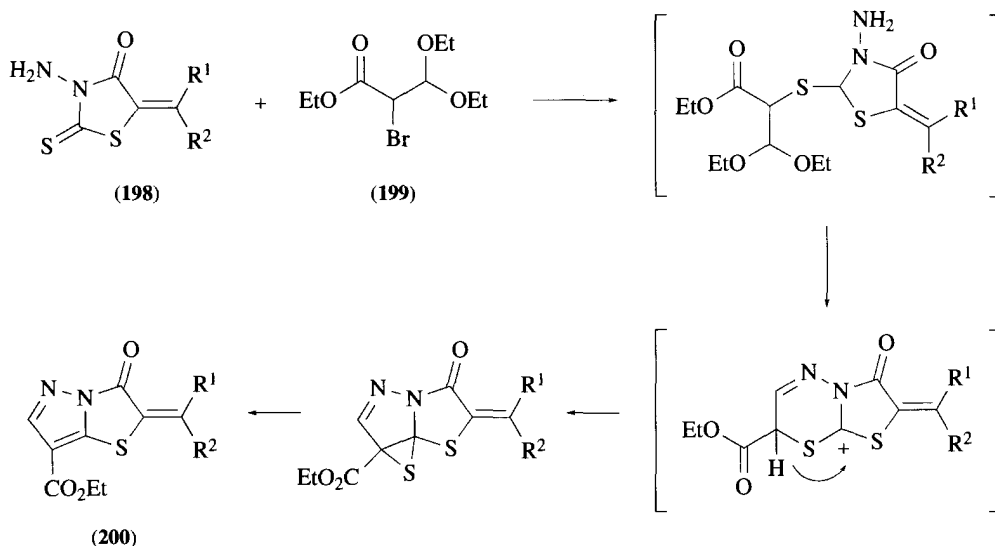
2-Thiobenzothiazole (**196**) readily adds to conjugated azoalkanes in methanol or tetrahydrofuran giving α -(benzothiazolylthio)hydrazones. The reaction takes place through the 1,4-addition of (**196**) to the azo-ene system of conjugated azoalkenes $\langle 95\text{JOC149} \rangle$.

The nucleophilicity of the sulfur atom in thiazolidine thiones has allowed the preparation of a series of gold(I) coordination compounds $\langle 94\text{POL753} \rangle$. 3-Aminorhodanines (**198**) react with ethyl 2-bromo-3,3-diethoxypropionate (**199**) to give pyrazolo[5,1-*b*]thiazoles (**200**) through a tandem



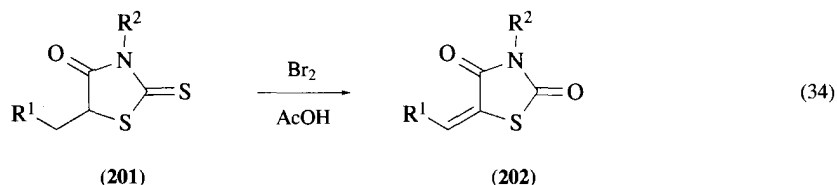
Scheme 47

condensation-sulfur extrusion reaction in which the first step is the nucleophilic substitution of the bromine atom by the sulfur atom (Scheme 48) <94JHC1719>. Thiazole-5-(4*H*)-thiones are oxidized at the sulfur atom with *m*-chloroperbenzoic acid giving the corresponding thione oxides <94HCA2133>.



Scheme 48

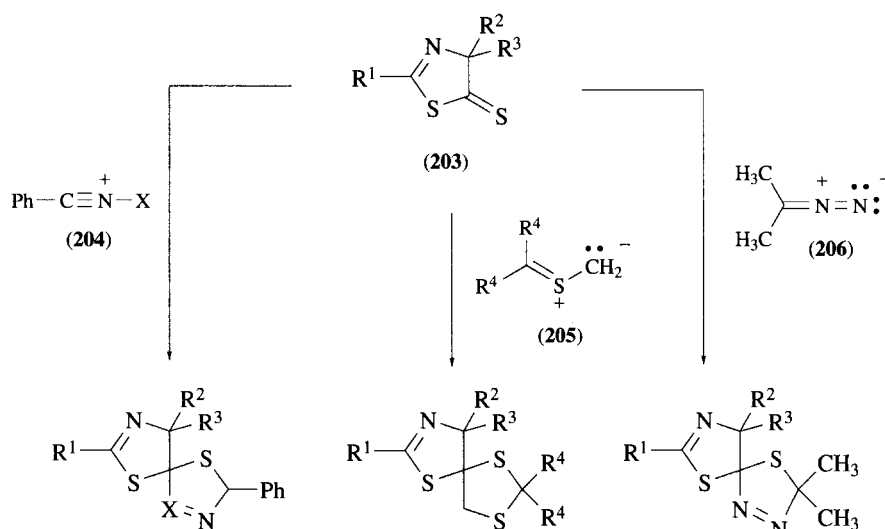
Oxidation of 5-substituted-2-thioxo-4-thiazolidinones (201) with bromine in acetic acid yield 2,4-thiazolidinediones (202) as shown in Equation (34) <91BCJ750>.



Treatment of rhodanines with an excess of zinc dust in acetic acid leads to the reduction of the thio group yielding 4-thiazolidinones <94TL6971>.

The exocyclic $\text{C}=\text{S}$ bond of 5-thioxo-2-thiazolines (203) can act as a dipolarophile towards several compounds. For instance, cycloaddition reactions have been reported with nitrilium betaines (204) to give heterocyclic spiro compounds <84HCA534>, with thiocarbonyl ylides (205) to give spirocyclic 1,3-dithiolanes <91HCA1386>, and with 2-diazopropane (206) to give thiadiazoles <92HCA1825>. On the other hand, the reaction of (203) with diazomethane leads to a mixture of five products (Scheme 49) <93HCA1715>.

Hetero-Diels-Alder reactions are also possible with (203) as dienophile. The reaction is reversible and the regioselectivity depends on the frontier orbital control as well as steric factors <88HCA2071>.

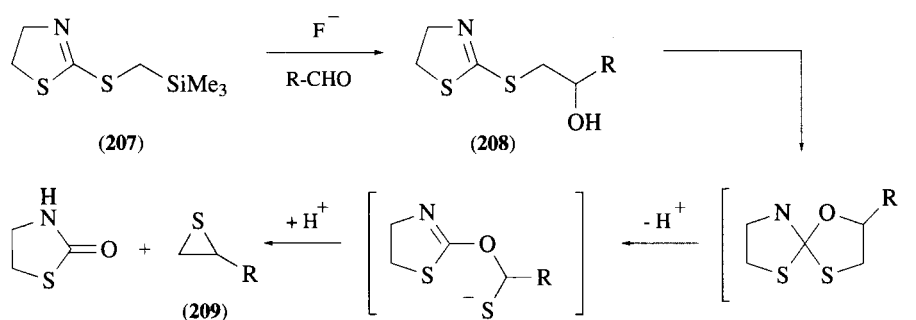


Scheme 49

3.06.7.8.2 Alkylthio groups

Deprotonation of 2-methylthiobenzothiazole is effectively carried by treatment with butyllithium at -78°C . The resulting anion can be alkylated with a variety of alkyl halides $\langle 87\text{JCS(P1)769} \rangle$.

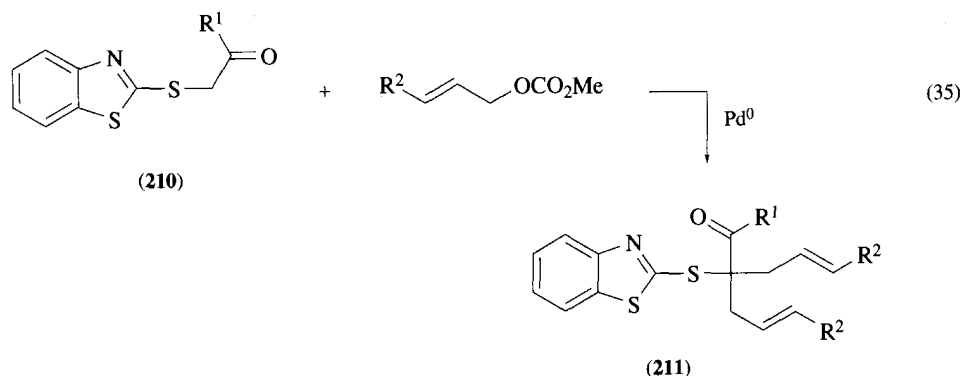
2-Trimethylsilylmethylthiobenzothiazole (207) reacts with aromatic aldehydes in the presence of fluoride ion $\langle 93\text{H(36)2673} \rangle$. When an equivalent amount of tris(dimethylamino)-sulfur(trimethylsilyl)difluoride (TASF) is used as the fluoride ion source, the expected thioethanol derivatives (208) are obtained. However, the use of caesium fluoride leads to thiirans (209) and thiazolidin-2-one (Scheme 50). The formation of thiirans may be considered to occur in a step-wise manner via (208) and promoted by the basicity of caesium fluoride. The same reaction takes place with 2-trimethylsilylmethylthiobenzothiazole.



Scheme 50

Methylthio groups can be oxidized to sulfoxides with *m*-chloroperbenzoic acid in a similar manner to thioxo groups $\langle 94\text{HCA2133} \rangle$ (see Section 3.06.7.8.1). Oxidation with potassium permanganate leads to sulfonyl derivatives. Nucleophilic substitution of a methylthio group can be attained in a cross-coupling reaction with Grignard reagents $\langle 91\text{H(32)2127} \rangle$.

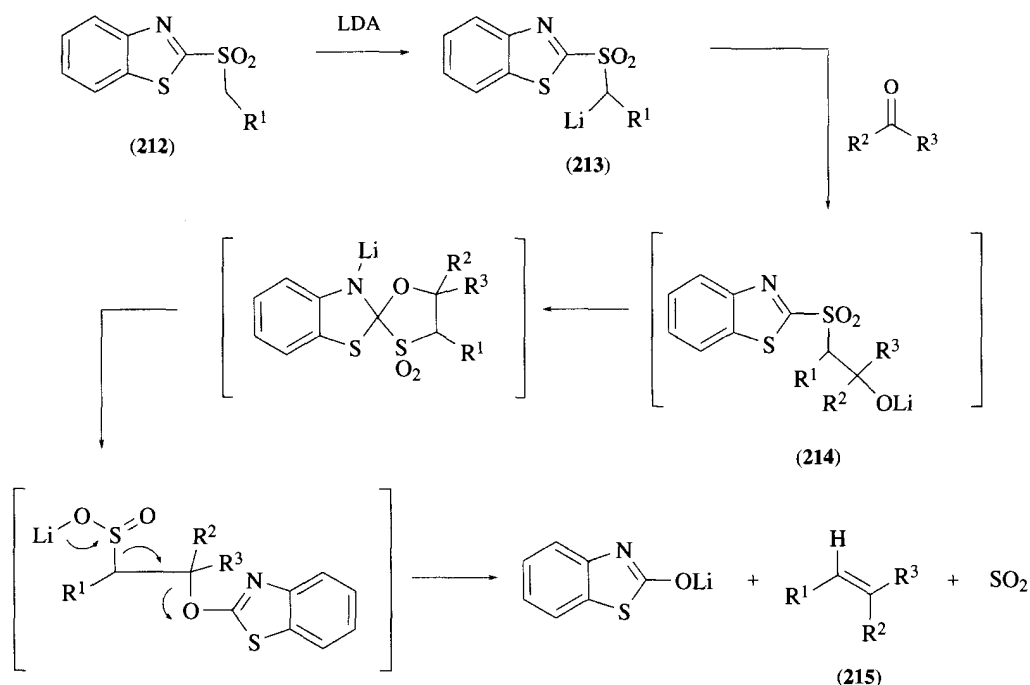
α -Ketosulfides of benzothiazole (210) react with allylic carbonates in the presence of palladium acetate and triphenylphosphine to give α,α -diallylated ketosulfides (211) in high yields (Equation (35)) $\langle 95\text{TL1913} \rangle$.



2-Methylthiothiazole is demethylsulfenylated by the action of lithium in liquid ammonia to give thiazole after hydrolysis with aqueous ammonium chloride <85S948>.

3.06.7.8.3 Other substituents

Alkylsulfonyl benzothiazoles (212) are readily metalated at α -position with LDA. The resulting α -lithio derivatives (213) react with carbonyl compounds to give lithium alkoxides (214). These intermediates undergo an intramolecular addition to the $\text{C}=\text{N}$ bond of the thiazole ring and the resulting spiro derivative evolves in such a way that simultaneous extrusion of sulfur dioxide and formation of 2-(3*H*)-benzothiazolone anion and alkenes occurs <91TL1175>. In this process, the alkenes (215) are formed through an *anti*-periplanar elimination (Scheme 51) <93BSF336>. The regioselectivity of the reaction depends on both aldehydes and sulfones. In general, (*E*)-alkenes are obtained except with propargylic benzothiazolyl sulfones and saturated or aromatic aldehydes in which case (*Z*)-alkenes are the major products <93BSF856>.

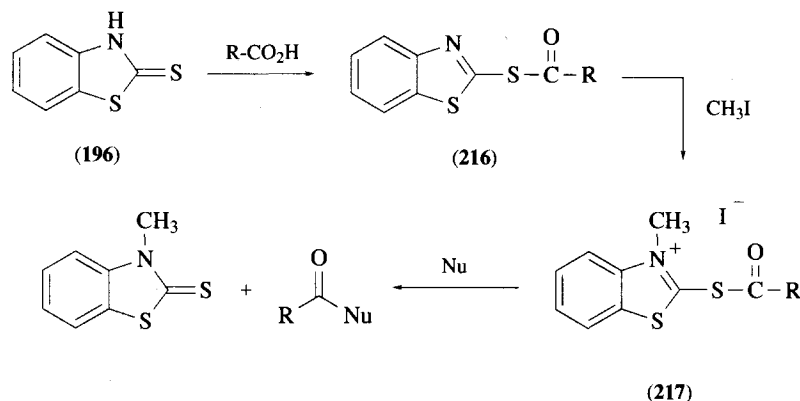


Scheme 51

2-Benzothiazolyl disulfide reacts with sugar hemiacetals to give, in a $\text{S}_{\text{N}}2$ process, the corresponding 2-benzothiazolyl thioglycosides. The reaction is promoted by phosphines bearing at least two alkyl groups <93LA1211>.

2-Thiobenzothiazole (196) also serves as activating agents of carboxylic acids by formation of

thioesters (**216**). These compounds can be quaternized with methyl iodide making the thio-benzothiazolyl group a more efficient leaving group when salts (**217**) are treated with nucleophiles (Scheme 52) <89TL6089>.

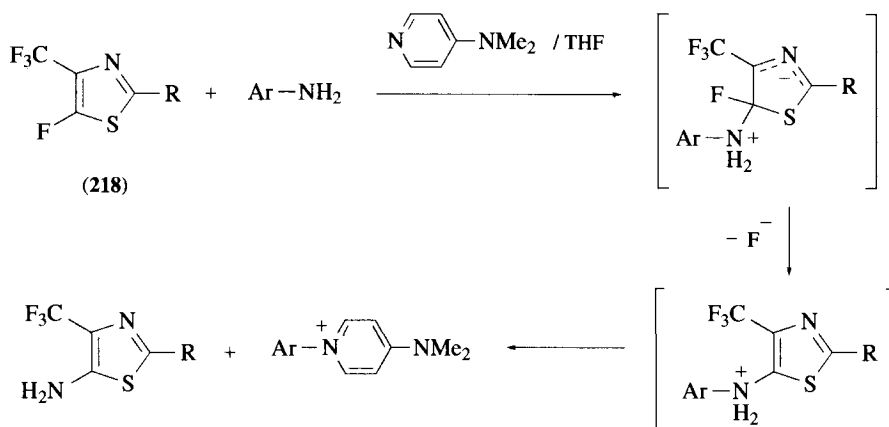


Scheme 52

3.06.7.9 Halogen Atoms

3.06.7.9.1 Nucleophilic displacement

Halothiazoles undergo nucleophilic displacement of the halogen atom by alkoxides and thiolates <84CHEC-I(4)232>. The reaction occurs also with nitrogen nucleophiles. For instance, 4-chlorothiazoles react with sodium azide in DMSO to give 4-azidothiazoles <92JCS(P1)973>. 5-Fluoro derivatives (**218**) give nucleophilic substitution reactions also with aromatic amines in the presence of *N,N'*-dimethylaminopyridine (dmap) to give 5-aminothiazole derivatives (Scheme 53) <90S357>.



Scheme 53

Similarly, 2-halothiazoles and 2-halobenzothiazoles undergo nucleophilic substitution reactions with aliphatic amines <91CC306>. The displacement of the halogen atom can also be made by other halogen atoms. Thionyl chloride substitutes bromine by chlorine in 2-bromo-5-thiazolyl carboxylic acid <93H(36)565>. 2-Fluorothiazoles are obtained by reaction of 2-chlorothiazoles with potassium fluoride <85JHC1621>. Treatment of 2-bromothiazole with a tertiary phosphine gives a reductive dehalogenation reaction <92PS(66)73>. When the reaction is carried out in hydroxyl-containing solvents, thiazole, and the phosphine oxide are obtained.

3.06.7.9.2 Halogen–lithium exchange

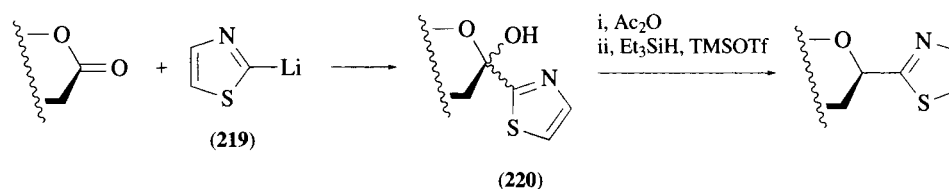
Only thiazoles bearing a bromine atom at C-2 and/or C-5 give halogen–lithium exchange. Thus, treatment of 2- and 5-bromothiazoles with butyllithium affords 2- and 5-lithiothiazoles, respectively. The reaction with 4-bromothiazole under the same conditions leads exclusively to deprotonation at C-2 <88JOC1748>, although a number of substituted 4-bromothiazoles react with butyllithium to give the corresponding 4-lithio derivatives <87S998>. The low reactivity of a bromine atom at C-4 is attributed to the effect of the adjacent nitrogen lone pair which destabilizes a developing negative charge at C-4 <92JCS(P1)215>. The dehalogenation reaction does not occur with chlorothiazoles which, instead, are deprotonated by lithium diisopropyl amide (LDA) or butyllithium <90JCS(P1)329>. In general, organolithium reagents such as butyllithium, phenyllithium, or methyllithium are preferred for bromine–metal exchange whilst lithium amides like LDA or KDA are used for deprotonation (see Section 3.06.5.7.1). The adequate choice of both base and substrate allows the selective metalation of polyhalothiazoles. While 2,4-dibromothiazole only affords 4-bromo-2-lithiothiazole upon treatment with butyllithium <86S757>, 2,5-dibromothiazole undergoes bromine–lithium exchange at both C-2 and C-5 <81JCS(P1)2335>. The products obtained upon treatment of polyhalothiazoles with one equivalent of butyllithium depend on time and temperatures of the reaction <92JCS(P1)215>.

3.06.7.10 Metals and Metalloid-linked Substituents

3.06.7.10.1 Lithium

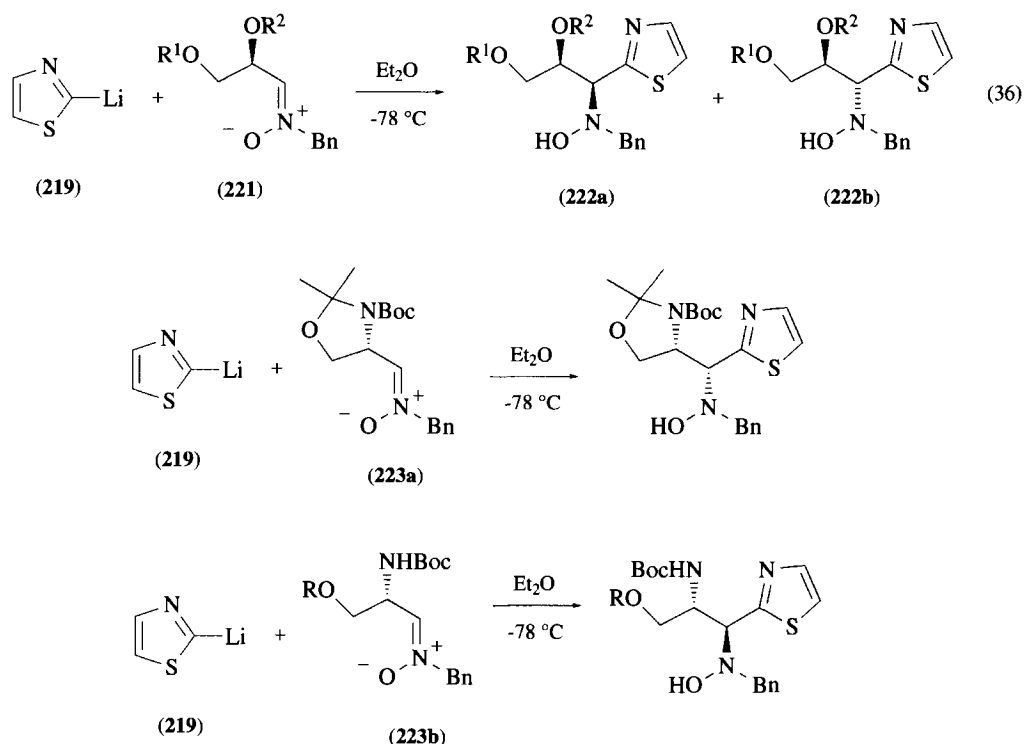
The reaction of lithiated thiazoles with electrophiles takes place smoothly in any position. Since the easiest position to metalate is C-2, most reactions have been described for 2-lithioderivatives. Both 2-lithiothiazole and 2-lithiobenzothiazole are unstable above -50°C and therefore particular care has to be taken for the *in situ* preparation of these organometallic reagents <94JOC6404>. Decomposition of 2-lithiobenzothiazole was demonstrated by the recovery of percentages of the parent heterocycle after quenching the anion solution with water at various temperatures <88BCJ3637>. Some reactions of 2-lithiothiazole (**219**) with various electrophiles have been already described <84CHEC-I(4)232>. New reactions are reported below and synthetic applications are given in Section 3.06.12.2. 5-Lithiothiazoles have been made to react with aromatic ketones to give the corresponding carbinols in good yields <88CJC1617> as well as other electrophiles (i.e., amides, acyl chlorides, chlorosilanes, disulfides) to give the corresponding adducts <91JHC1017>.

Among the new reactions of (**219**), quite significant for their potential in synthetic methodologies (see Section 3.06.12.2) are the substitution on esters to give thiazolyl ketones <89T5141, 91CC1313, 91CC1576, 93SI1162> and the addition to sugar lactones to give thiazolyl ketols (**220**) <93TL7319, 94JOC6404>. In the latter case either the kinetic and thermodynamic anomer can be trapped as the corresponding *O*-acetyl derivative. The silane reduction of these compounds leads to thiazolyl glycosides (Scheme 54). The thermolysis of ketols (**220**) either in solution (toluene, DMSO) or in the absence of solvent, gives thiazole and the corresponding sugar lactones almost quantitatively. The elimination of thiazole as thiazolium 2-ylide is suggested to be the driving force of this unusual reaction <96UP 306-01>.



Scheme 54

2-Lithiothiazole (**219**) also reacts with C=N electrophiles such as nitrones to give thiazolyl hydroxylamine derivatives. When the reaction is carried out with chiral α,β -dialkoxynitrones (**221**) (Equation (36)) the major product is the *syn* adduct (**222a**). A reversal of diastereoselectivity in favor of the *anti* isomer (**222**) is achieved through the precomplexation of the nitron with diethyl aluminum chloride <92TL4221, 93TL5475, 95MI 306-01>. On the other hand, the *syn-anti* stereocontrol of the addition to L-serine derived nitrones (**223a**) and (**223b**) appeared to be effectively achieved by the double or single protection of the α -amino group (Scheme 55) <94CC1731>.



Scheme 55

The addition of (219) to α,β -dialkoxynitrones (220) can be rationalized by assuming a transition state model A (Figure 2) similar to that involved in nucleophilic addition to $\text{C}=\text{C}$ (Houk model) <82JA7162>. The reversal of stereoselectivity induced by diethyl aluminum chloride is consistent with a β -chelation model B. The scope and the synthetic utility of these reactions have been amply demonstrated <95MI 306-01>.

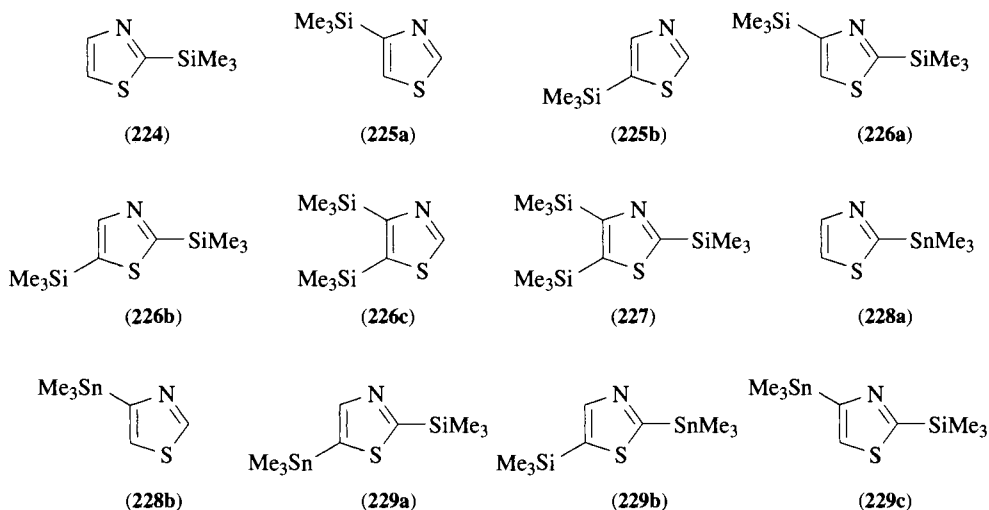


Figure 2 Conformation of the α -alkoxynitrones and sites of addition of (213) to the $\text{C}=\text{N}$ bond (see arrows).

The reaction of 2-lithiothiazole (219) with isothiocyanates affords thioamides <86KGS1405>. Lithiothiazoles have been employed in preparing amino(thio)carbene complexes of chromium <85OM275> and gold <90CC1722>. Organometallic complexes with iron can also be obtained using (219) as a source of thiazole <92JCS(D)1009>.

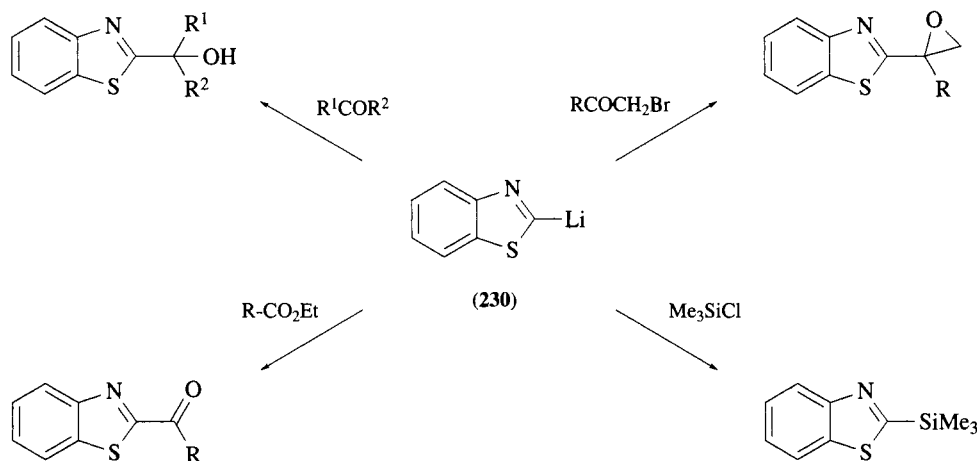
Lithiothiazoles are the starting material for the preparation of other metalated thiazoles. The generation of (219) from 2-bromothiazole and butyllithium followed by transmetalation with trimethylsilyl chloride can be carried out in one-pot and multigram scale to give the stable and synthetically important organometallic reagent 2-trimethylsilylthiazole (224) <81CC655, 95OS(72)21>. A less practical synthesis of (224) through (219) generated from thiazole has been also reported <B-87MI 306-04>. By this technique, all possible mono- and bis-trimethylsilylthiazole regioisomers (225) and (226), and the tris-trimethylsilyl derivative (227) have been prepared <88JOC1748>. In the same way, 2- and 4-trimethylstannylthiazoles (228a) and (228b) were obtained from the corresponding

lithio derivatives and trimethyltin chloride $\langle 86S757 \rangle$. Mixed silyl and stannyl thiazoles (**229**) have been also prepared $\langle 86S757 \rangle$. It is noteworthy that all silyl and stannyl thiazoles are isolable and stable organometallic reagents.



Unstable metalated thiazoles can be generated *in situ* from 2-lithiothiazole (**219**) by transmetalation with an appropriate reagent. The cuprate is obtained by the use of a suspension of copper(I) bromide in THF $\langle 87JOM(332)95 \rangle$; the magnesium bromide and ethylaluminum chloride are obtained by the use of magnesium bromide etherate or diethylaluminum chloride, respectively $\langle 93SL78, 93TL5475 \rangle$.

In a similar way to 2-lithiothiazole (**219**), 2-lithiobenzothiazole (**230**) reacts with C-electrophiles as indicated in Scheme 56 $\langle 85H(23)295 \rangle$. Particularly interesting is the reaction of (**230**) with carbonyl compounds, i.e., aldehydes and ketones $\langle 88BCJ3637 \rangle$, due to its potential application in organic synthesis (see Section 3.06.12.2). Transmetalation of (**230**) with Me_3SiCl leads to 2-trimethylsilylbenzothiazole $\langle 73CB594, 82JOC1489 \rangle$.

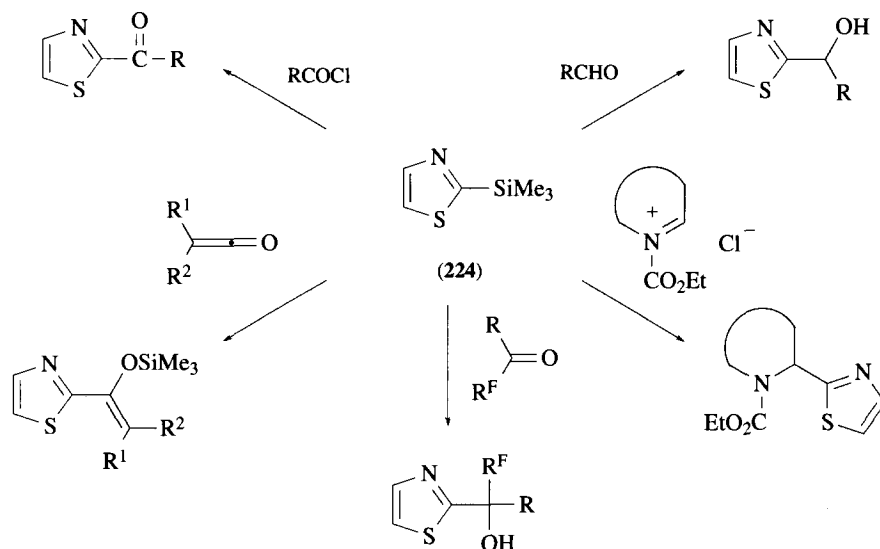


Scheme 56

3.06.7.10.2 Silicon

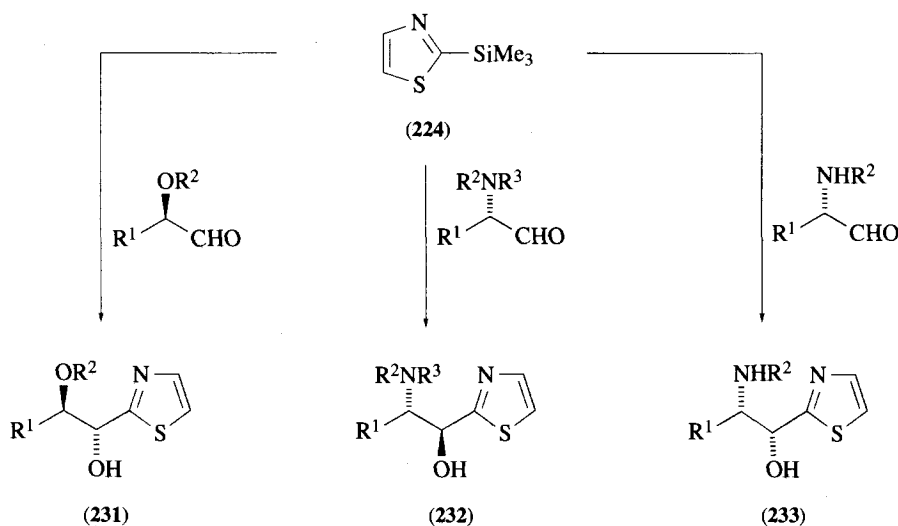
2-Trimethylsilylthiazole (**224**) reacts smoothly with various C-electrophiles to give the corresponding products of carbodesilylation reaction (See Scheme 57). In early work, Dondoni and co-workers have described reactions with ketenes $\langle 81CC655 \rangle$, acid chlorides $\langle 83TL2901 \rangle$, heteroaryl cations $\langle 84TL3637 \rangle$, and aldehydes $\langle 88JOC1748 \rangle$. In the mid-1990s, reaction with fluorinated ketones

has been reported by the same group <95S654>. It is noteworthy that all the reactions of Scheme 57 occur without activation by any added fluoride ion source. This peculiar feature is the basis of a mechanistic rationale which has been advanced for these reactions as shown in Scheme 59.



Scheme 57

Among the reactions of 2-trimethylsilylthiazole (224) shown in Scheme 57, that with chiral aldehydes is of considerable synthetic potential (see Section 3.06.12.2) because of its generality, high yield, and level of stereoselectivity <85TL5477, 86AG(E)835, 92S201, 93OS(72)21>. The reaction with α -alkoxy aldehydes leads to the *anti* adducts (231) preferentially <89JOC693>. This stereochemical outcome has been confirmed in further studies <92S201, 94CJC237>. The *anti* adducts (232) are also obtained with *N,N*-diprotected α -amino aldehydes whereas with *N*-monoprotected derivatives the *syn* adducts (233) are the major products (Scheme 58) <90JOC1439, 95JOC8074>. The enormous synthetic potential of these reactions is discussed in Section 3.06.12.2.1.



Scheme 58

The *anti*-addition is in agreement with the classical open-chain Felkin–Ahn <82JA7162> transition state model **A** whereas the *syn*-addition can be explained by model **B** that is formed by intramolecular

hydrogen bonding (Figure 3). The latter model is reminiscent of the Cram model that, however, originates from the intervention of external chelating agents <63JA1245>.

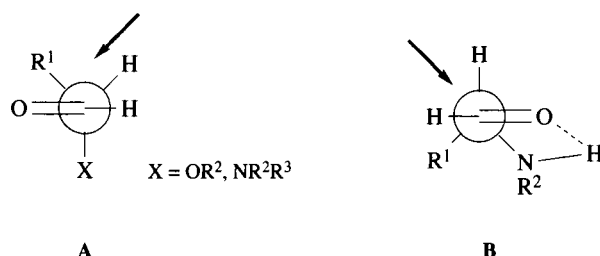
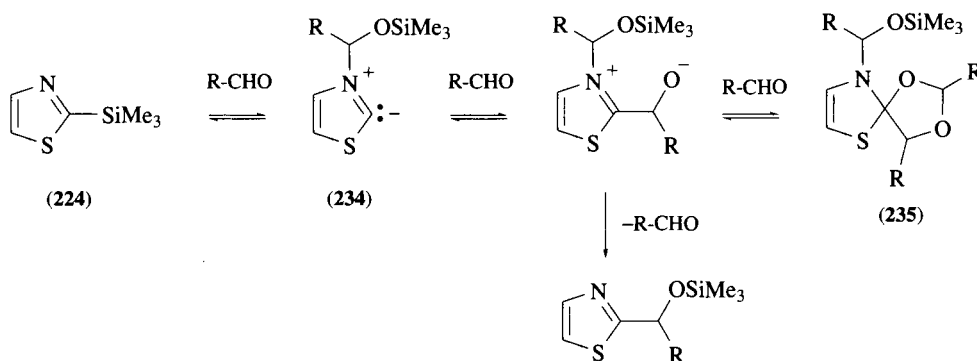


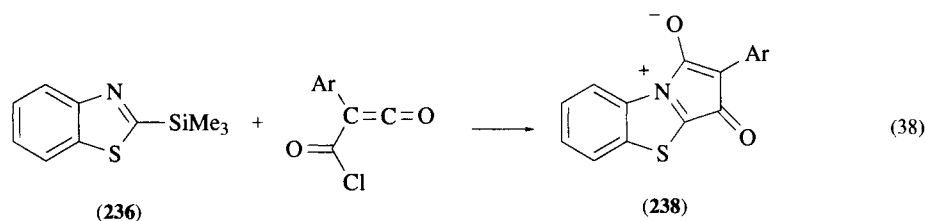
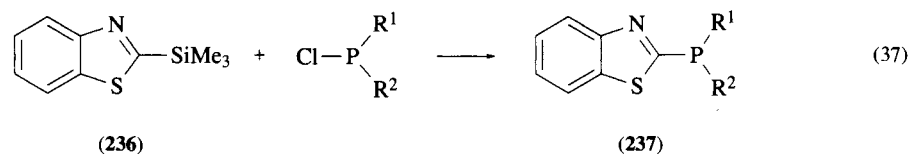
Figure 3 Proposed transition states for the addition of (224) to alkoxy and amino aldehydes.

The mechanism of the reaction between 2-trimethylsilylthiazole (224) and aldehydes has been investigated <93JOC3196>. The kinetic of the reaction and the detection by NMR spectroscopy of a transient aldehyde-thiazole 3:1 adduct (235) led to formulate the multi-step process shown in Scheme 59. This is in line with an earlier mechanistic proposal for this reaction <89JOC693>. The self activation of the system through the formation of the 2-ylide (234) explains why this carbodesilylation reaction does not require any activation by added fluoride ion. The same type of mechanism is very likely to be followed for all the reactions of (224) shown in Scheme 57.



Scheme 59

2-Trimethylsilylbenzothiazole (236) also reacts with various carbonyl compounds such as ketones, aldehydes, acid chlorides, and anhydrides <71JHC257, 83JHC1011>. The reactions have been carried out also under fluoride ion <82TL5079> and base catalysis <85CB3872>. Compound (236) appears to react with a model chiral alkoxy aldehyde less stereoselectively than the parent 2-trimethylsilylthiazole (224). The synthetic potential of the carbodesilylation reactions of (236) have not yet been demonstrated. Benzothiazolyl phosphines can be prepared from 2-trimethylsilylbenzothiazole (236) and phosphorous chlorides (Equation (37)) <82JOC1489>. Condensation of (236) with aryl(chlorocarbonyl)ketenes affords betaines (238) (Equation (38)) <88JOC2889>.

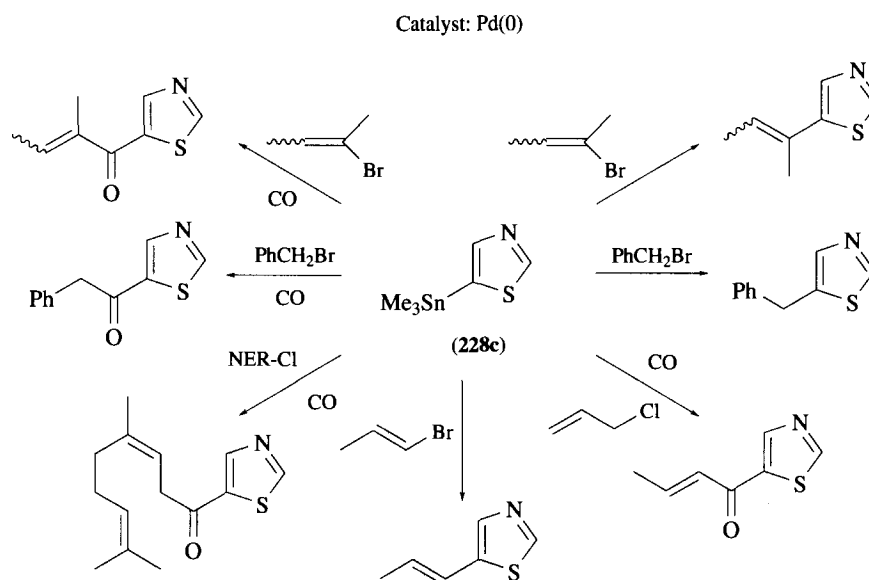


The lability of the silicon-carbon bond in silylthiazoles and benzothiazoles is evidenced by the fact that hydrolytic cleavage can be achieved under mild conditions <73CB594, 81JCS(P2)1051>.

3.06.7.10.3 Tin

The Pd⁰-catalyzed cross-coupling reactions between stannylthiazoles and bromothiazoles represent an interesting route towards thiazole oligomers which are potential precursors to thiazole polymers <87S185, 88G211>. These cross-coupling reactions allow the preparation of both dimers and trimers (276).

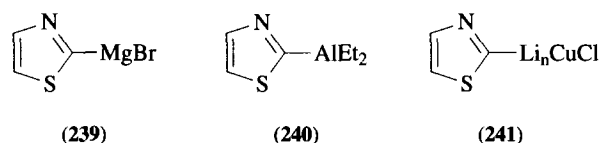
4- and 5-Stannylthiazoles also react with a variety of organic halides through Pd⁰-mediated cross-coupling reactions as shown in Scheme 60 <88G211>.



Scheme 60

3.06.7.10.4 Other metals

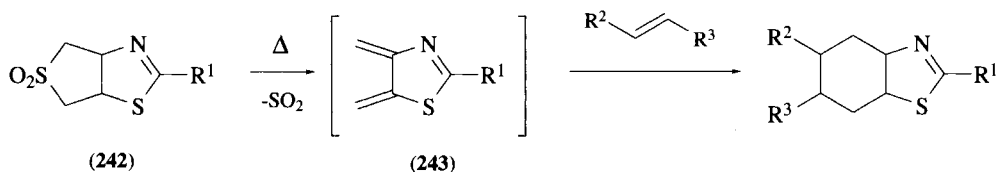
The behavior of 2-thiazolylmagnesium bromide (239) and diethyl 2-thiazolylaluminum chloride (240) is similar to that of 2-lithiothiazole (219). Magnesium and aluminum derivatives of thiazole exhibit a lower reactivity towards electrophiles. For diastereoselective processes the diastereoselectivity is also lower <95MI 306-01, 95UP 306-02>. Thiazolylcuprates (241) lead to monocarbene complexes of copper when they are treated with methyl trifluoromethanesulfonate <94AG(E)672>. Upon treatment with carbon disulfide and methyl iodide lithium 2-thiazolylcuprate affords the corresponding thioester <87JOM(332)95>.



The reaction of a 2-selenobenzothiazole derivative with tributylphosphine is used in the synthesis of 2-alkylselenobenzothiazoles <93CL549>.

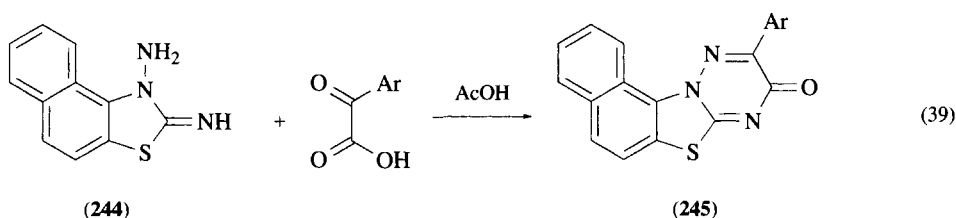
3.06.7.11 Fused Heterocyclic Rings

Thiazole fused 3-sulfolenes (**242**) undergo condensation reactions with typical dienophiles under thermal conditions. The reaction proceeds via the intermediate *o*-dimethylene thiazolines (**243**) as shown in Scheme 61 <92TL4201>.

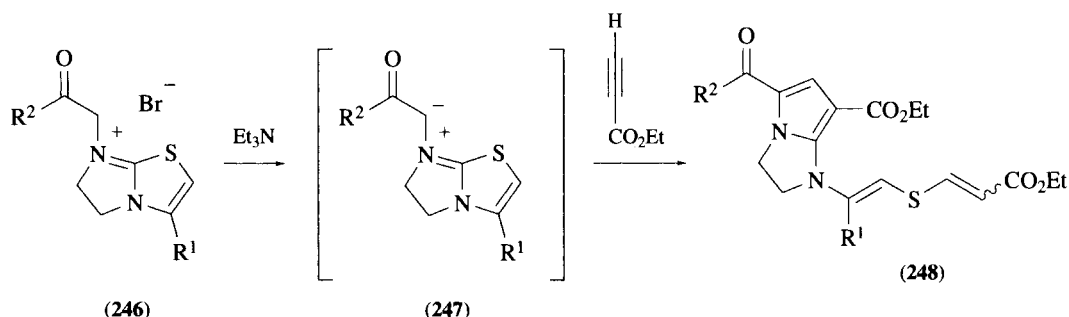


Scheme 61

Naphtho[1,2-*d*]thiazole (**244**) cyclocondensates with glyoxilic acid derivatives to give naphtho-[1',2':4,5]thiazolo[3,2-*b*][1,2,4]triazin-9-ones (**245**) (Equation (39)) <93JHC1331>.



Imidazo[2,1-*b*]thiazolium bromides (**246**) react with ethyl propiolate to give pyrrolo[1,2-*a*]imidazoles (**248**). The reaction must be carried out in the presence of triethylamine which generates the intermediate betaine (**247**) as indicated in Scheme 62 <92JOC2347>.

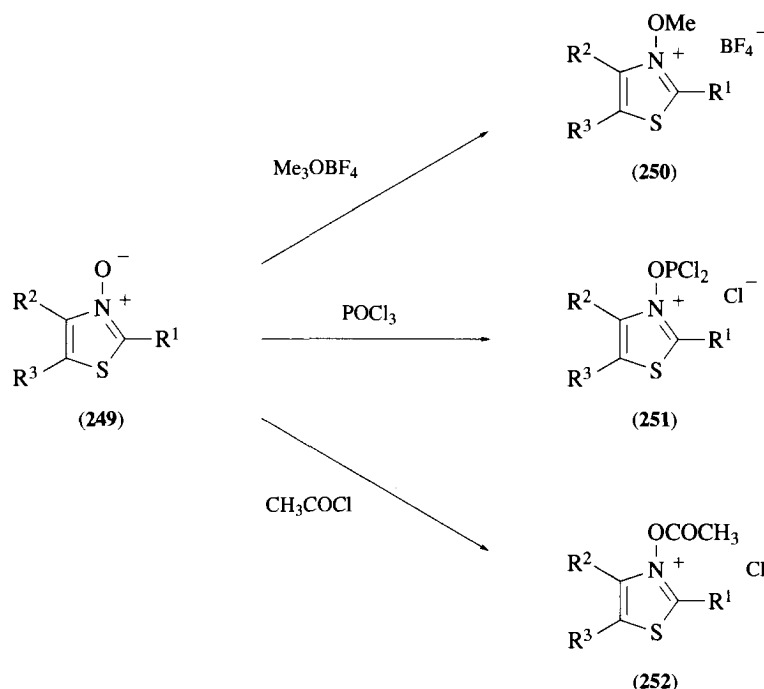


Scheme 62

3.06.8 REACTIVITY OF SUBSTITUENTS ATTACHED TO RING HETEROATOMS

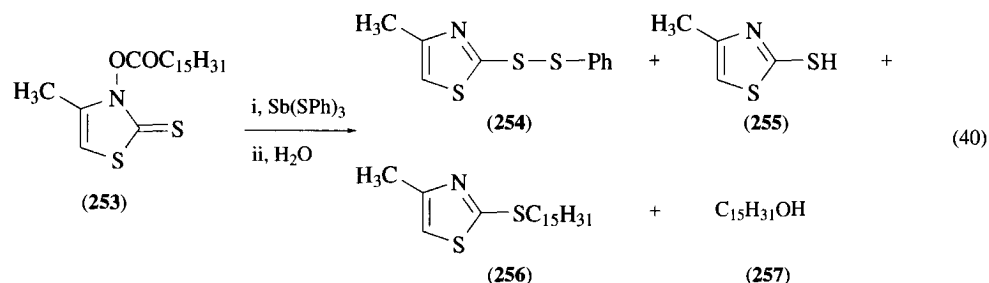
3.06.8.1 Substituents Attached to Ring Nitrogen Atom

Thiazole *N*-oxides (**249**) are readily *O*-alkylated by trimethyloxonium tetrafluoroborate to give *N*-methoxythiazolium salts (**250**). The reaction of (**249**) with phosphorus oxychloride presumably gives the *O*-phosphorylated adduct (**251**). However, the liberated chloride ions are capable of attacking the thiazole nucleus giving rise to chlorothiazoles with elimination of the phosphorus moiety <92ACS372>. Similarly, compound (**252**) cannot be isolated from the reaction of (**249**) with acetyl chloride. The *N*-acyloxythiazolium salt (**252**) readily evolves to give chlorothiazoles, too (Scheme 63). The *N*-acylation of thiazole *N*-oxides has been invoked to explain the mechanism of the acylation of some thiazole derivatives <84JHC1097>.



Scheme 63

Heating of the acyloxy-2-thioxo-4-thiazoline (253) in the presence of two equivalents of antimony trisphenylsulfide and subsequent hydrolytic work-up affords a mixture of thiazole containing sulfur compounds, i.e., disulfide (254), thiol (255), and a small amount of sulfide (256). In addition, pentadecanol (257) is obtained (Equation (40)) <89T2615>.

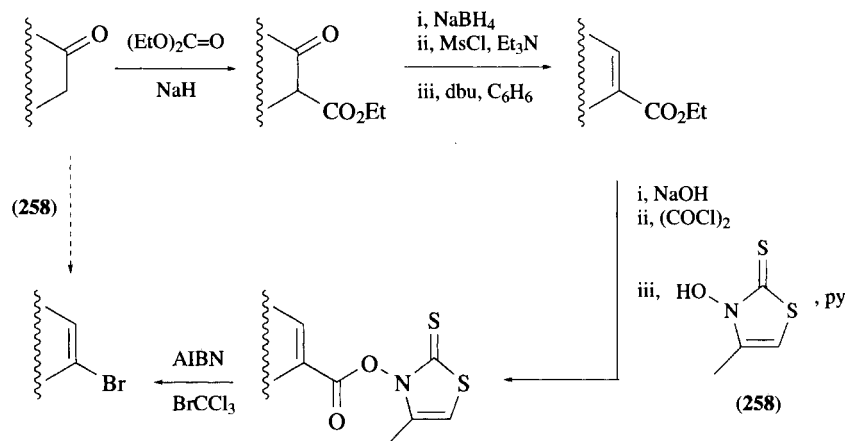


N-Hydroxy-4-methylthiazolethione (258) reacts with cyclohexyl isocyanate to give a carbamate <91JOC1309>. Compound (258) has been used in the conversion of cycloalkanones to vinyl bromides (Scheme 64) <91JOC6199>.

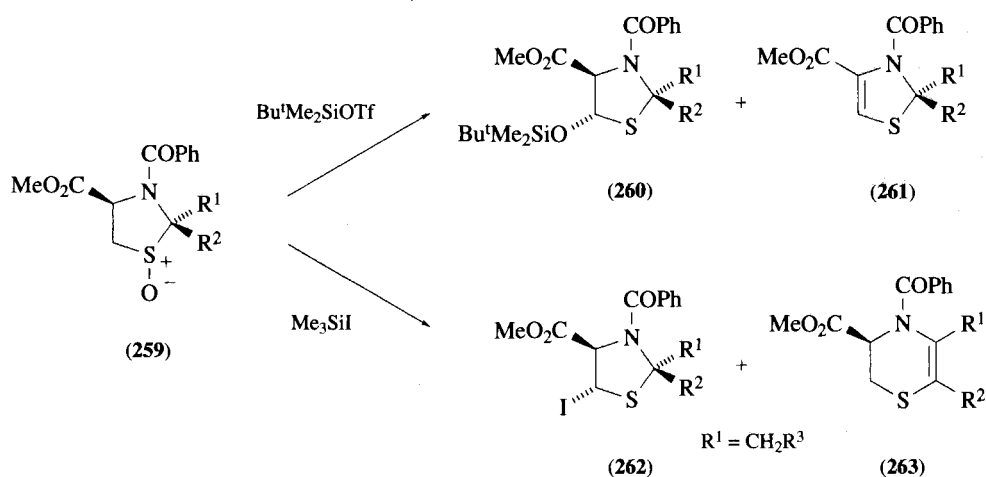
Thiazole *N*-oxides are easily deoxygenated to the parent thiazoles by a variety of reagents such as phosphorus trichloride <55JPJ121>, sodium dithionite <85CPB618>, dimethylformamide at reflux <82JHC77>, or triethyl phosphite <91JMC108>.

3.06.8.2 Substituents Attached to Ring Sulfur Atom

Optically active thiazolidine *S*-oxides (259) undergo the silicon Pummerer reaction with *t*-butyldimethylsilyl trifluoromethanesulfonate or iodotrimethylsilane <87TL5903>. When the former is used as silylating agent, thiazolidines (260) and 4-thiazolines (261) are obtained. With iodotrimethylsilane, the iodothiazolidines (262) and the dihydro-1,4-thiazine (263) are obtained (Scheme 65).

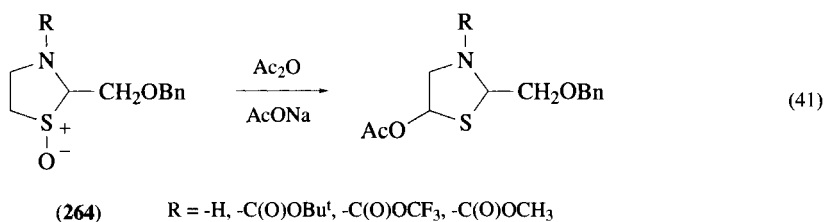


Scheme 64



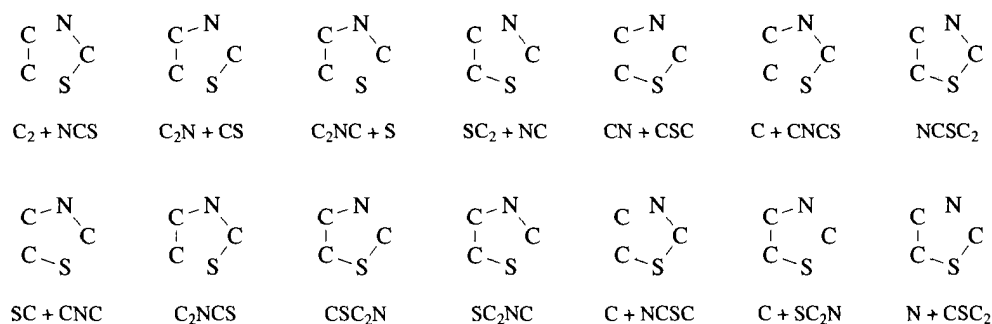
Scheme 65

In a similar manner compounds (264) react with acetic anhydride and sodium acetate to give the corresponding Pummerer rearrangement product (Equation (41)) <94JHC1465>.



3.06.9 RING SYNTHESSES CLASSIFIED BY NUMBER OF RING ATOMS IN EACH COMPONENT

There have been numerous syntheses of thiazoles and benzothiazoles reported since 1984 (for syntheses prior to 1984 see (CHEC-I <84CHEC-I(6)253>). These approaches are classified according to a retrosynthetic analysis taking into account the fragments which join to form the heterocyclic nucleus. For thiazoles, thiazolines, and thiazolidines the followed classification is shown in Scheme 66.



Scheme 66

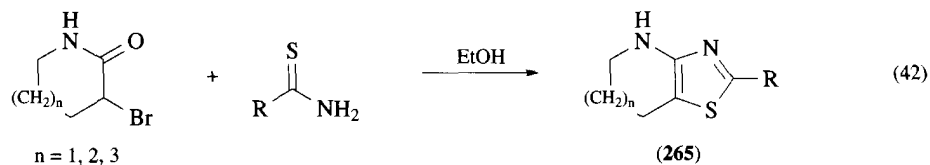
3.06.9.1 Synthesis of Thiazoles

3.06.9.1.1 Synthesis from $C_2 + NCS$ components

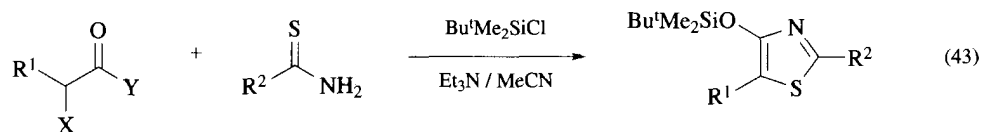
(i) Synthesis from α -halocarbonyl compounds (Hantzsch's synthesis)

The most widely employed synthetic approach for the preparation of thiazoles is the condensation of an α -halocarbonyl compound with a reactant bearing the N—C—S fragment such as thioamides, thioureas, or dithiocarbamic acid derivatives (84CHEC-I(6)294). When the Hantzsch's synthesis is employed for the preparation of chiral substituted thiazoles such as 2-aminomethyl thiazoles some foresight must be considered in order to prevent racemization (see Section 3.06.11).

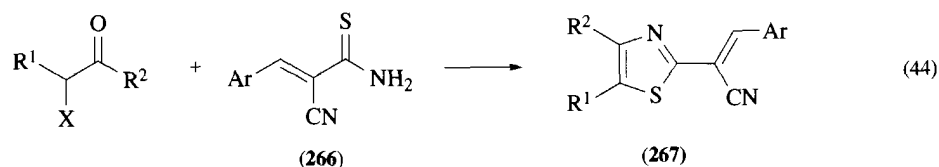
The reaction of α -bromolactams with thioamides leads to condensed 4-aminothiazole derivatives (265). The reaction is applied to six-, seven-, and eight-membered cyclic amides (Equation (42)) (94JHC1545).



4-Hydroxythiazoles can be prepared from α -haloacid halides and thioamides; if the reaction is conducted in the presence of *t*-butyldimethylsilyl chloride, 4-*t*-butylsilyloxy thiazoles are obtained in good yields (Equation (43)) (88TL3765).



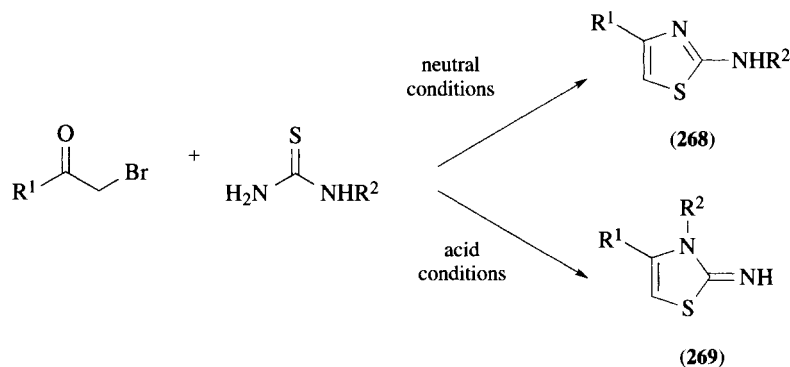
The reaction of α -haloketones with α -thiocarbamoylcinnamionitriles (266) affords the thiazole derivatives (267) (Equation (44)) (88T241).



Condensation of α -halocarbonyls with thioureas yields 2-aminothiazoles. There are many versions of this type of synthetic approach, some of which are reported in this section.

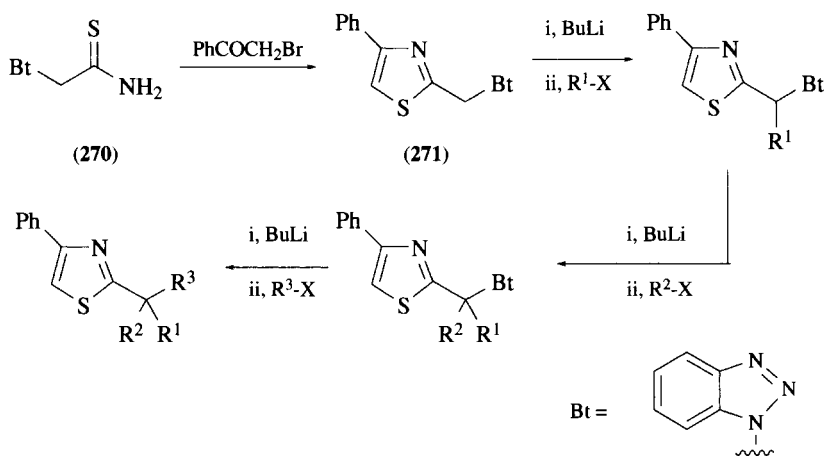
The reaction of substituted α -haloketones with thioureas leads to 4-substituted-2-aminothiazoles. Compounds which have been prepared include 4-trifluoromethyl (91JHC907), 4-tropolone (89JHC601), 4-hetaryl (93JJC(B)848), 4-ethoxycarbonyl (91JHC1003), or 4-aminoalkyl (92JMC3239)

derivatives. When the α -haloketones bear another α -substituent, the reaction leads to 4,5-disubstituted thiazoles $\langle 93\text{KGS1120} \rangle$. α,α -Dihalocompounds condensate with thioureas to give 2-amino-4-substituted thiazoles instead of the expected 2-amino-4-substituted-5-halothiazoles $\langle 87\text{SC333} \rangle$. The regioselectivity of the reaction changes when the condensation of α -haloketones with thioureas is carried out under acidic conditions $\langle 87\text{JCS(P1)639} \rangle$. Thus, *N*-monosubstituted thioureas lead to mixtures of 2-(*N*-substituted-amino)thiazoles (**268**) and 3-substituted-2-imino-2,3-dihydrothiazoles (**269**) in different ratios depending on the reaction conditions (Scheme 67).



Scheme 67

α -Bromoketones also react with salts and esters of thiocarbamic acid to yield 2-hydroxythiazoles which are predominantly in the oxo tautomeric form. This reaction has been employed in the synthesis of 4,5,6,7-tetrahydro-2-benzothiazolinones starting from 2-chlorocyclohexanone $\langle 86\text{JHC641} \rangle$. With salts and esters of dithiocarbamic acid the reaction leads to 2-thiothiazoles. 2-Substituted thiazoles can be obtained from (benzotriazol-1-yl)thioacetamide (**270**) and α -bromoketones. The resulting 2-(benzotriazol-1-ylmethyl)-4-phenylthiazole (**271**) can be sequentially alkylated at the α -position (Scheme 68) $\langle 95\text{JOC5638} \rangle$.

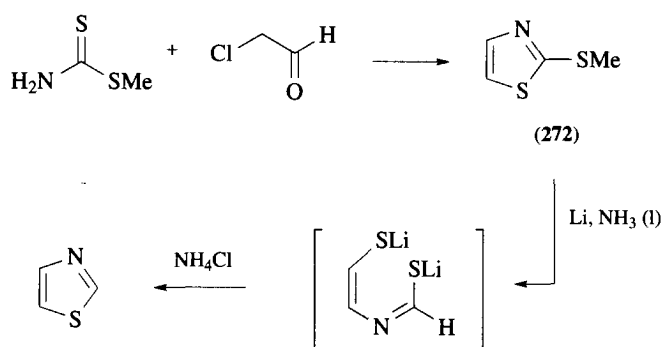


Scheme 68

A large-scale synthesis of the unsubstituted thiazole has been described starting from chloroacetaldehyde and methyl dithiocarbamate $\langle 85\text{S948} \rangle$. Condensation of the two reagents affords 2-methylthiothiazole (**272**) which upon treatment with lithium in liquid ammonia and protonation with ammonium chloride yields thiazole (Scheme 69).

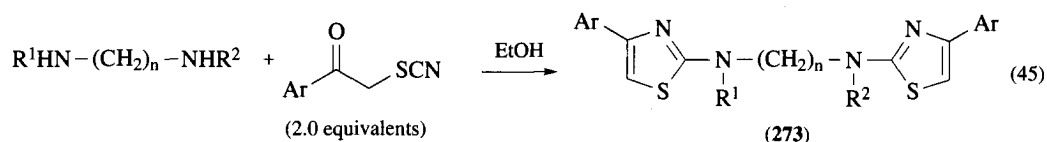
(ii) *Synthesis from α -thiocyano ketones (Tcherniac's synthesis)*

The Tcherniac's synthesis of thiazoles consisting of the rearrangement of α -thiocyano ketones $\langle 84\text{CHEC-I(6)299} \rangle$ has been used in the preparation of bisthiazolyl compounds (**273**) starting from diaminoalkanes $\langle 90\text{JPR723} \rangle$. The reaction cannot be applied to α -thiocyanato- β -dicarbonyl deriva-



Scheme 69

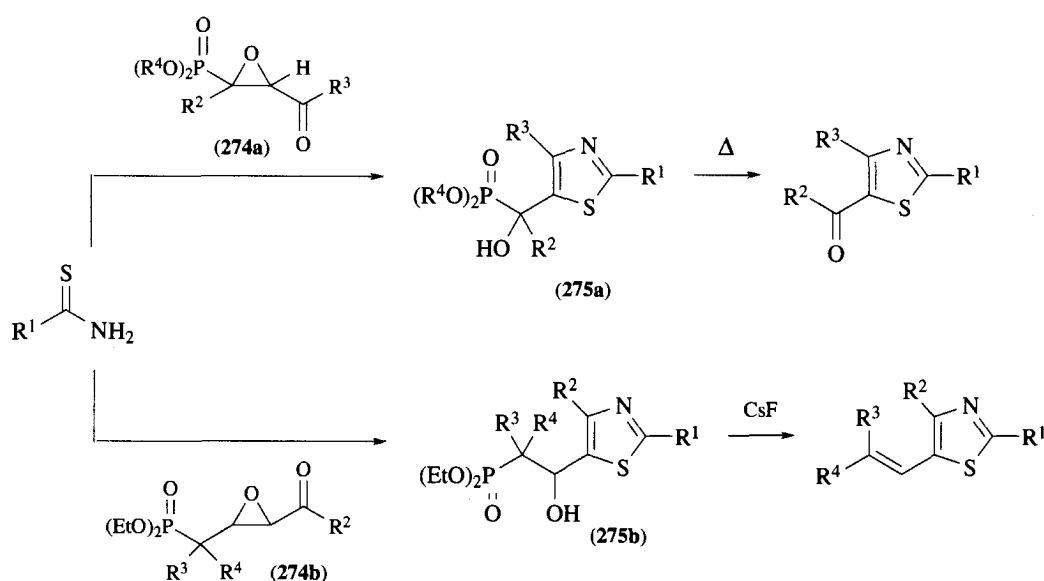
tives since these compounds dimerize to give thiazoles by another route (Equation (45)) (see Section 3.06.9.1.4) <87TL117>.



(iii) Other syntheses

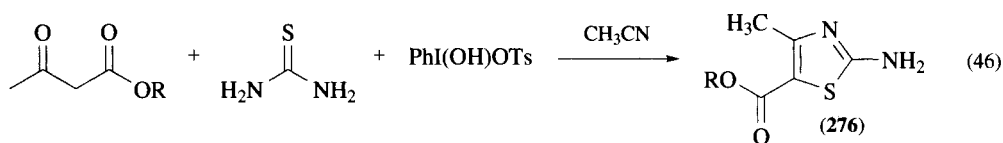
Thioamides react with dialkyl (1,2-epoxy-3-oxoalkyl)phosphonates (**274a**) to give (1-hydroxy-1-thiazolylalkyl) phosphonates (**275a**) which upon treatment with alkali or by pyrolysis afford 5-acylthiazoles <85CB4099> (Scheme 70). Application of this reaction to 2,3-epoxy derivatives (**274b**) leads to phosphonates (**275b**) which are readily converted to 5-alkenylthiazoles upon treatment with caesium fluoride <88CB533>. With cyclic compounds 4,5,6,7-tetrahydrobenzothiazole derivatives can be obtained <93M763>.

Hypervalent iodine reagents has been used in modified Hantzsch thiazole synthesis. Treatment

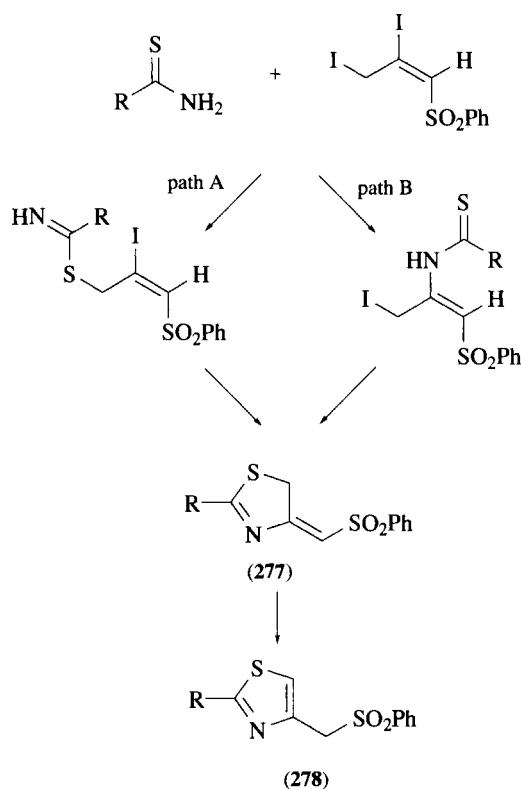


Scheme 70

of β -dicarbonyl compounds with [hydroxy(tosyloxy)iodo]benzene and thioureas furnishes, after basic work-up, 5-acyl-4-methyl-2-aminothiazoles (**276**) (Equation (46)) <92S845>.



The same hypervalent iodine reagent has been employed in the preparation of 4-aryl and 4-thienyl-2-substituted thiazoles by condensing methylketones with thioamides <94SL221>. The reaction of enolizable ketones with thioamides to give 2-substituted thiazoles can be also carried out by using thallium(III) *p*-tolylsulfonate <93JCB364>. Condensation of thioamides with 2,3-diiodo-1-(phenylsulfonyl)-1-propene (**277**) affords 2-substituted-4-(phenylsulfonylmethyl)thiazoles (**278**). The mechanism of this process can be rationalized by two different pathways as indicated in Scheme 71 <92JOC1161>.



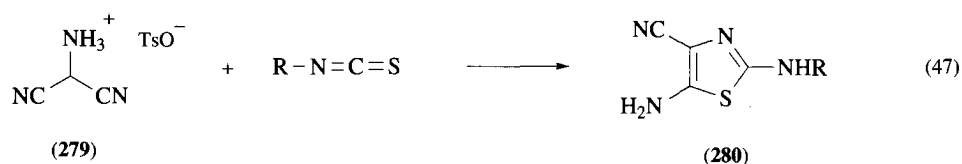
Scheme 71

Aryl- and alkylthioamides react with ethyl diazopyruvate in the presence of boron trifluoride etherate to give 2-substituted-4-carboxythiazoles <95JHC937>.

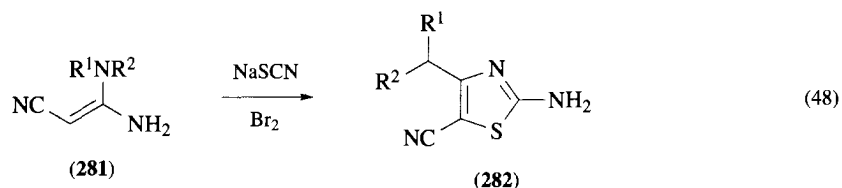
3.06.9.1.2 Synthesis from $C_2N + CS$ components

The synthesis of thiazoles using α -aminonitriles as starting materials is known as the Cook–Heilbron's synthesis. Some variants have been described using other substrates <84CHEC-I(6)300>.

Aminomalonnitrile *p*-toluensulfonate (**279**) reacts with alkyl and aryl isothiocyanates yielding 2-alkylamino and 2-aryl-amino-4-cyano-5-aminothiazoles (**280**) in good yields (Equation (47)) <91JOC4645>.

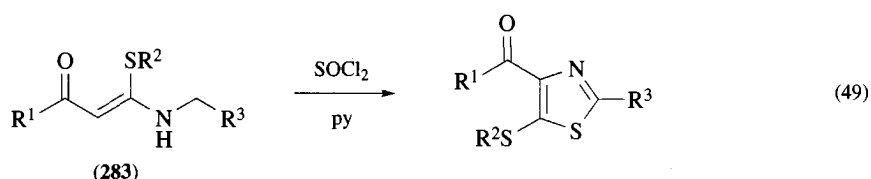


The 5-cyano derivatives (282) can be obtained by treatment of 3-amino-3-(dialkylamino)propanenitriles (281) with sodium thiocyanate in the presence of bromine (Equation (48)) <93S199>.

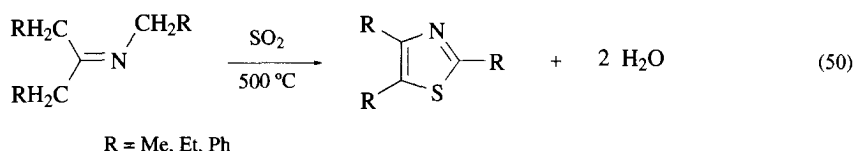


3.06.9.1.3 Synthesis from $\text{C}_2\text{NC} + \text{S}$ components

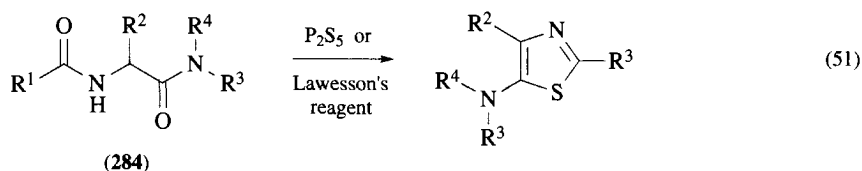
5-Thiothiazoles are obtained by direct heterocyclization of ketoketene *S,N*-acetals (283), the sulfurating agent being thionyl chloride (Equation (49)) <84S250>.



High-temperature reaction between imines and sulfur dioxide affords thiazoles in a process that can be used to prevent environmental problems since only water is produced as a by-product (Equation (50)) <84H(22)1947>.



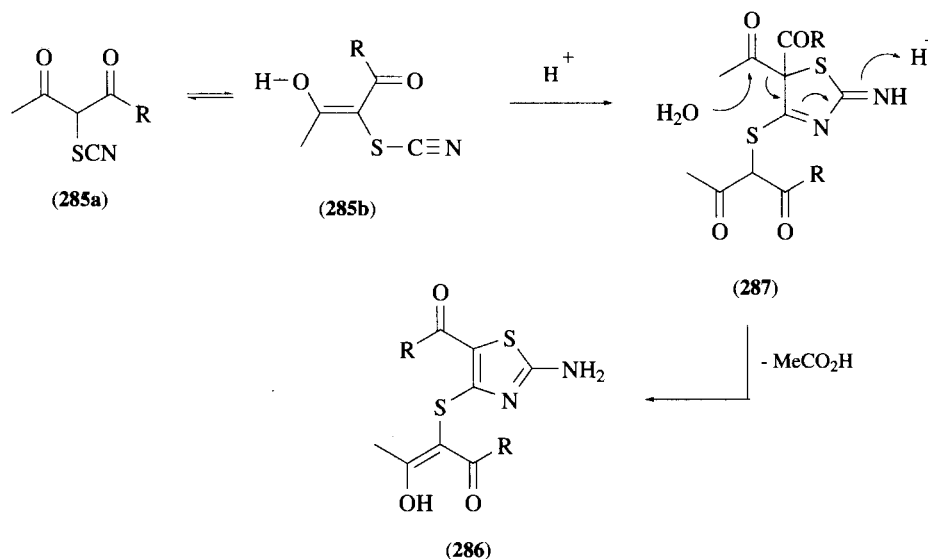
Both phosphorus pentasulfide and Lawesson's reagent can be used as sulfurating agent in the synthesis of 5-aminothiazoles from amides (284) (Equation (51)) <87RRC1175, 94JHC877>.



3.06.9.1.4 Synthesis from $\text{CN} + \text{CSC}$ components

α -Thiocyanato carbonyl compounds are the starting materials for the Tcherniac's synthesis of thiazoles (see Section 3.06.9.1.1). α -Thiocyanato- β -dicarbonyl compounds (285) undergo dimerization to give 2-aminothiazoles (286). The proposed mechanism is outlined in Scheme 72 <87TL117>. The dimerization should proceed by the acid catalyzed condensation between the enolized (285b)

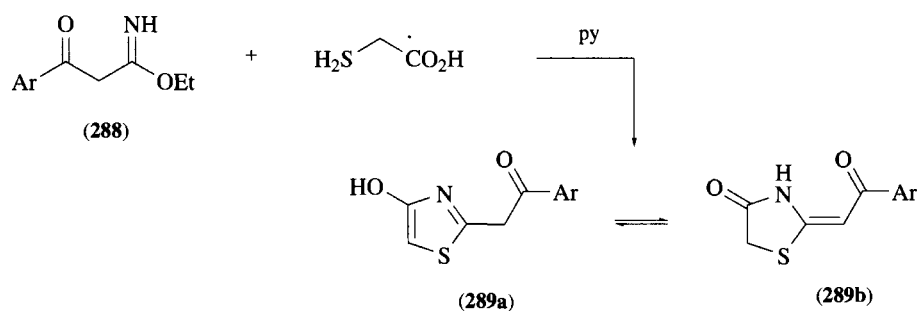
and non-enolized (**285a**) form to give an intermediate (**287**) which is deacetylated by nucleophilic attack of water. The enol form of compound (**286**) has been characterized by spectroscopic techniques <94T7253>.



Scheme 72

3.06.9.1.5 Synthesis from $SC_2 + NC$ components

Thioglycolic acid reacts with active methylene compounds such as (**288**) to give 4-hydroxythiazoles (**289**). The spectral analysis shows that the predominant tautomeric form is (**289b**) both in solid state and DMSO solution (Scheme 73) <92T9295>.

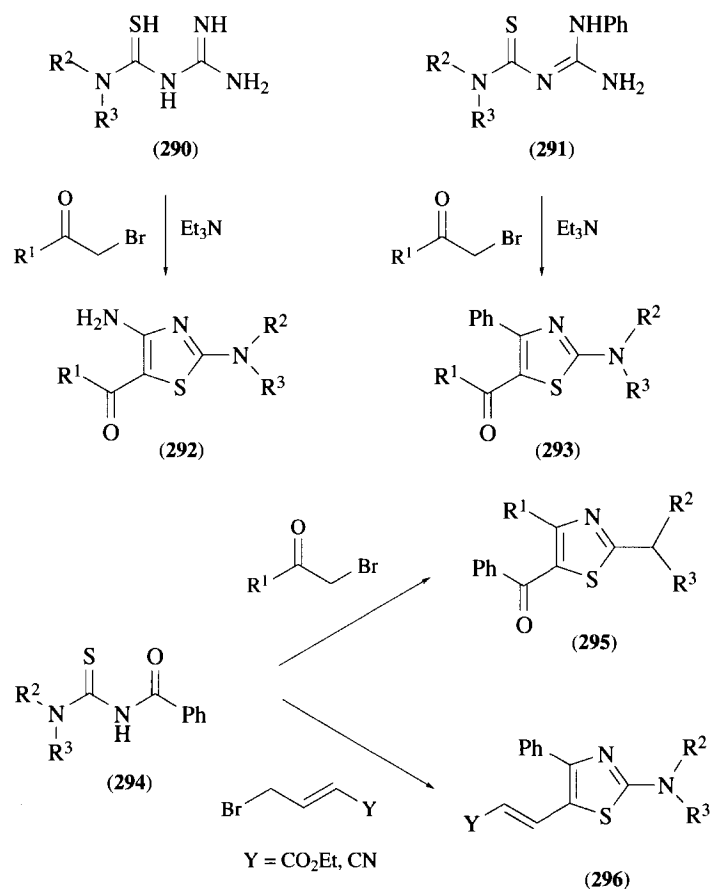


Scheme 73

3.06.9.1.6 Synthesis from $C + CNCS$ components

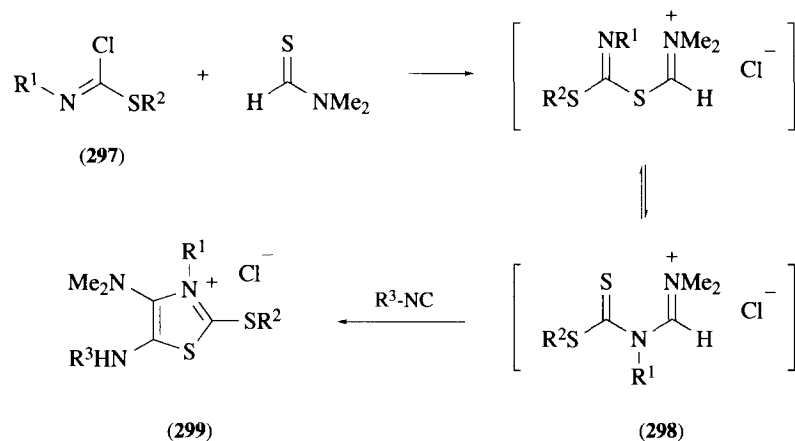
This type of approach constitutes a convenient synthesis of 5-functionalized thiazoles. 2,4-Diamino-5-acylthiazoles (**292**) can be prepared by reacting α -haloketones with alkyl- or aryl-3-amidinothioureas (**290**) in the presence of triethylamine <86S353>; with *N*-(anilino)benzylidene-*N,N'*-disubstituted thioureas (**291**), the reaction affords 2-amino-4-aryl-5-acylthiazoles (**293**). In contrast, the corresponding *N*-benzoylthioureas (**294**) afford mainly 5-benzoyl derivatives (**295**)

<87JCS(P1)1153>. On the other hand, compounds (294) give the expected 5-substituted thiazoles (296) when are treated with γ -bromo crotonic acid derivatives (Scheme 74) <92LA415>.



Scheme 74

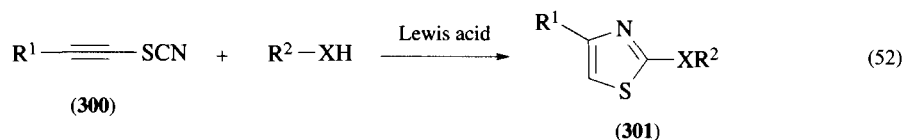
In a quite different approach, isocyanides react with formamidinium chlorides (298) to furnish thiazolium salts (299) in a reaction described as thioamidoalkylation of isocyanides <93JOC6022>. Compounds (298) are generated *in situ* from iminochlorosulfides (297) and dimethylthioformamide (Scheme 75).



Scheme 75

3.06.9.1.7 Synthesis from NCSC₂ component

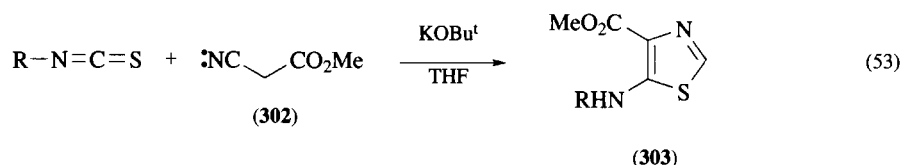
Reaction of 1-alkynyl thiocyanates (**300**) with alcohols, phenols, thiols, or secondary aliphatic amines in the presence of a Lewis acid (anhydrous zinc chloride or boron trifluoride diethyl etherate) affords 2,4-disubstituted thiazoles (**301**) in good yields (Equation (52)) <82RTC310>.



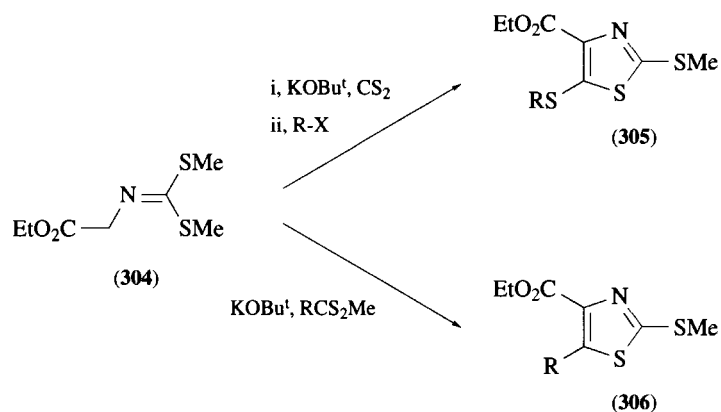
Similar reactions occur between *vic*-halothiocyano ketones and secondary amines <88JPR65, 89ZC255> to give 2-aminothiazoles.

3.06.9.1.8 Synthesis from SC + CNC components

Alkyl- and arylisothiocyanates react with methyl α -isocyanoacetate (**302**) in the presence of potassium *t*-butoxide to give 5-amino-4-ethoxycarbonylthiazoles (**303**) (Equation (53)) <82S874>.

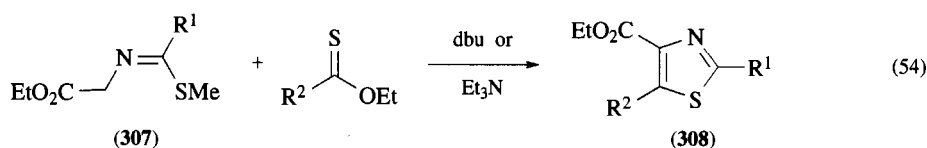


A cyclocondensation reaction between dimethyl *N*-(ethoxycarbonylmethyl)imino-dithiocarbonate (EMIC, **304**) and carbon disulfide has been described to give 4-carbethoxy-5-thio-2-methylthiothiazole <87TL6667, 87ZC212>. The treatment of the reaction mixture with alkyl halides leads to the 5-alkylthio derivatives (**305**). The overall yields of this synthesis range between 17% and 50%. The reaction can be extended to thioesters and to other iminodithiocarbonate derivatives in order to obtain 5-substituted 2-methylthiothiazoles (**306**) (Scheme 76) <89BSB215, 91H(32)2127>. Thioesters also react with isothiocyanate acetate in the presence of sodium hydride to give the same thiazole derivatives (**306**) <90S733>.



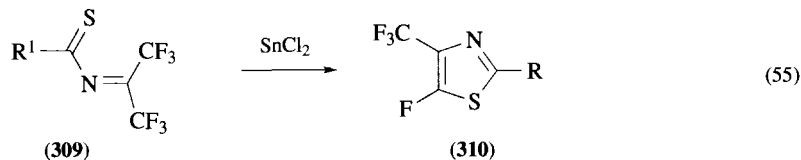
Scheme 76

The reaction of *N*-(methylthioalkylidene)glycine ethyl ester (**307**) with thioesters affords 2,5-disubstituted-4-ethoxycarbonyl thiazoles (**308**). The reaction needs basic catalysis by dbu or triethylamine (Equation (54)) <94S1467>.

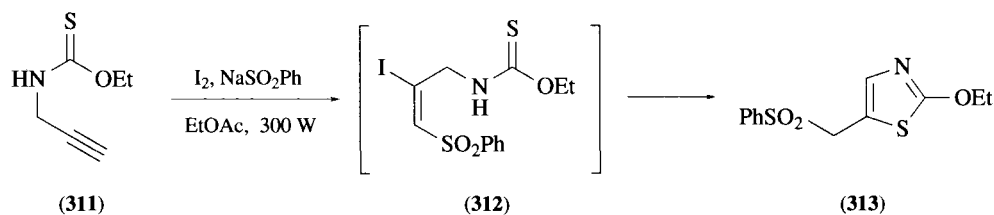


3.06.9.1.9 Synthesis from C_2NCS component

5-Fluorothiazoles (**310**) are obtained when 4,4'-bis(trifluoromethyl)thiocarboxamides (**309**) are treated with tin(II) chloride (Equation (55)) <88S189>.



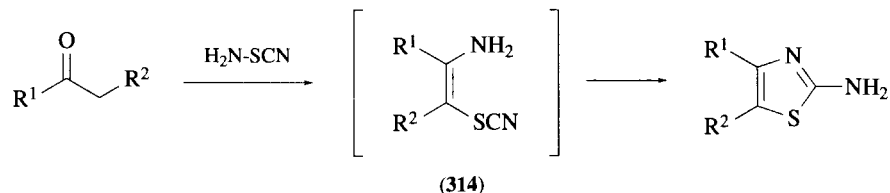
Intramolecular cyclization of the alkene (**312**), generated *in situ* from thiocarbamate (**311**), leads to the 2-ethoxythiazole derivative (**313**) (Scheme 77) <93TL71>.



Scheme 77

3.06.9.1.10 Synthesis from CSC_2N component

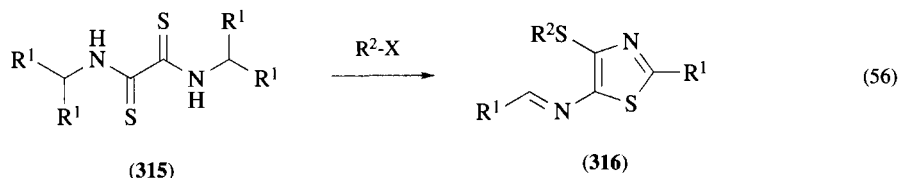
4,5-Disubstituted 2-aminothiazoles can be synthesized from enamines (**314**) prepared from enolizable ketones and aminothiocyanoen (Scheme 78) <90AQ418>.



Scheme 78

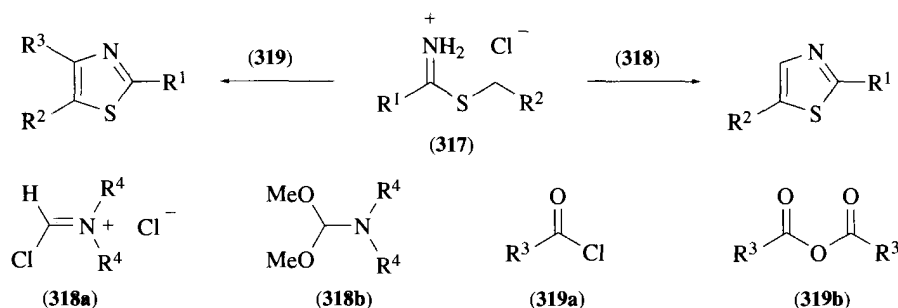
3.06.9.1.11 Synthesis from SC_2NC component

Rearrangement of N,N' -bis-(α -aminoalkyl)dithioamides (**315**), easily available from dithioamides, aromatic aldehydes, and secondary amines, gives in the presence of alkylating or acylating agents, the thiazole derivatives (**316**) (Equation (56)) <84N43>.



3.06.9.1.12 Synthesis from $C + NCSC$ components

Isothiuronium chlorides (**317**) undergo condensation reactions with formamidinium chloride (**318a**) or substituted formamide acetals (**318b**), and with acyl chlorides (**319a**) or anhydrides (**319b**) furnishing 2,5-disubstituted or 2,4,5-trisubstituted thiazoles in moderated yields (Scheme 79) <85S414>.

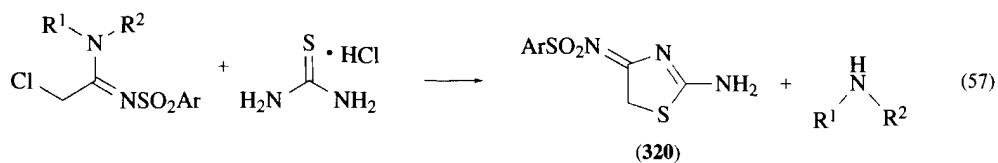


Scheme 79

3.06.9.2 Synthesis of 2-Thiazolines

3.06.9.2.1 Synthesis from C_2 + NCS components

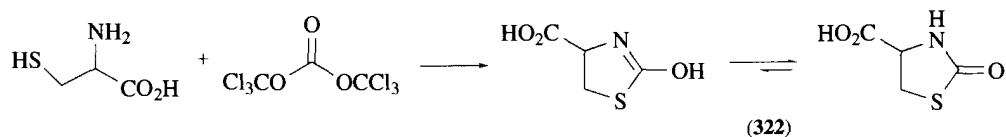
Condensation of thioamides with α -bromoketoesters under mild conditions gives 4-hydroxy-2-thiazolines which are easily dehydrated to afford thiazoles <86JHC577, 86S992, 88JHC289>. 2-Amino-4-arylsulfonylimino-2-thiazolines (**320**) can be prepared by reacting thiourea (or thiourea hydrochloride) with *N*-alkyl- or *N,N*-dialkyl-*N'*-*p*-toluensulfonyl- α -chloroacetamides (Equation (57)) <88JHC1849>.



2-Amino-2-thiazolines (**321**) can also be prepared by treating a mixture of phenylpropionic acid chloride and amine with potassium thiocyanate (Equation (58)) <88ZC329>.



Reaction of perfluoro-2-methyl-2-pentene with thiourea in aprotic polar solvents also gives 2-amino-2-thiazolines <93KGS253>. 4-Carboxy-2-thiazolidinone (**322**) is accessible from cysteine by reaction with bis(trichloromethyl)carbonate (triphosgene) in a basic medium (Scheme 80) <93SC2839>. The procedure has the advantage of avoiding phosgene as a reagent giving better results than other carbonylating agents.

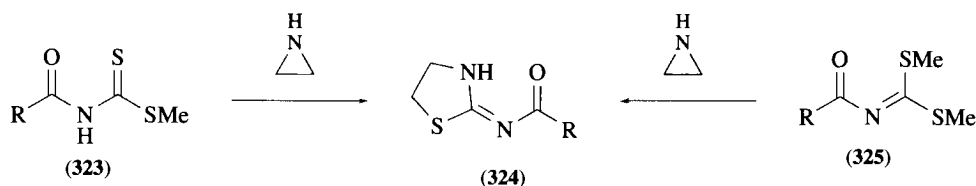


Scheme 80

3.06.9.2.2 Synthesis from C_2N + CS components

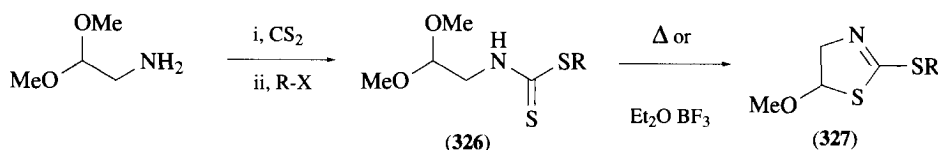
Ring opening of aziridines with dithiocarbamate (**323**) affords thiazolines (**324**). The reaction can also be made with the dithiocarbonimidate (**325**) (Scheme 81) <84ZC63>.

5-Methoxy-2-alkylthiothiazolines (**327**) are obtained by thermal or diethyl ether–boron trifluoride mediated intramolecular cyclization of the intermediate dithiocarbamate (**326**) which is prepared



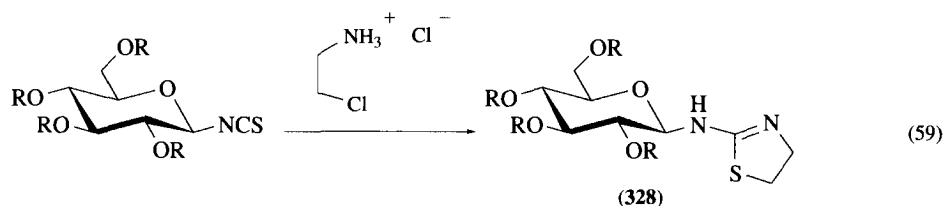
Scheme 81

from aminoacetaldehyde dimethyl acetal, carbon disulfide, and an alkylating agent (Scheme 82) <91S494>. The yield of both steps range between 60% and 90%.



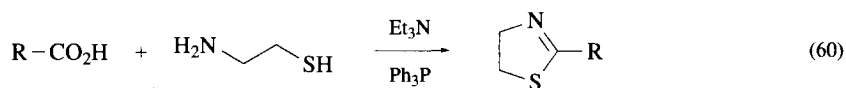
Scheme 82

Glucosylamino-2-thiazolines (**328**) are prepared by the reaction of glucosyl isothiocyanates with 2-chloroethylamine hydrochloride (Equation (59)) <92T6413>.



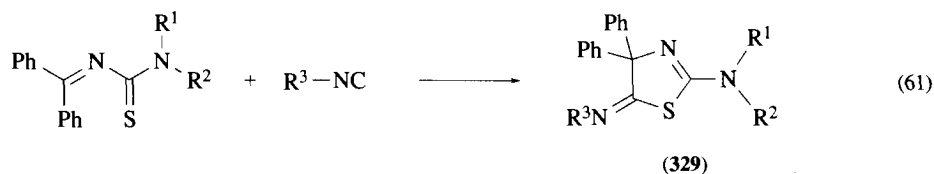
3.06.9.2.3 Synthesis from C + SC₂N components

Carboxylic acids react with 2-thioethylamine in the presence of triphenylphosphine and triethylamine to afford 2-substituted-2-thiazolines as outlined in Equation (60) <93T9353>. Although the reaction can be applied successfully for the synthesis of oxazolines (upon treatment with 2-ethanolamine), the preparation of thiazolines by this method only affords the desired products in modest yields (40–50%).



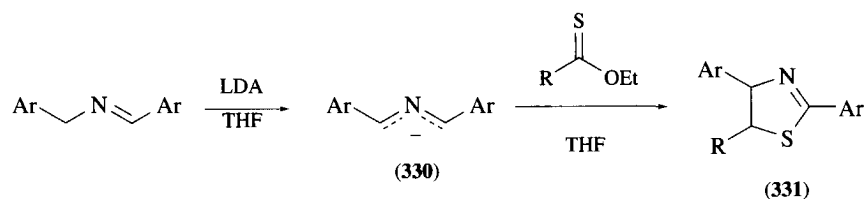
3.06.9.2.4 Synthesis from C + CNCS components

The reaction of isocyanides with azathiabutadienes gives 2-amino-4,4-diphenyl-5-imino-2-thiazolines (**329**) through a [1 + 4] cycloaddition (Equation (61)) <90JOC1721>.



3.06.9.2.5 Synthesis from SC + CNC components

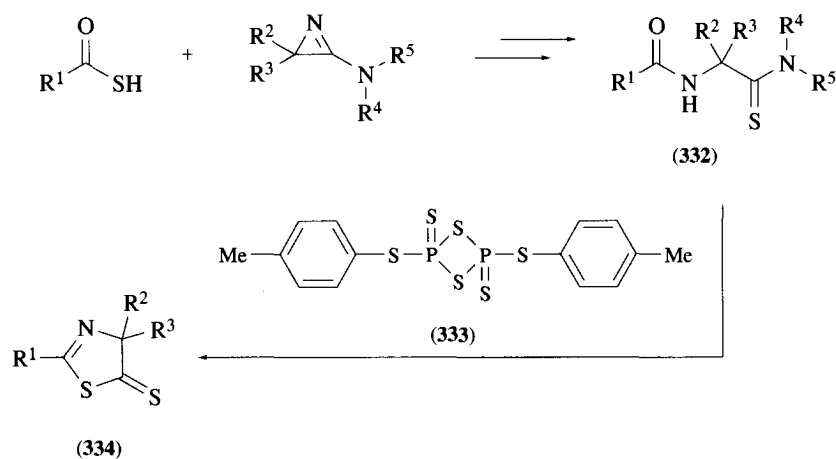
2,4-Diaryl-2-thiazolines (**331**) are synthesized by reaction of 1,3-diaryl-2-azaallyl anions (**330**) with *O*-ethyl thiocarboxylates (Scheme 83). The anions (**330**) are generated *in situ* from imines <95SL809>.



Scheme 83

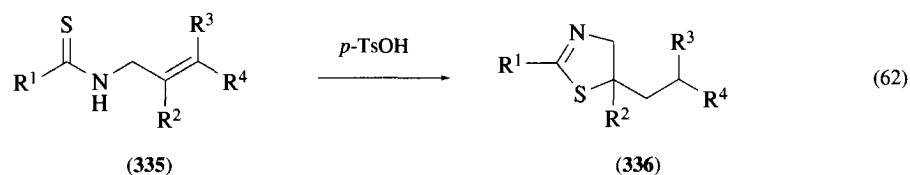
3.06.9.2.6 Synthesis from C_2NCS components

5-Thioxo-2-thiazolines (**334**) can be synthesized by treatment of *N,N*-disubstituted thioamides (**332**) with dithiaphosphetane (**333**), an easily available sulfurating agent similar to the Lawesson's reagent. In turn, compounds (**332**) can be prepared from azirines and thiocarboxylic acids (Scheme 84) <87HCA1001>.

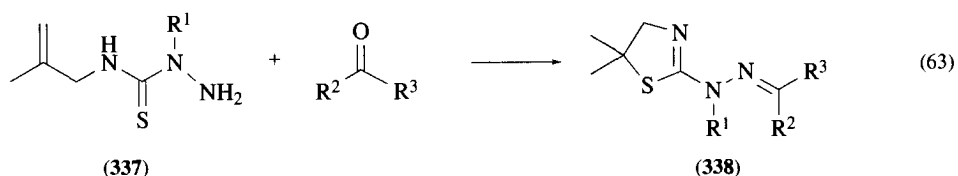


Scheme 84

Proton-induced cyclization of allylic thioamides (**335**) leads to 2-thiazolines (**336**). The cyclization can also be induced by phenylselenenyl bromide and subsequent reductive removal of the phenylselenenyl group (Equation (62)) <91JOC3425>.

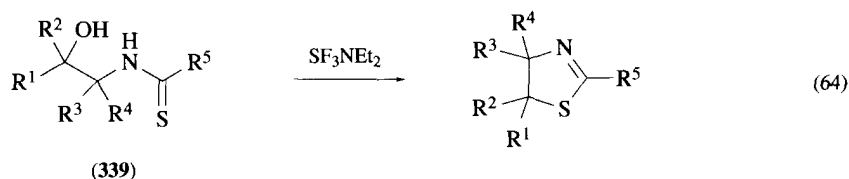


Condensation of 2-substituted-4-methallylthio semicarbazides (**337**) with carbonyl compounds under strong acidic conditions affords 2-thiazolines (**338**) after neutralization in 56–81% chemical yields (Equation (63)) <91JPR407>.



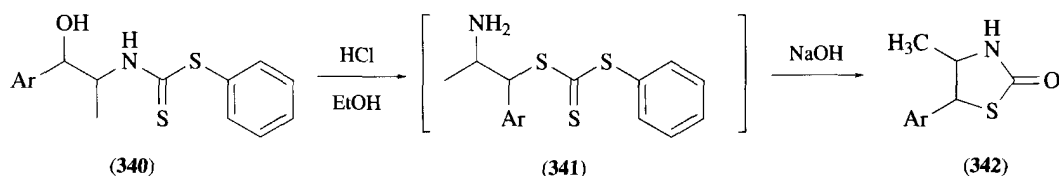
Similarly, *N*-allylthioamides derived from carboxylic acids cyclize to 2-thiazoline derivatives by the action of the bromine-dioxane complex <93PJC1043>. The Mitsunobu reaction can be efficiently used for preparing 4-carboxy-2-thiazolines from β -hydroxy- α -amino acids <92TL2807>. Diethyl-

aminosulfur trifluoride (DAST) is an efficient reagent for the synthesis of 2-thiazolines starting from the corresponding (1,2)-thioamido alcohols (**339**) (Equation (64)) <95SL171>.



3.06.9.2.7 Synthesis from CSC_2N component

2-Thiazolidinones (**342**) are prepared by this type of synthesis starting from dithiocarbamates (**340**) which generate intermediates (**341**) upon acidic treatment as shown in Scheme 85 <91MI 306-04>.

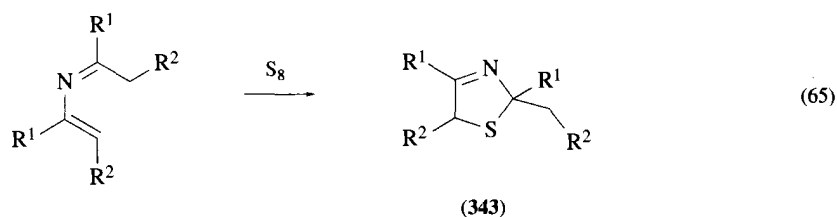


Scheme 85

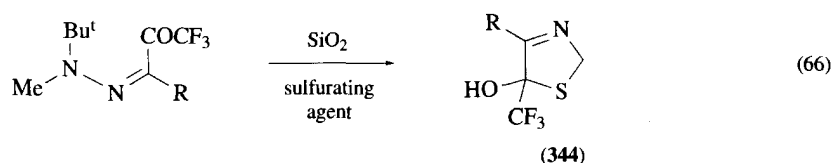
3.06.9.3 Synthesis of 3-Thiazolines

3.06.9.3.1 Synthesis from $\text{C}_2\text{NC} + \text{S}$ components

A general procedure for the synthesis of 3-thiazoline (**343**) employs the aza-1,3-dienes and elemental sulfur (Equation (65)) <92T9745>.



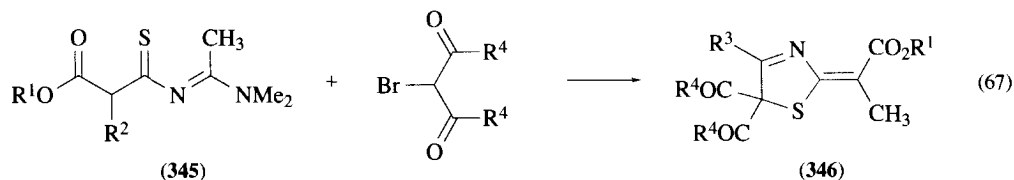
5-Trifluoromethyl-5-hydroxy-3-thiazolines (**344**) have been obtained by this route with the use of silica gel as an effective catalyst for introducing the sulfur atom from several sulfurating agents <94H(38)803>. The sulfurating agents employed were ammonium sulfate, sodium sulfide, and phosphorus pentasulfide (Equation (66)).



(66)

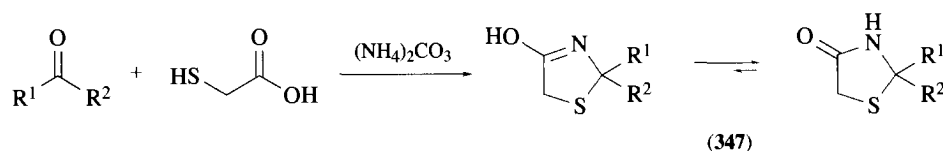
3.06.9.3.2 Synthesis from C + CNCS components

1,3-Dicarbonyl compounds react with acetamidines (**345**) to afford 3-thiazolines (**346**) (Equation (67)) <87SUL49>.



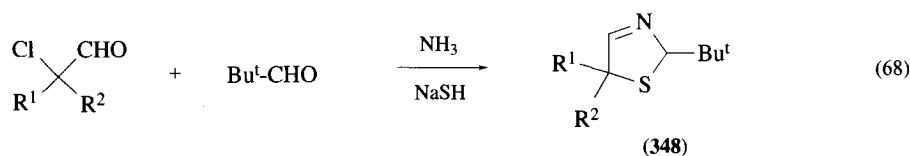
3.06.9.3.3 Synthesis from more than two components

Hydroxythiazolines (**347**) are obtained by reacting α -thioacetic acid with carbonyl compounds in the presence of ammonium carbamate as a source of nitrogen (Scheme 86) <86ZN(B)134>.



Scheme 86

α -Chloroaldehydes react with pivalaldehyde in the presence of ammonia and sodium hydrogen sulfide to afford the corresponding 3-thiazolines (**348**) (Equation (68)) <90SUL263>.

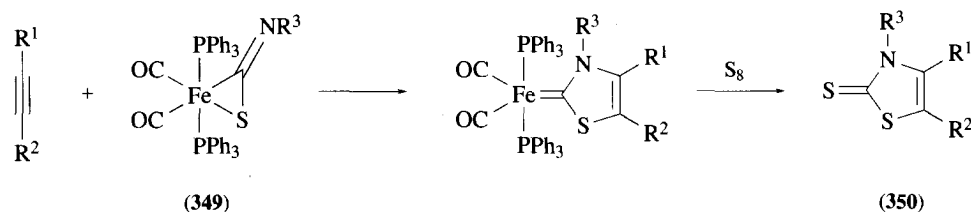


3.06.9.4 Synthesis of 4-Thiazolines

3.06.9.4.1 Synthesis from C₂ + NCS components

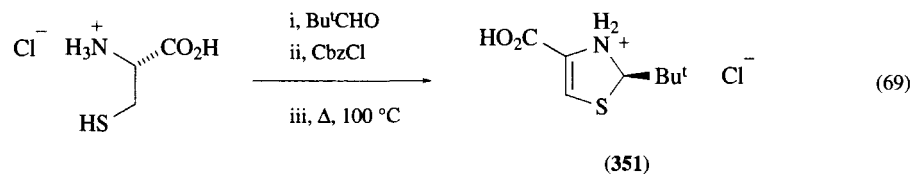
4-Thiazoline-2-thiones (**350**) can be prepared by treatment of alkynes with iron complexes (**349**). Treatment with elemental sulfur of the resulting adducts affords compounds (**350**) (Scheme 87) <82JOC4000>.

Thiazolines (**350**) are also formed in the reaction of dithiocarbamic acid derivatives and α -



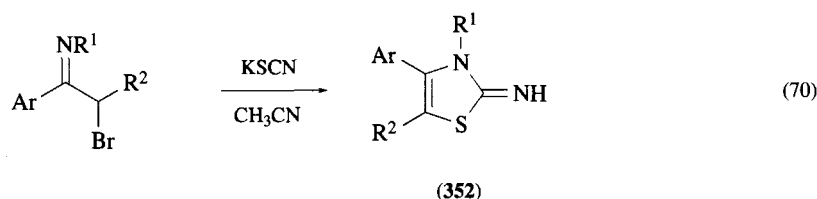
Scheme 87

chloroketones <88TL1325>. The chiral thiazolidine **(351)** has been prepared from the reaction of L-cysteine hydrochloride with pivalaldehyde in ethanol (Equation (69)) <89C314>.



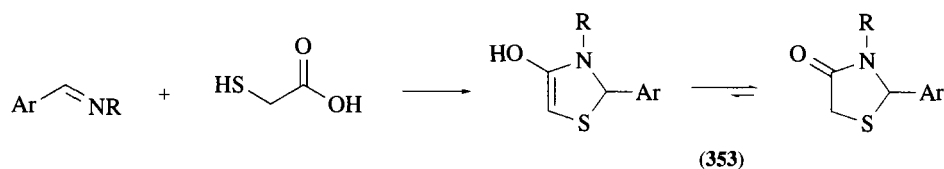
3.06.9.4.2 Synthesis from $\text{C}_2\text{N} + \text{CS}$ components

The reaction of α -bromoketimines with potassium thiocyanate in acetonitrile leads to 2-imino-4-thiazolines **(352)** (Equation (70)) <93T3411>.



3.06.9.4.3 Synthesis from $\text{SC}_2 + \text{NC}$ components

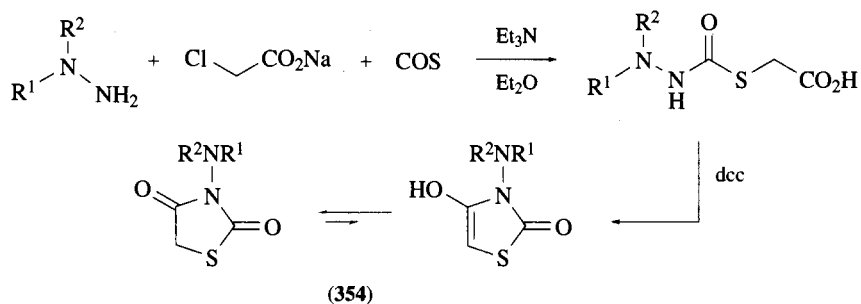
4-Hydroxythiazolines **(353)** which are in tautomeric equilibrium with the oxothiazolidine form are prepared by addition of α -thioacetic acid to imines (Scheme 88) <92JMC2910, 94MI 306-03>. The thiazolines **(353)** are obtained in 33–86% chemical yield.



Scheme 88

3.06.9.4.4 Synthesis from NCSC_2 component

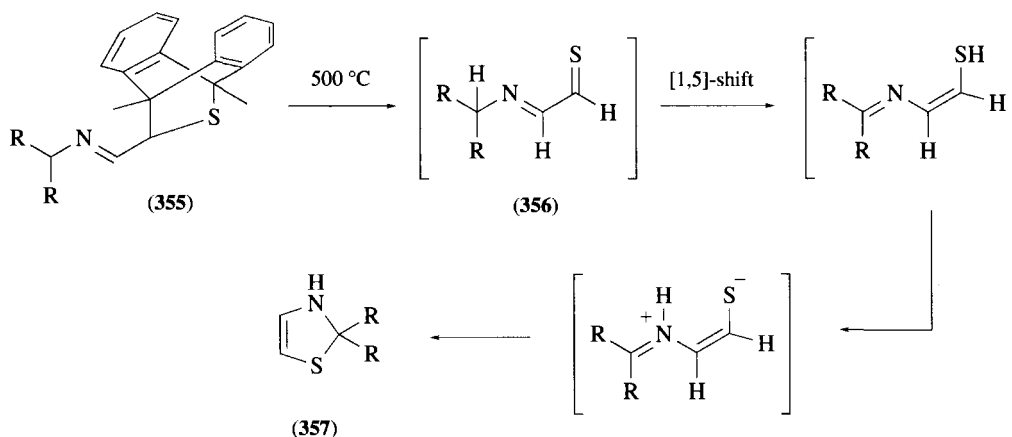
A ring closure of this type is carried out for the synthesis of 4-hydroxythiazolin-2-ones **(354)** using N,N -disubstituted hydrazines, sodium α -chloroacetate, and carbonyl sulfide as starting materials (Scheme 89) <87AP(108)367>.



Scheme 89

3.06.9.4.5 Synthesis from CSC_2N component

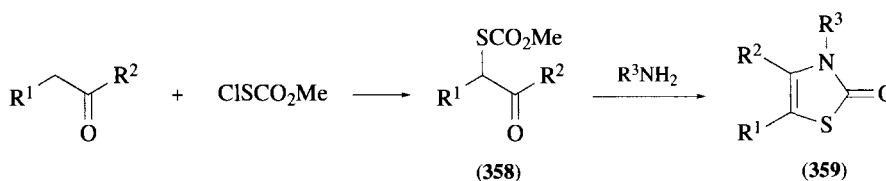
α -Iminothioaldehydes (**356**) cyclize to 4-thiazolines (**357**) through a [1,5] sigmatropic shift. The mechanism of the process is illustrated in Scheme 90. The quite unstable thioaldehydes (**356**) are generated *in situ* from thioformylimine-dimethylantracene adducts (**355**) by a retro Diels–Alder reaction under flash vacuum thermolysis conditions (Scheme 90) <94TL8389>.



Scheme 90

3.06.9.4.6 Synthesis from $N + CSC_2$ components

2-Oxo-4-thiazolines (**359**) are obtained by treating carbonyl compounds (**358**) bearing an α -methoxycarbonylsulfonyl group with primary amines <92JOC1053>. Ammonium acetate can also be used as a source of nitrogen in this reaction thus leading to *N*-unsubstituted products. Compounds (**358**) are easily prepared by the addition of the corresponding aldehydes or ketones to (methoxycarbonyl)sulfonyl chloride (Scheme 91).

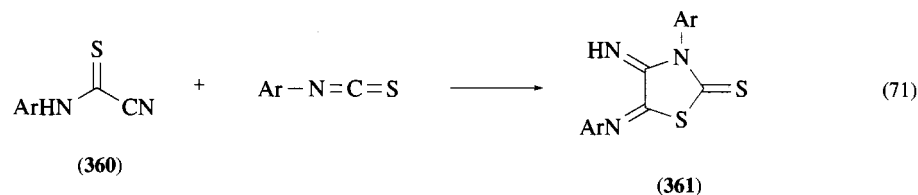


Scheme 91

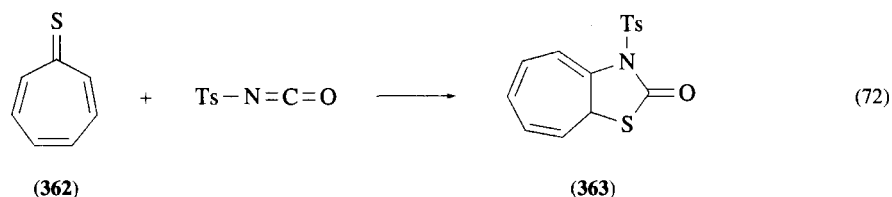
3.06.9.5 Synthesis of Thiazolidines

3.06.9.5.1 Synthesis from $SC_2 + NC$ components

Thiazolidinethiones (**361**) can be obtained from cyanothioformanilides (**360**) and aryl isothiocyanates. Imidazolidinedithiones are obtained in some cases depending on the type of bases used, reaction temperature and the nature and position of substituents in compounds (**360**) (Equation (71)) <87JHC1781>. The strong dependence upon the type of bases used often leads to low yields (below 30%).

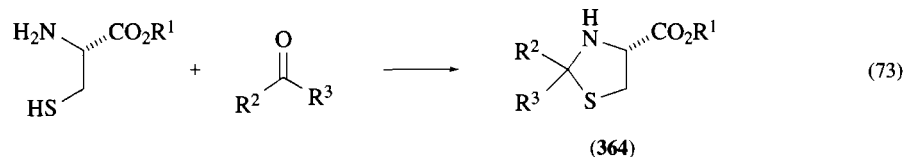


2-Iminothiazolidines are prepared by the reaction of alkynes with *N,N'*-disubstituted thioureas <88SC197>. 2-Oxathiazolidine (363) is formed when the cyclic thione (362) is treated with *p*-toluenesulfonyl isocyanate in a [8 + 2]-type cycloaddition reaction (Equation (72)) <92H(34)1415>.



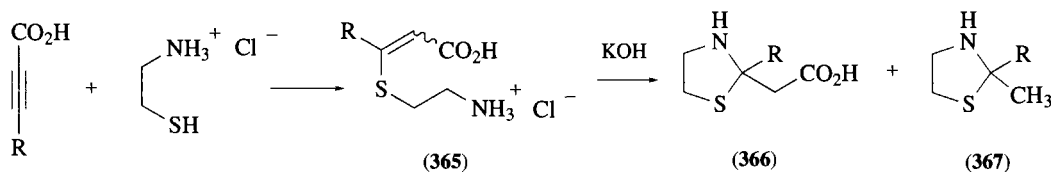
3.06.9.5.2 Synthesis from $\text{SC}_2\text{N} + \text{C}$ components

Condensation of L-cysteine with carbonyl compounds has been widely employed in the preparation of chiral thiazolidine 4-carboxylic acids <87JMC1891>. α -Hydroxyketenes <87JHC1629> or sugar-derived aldehydes <89CAR(187)223> have been used to form 2-(polyhydroxyalkyl)thiazolidines (Equation (73)) <94CAR(262)147>. This reaction has been also employed in peptide synthesis <94JA4149>.



3.06.9.5.3 Synthesis from CSC_2N component

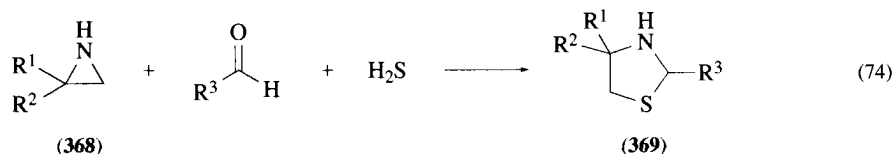
This type of approach is involved in the cyclization of thiobutenoic acids (365) to give a mixture of thiazolidines (366) and (367) (Scheme 92). Compounds (365) are prepared by a Michael-type addition of 2-aminoethanethiol to propiolic acids <94BCJ3021>.



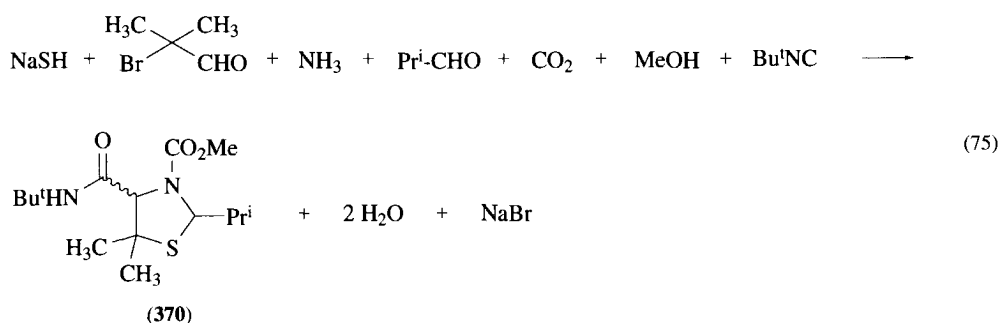
Scheme 92

3.06.9.5.4 Synthesis from more than two components

The regioselective ring opening of 2-dialkylaziridines with aldehydes in the presence of hydrogen sulfide affords 4,4-dialkylthiazolidines (369) (Equation (74)) <87CB1073>.



Thiazolidine (370) is obtained in a seven-component reaction (Equation (75)) <93AG(E)563>.



3.06.9.6 Synthesis of Benzothiazoles

3.06.9.6.1 Ring closure of *o*-aminothiophenols

The most general method for the synthesis of benzothiazoles and benzothiazolines is the cyclization of *ortho*-disubstituted benzenes, *o*-aminothiophenols, or naphthols with electrophilic reagents. This approach is well-documented in CHEC-I <84CHEC-I(6)321>.

Alkyl-, aryl-, and hetaryl aldehydes react with *o*-aminothiophenol in DMSO to give the corresponding 2-substituted benzothiazoles (371) (Equation (76)) <90DP243>. Similar reactions with carboxylic acids <90MI 306-02>, esters, and nitriles <92MI 306-03> have been described.



Aryl- and hetaryldithiocarbamates have been employed in condensation reactions to prepare 2-amino substituted benzothiazoles (372) (Equation (77)) <87S368, 90SC2327>.

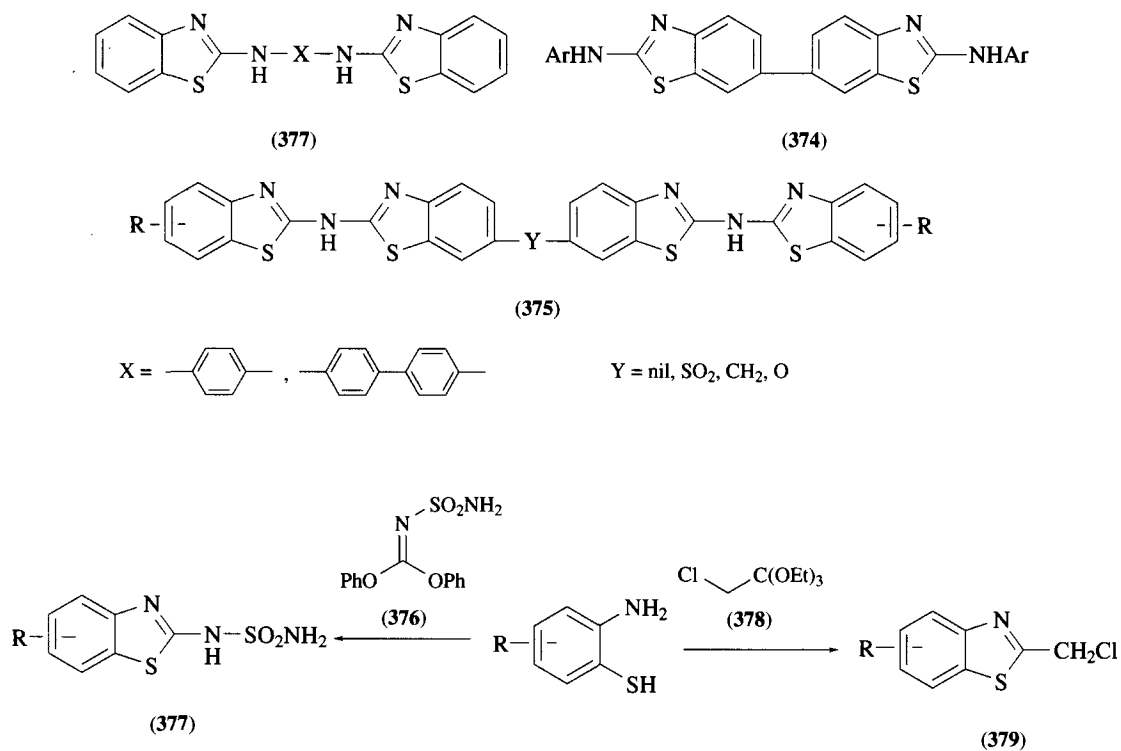


These reactions have also been employed for the preparation of bisbenzothiazolyl compounds such as (373) <90JHC221>, (374) <90JHC321>, or (375) <89SC2389, 90JHC321>. Interest for these compounds stems from their use as oligomers for the construction of heterocyclic polymers as well as their use as tetradentate ligands <94AQ487>.

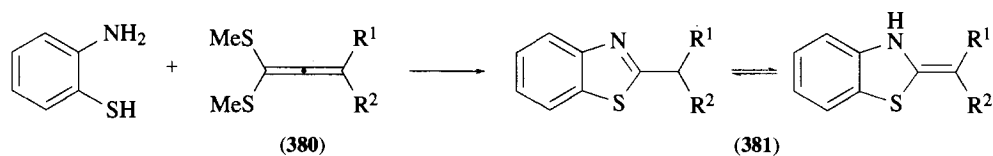
The reaction of aryl isothiocyanates with *o*-aminothiophenol also affords the corresponding 2-amino substituted benzothiazoles (372) <91JHC359>. Diphenyl *N*-sulfamoylcarbonimidate (376) and *o*-aminothiophenols are used for the synthesis of sulfonamides (377) <91S753>. The same thiophenols and ethyl α -chloroorthoacetate (378) leads to 2-chloromethyl benzothiazoles (379) (Scheme 93) <89SC2921>.

Dimethyldithioallenes (380) are also capable of reacting with *o*-aminothiophenol affording 2-substituted benzothiazoles (381) (Scheme 94) <90CB541>.

The synthesis of 2-substituted benzothiazoles has been also described by using *o*-aminothiophenol

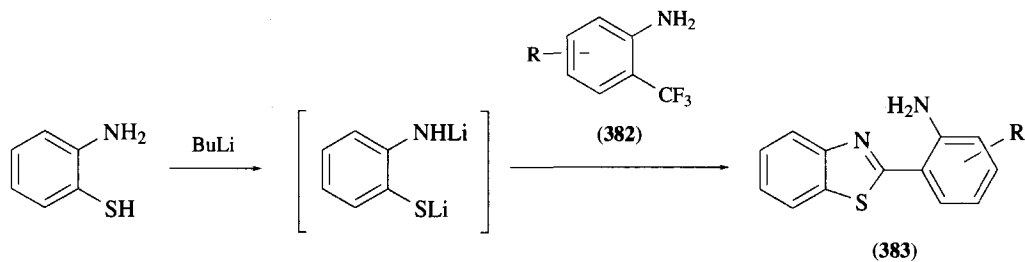


Scheme 93



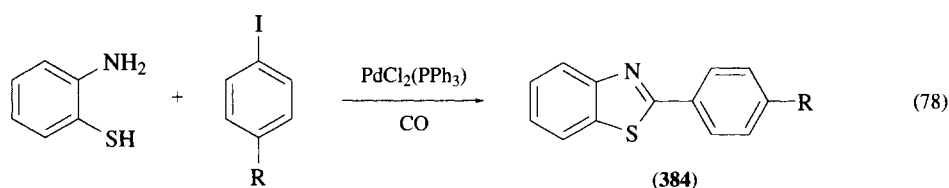
Scheme 94

and aryl- and hetaryl trifluoromethanes. The *in situ* generated dianion of *o*-aminothiophenol reacts with the *o*-trifluoromethyl anilines (382) to give the corresponding 2-aryl- and 2-hetaryl-benzothiazoles (383) (Scheme 95) (94H(37)775). The reaction should proceed by sequential nucleophilic substitution reaction of the fluorine atoms of the trifluoromethyl group.

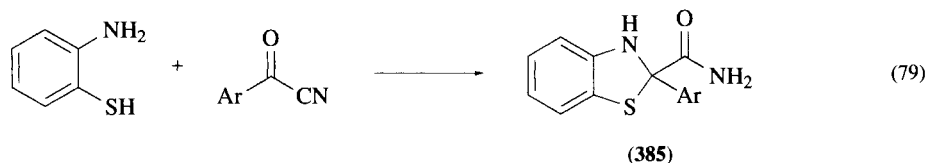


Scheme 95

2-Arylbenthiazoles (384) can be obtained from *o*-aminothiophenol and iodobenzenes in a palladium-catalyzed carbonylation reaction (Equation (78)) (94OM3346).



Condensation reactions with *o*-aminothiophenol can also give rise to benzothiazolines. Thus, the reaction with benzoyl cyanides affords compounds (385) (Equation (79)) <93OPP705>.

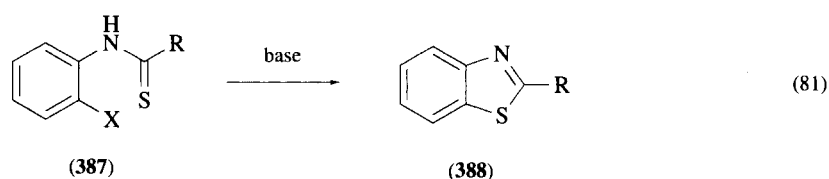


Condensation of aldehydes or ketones with *N*-methyl-*o*-aminothiophenol gives the corresponding benzothiazolines (386). The reaction is carried out under neutral conditions (Equation (80)) <85H(23)2509>.

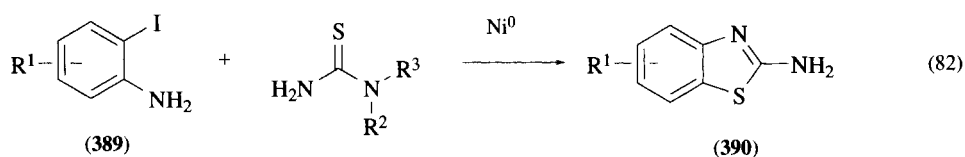


3.06.9.6.2 Other methods

An intramolecular aromatic nucleophilic substitution has been used for the preparation of 2-substituted benzothiazoles (388) in high yields from *o*-halothioanilides (387), the halogen atoms being iodine, bromide, or chlorine <82TL5093>. This reaction can also be carried out with naphtho-derivatives <89IJC(B)597>. Moreover, in the presence of sodium carbonate, the reaction can be extended to fluorine-substituted substrates (Equation (81)) <89JHC1039>.

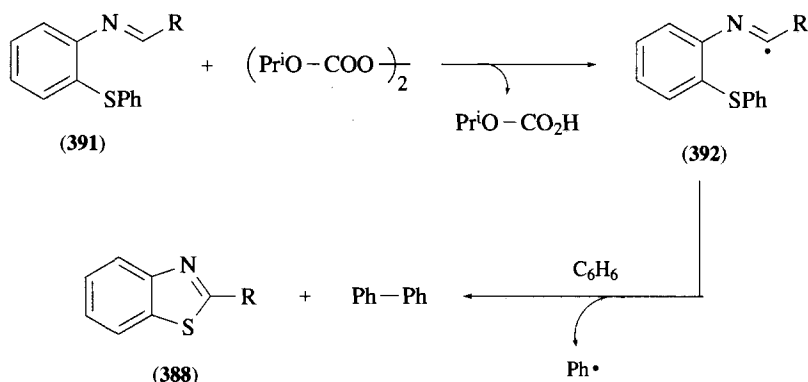


1,2-Aminoiodoarenes (389) undergo cyclization with thioureas in the presence of Ni^0 complexes generated *in situ* from $(\text{Et}_3\text{P})_2\text{NiCl}_2$ and sodium cyanoborohydride to form 2-aminobenzothiazoles (390) (Equation (82)) <86CL265>. These compounds are also accessible from anilines by reaction with thiocyanogen generated by electrochemical means <87NKK1497>.



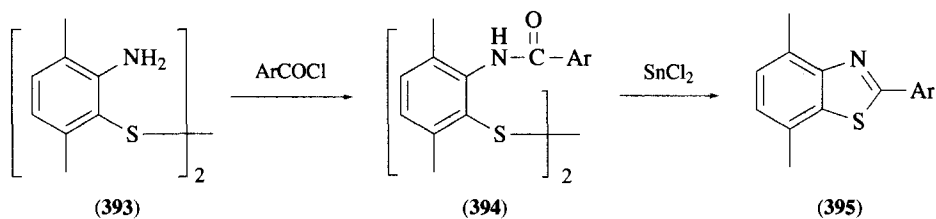
2-Phenylthioarylimines (391) cyclize to 2-substituted benzothiazoles (388) upon treatment with diisopropylperoxydicarbonate (DPDC). The formation of biphenyl alongside (388) has been con-

sidered as evidence of a free-radical mechanism via the intermediate (392) as outlined in Scheme 96 <92T3961>.



Scheme 96

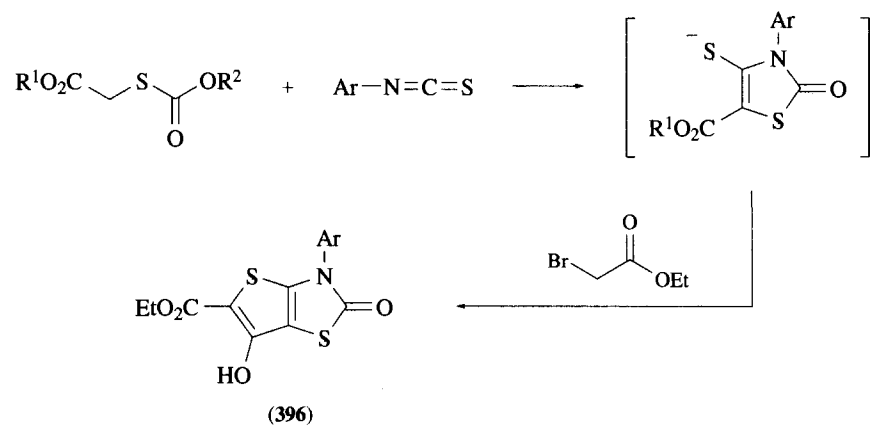
Benzothiazoles bearing a substituted phenyl group at C-2 can be prepared from the corresponding bis-(2-aminophenyl)disulfide (393). Treatment of (393) with an aroyl chloride affords the intermediate (394) which cyclizes to 2-arylbenzothiazoles (395) upon treatment with tin(II) chloride (Scheme 97) <93SC663>.



Scheme 97

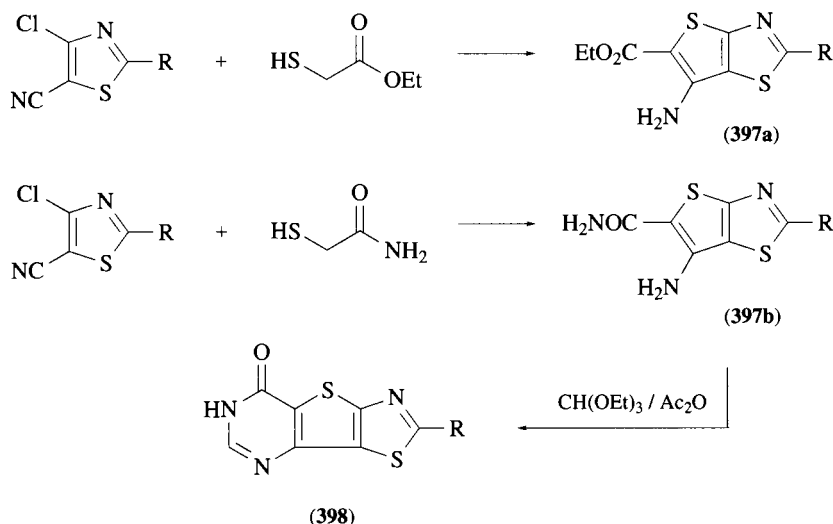
3.06.9.7 Synthesis of Fused Systems

Thieno[2,3-*d*]thiazoles (396) have been prepared from aryl isothiocyanates and thiocarbonates, through the alkylation of the thiolate intermediate with ethyl α -bromoacetate (Scheme 98) <90S621>.



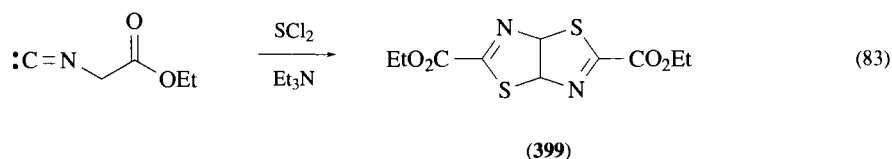
Scheme 98

Compounds **(397)** can be prepared by reaction of 4-chloro-thiazole-5-carbonitriles with ethyl 2-thioacetate or a 2-thioacetamide <92T7689>. The thieno [2,3-*d*]thiazole-5-carboxamides **(397b)** obtained in that way lead to thiazolo[4',5';4,5]-thieno[3,2-*d*]pyrimidin-5(6*H*)-one **(398)** upon treatment with triethyl orthoformate in acetic anhydride (Scheme 99).

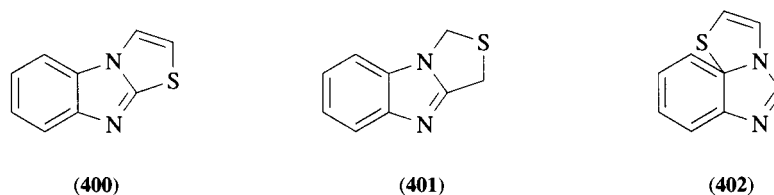


Scheme 99

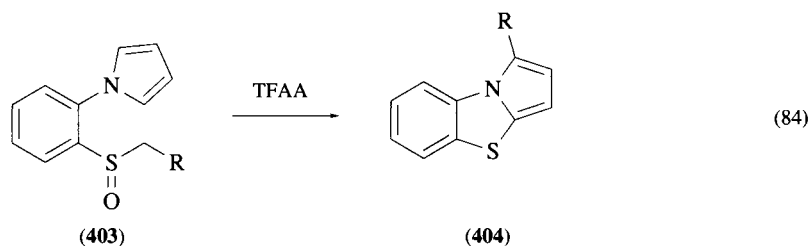
Thiazolo[5,4-*d*]thiazoles (**(399)**) are formed by the reaction between ethyl isocyanoacetate and sulfur dichloride in the presence of triethylamine (Equation (83)) <87S1138>.



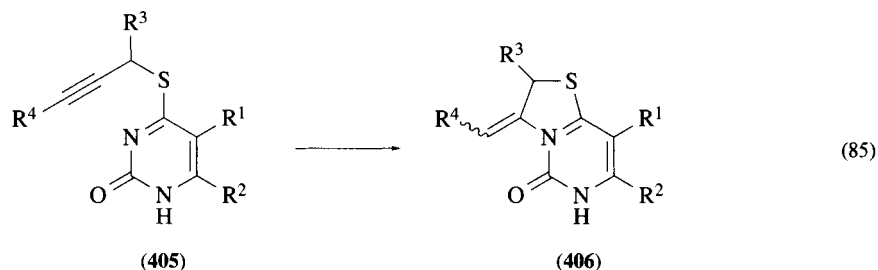
An extensive revision concerning the synthesis of thiazolo[3,2-*a*]benzimidazoles (**(400)**), thiazolo[3,4-*a*]benzimidazoles (**(401)**), and thiazolo[3,2-*c*]benzimidazoles (**(402)**) has been reported <88H(27)1975>. All synthetic approaches to these systems involve the use of 2-thiobenzimidazole derivatives as starting materials; the construction of the thiazole ring is carried out by intramolecular cyclization with a variety of reagents. The only exception is the preparation of compound (**(402)**) which is formed by the reaction of imidazo[5,1-*b*]thiazoles with dialkyl acetylenedicarboxylate.



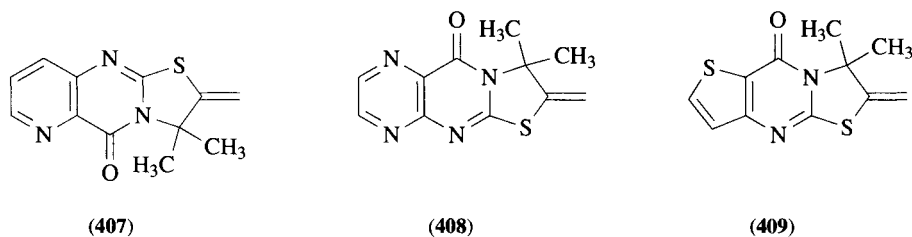
Treatment of sulfoxides (**(403)**) with trifluoroacetic anhydride (TFAA) in hot toluene affords pyrrolo[2,1-*b*]benzothiazoles (**(404)**) (Equation (84)) <92JOC3094>.



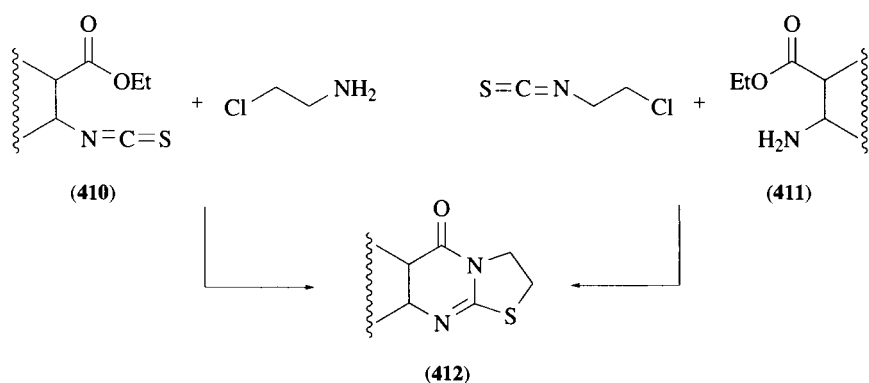
Propargylthiopyrimidines (**405**) give thiazolo[3,2-*c*]pyrimidinones (**406**) under the catalytic action of a Pd^{II} salt <86T305>. The reaction proceeds via nucleophilic addition of the amide nitrogen to the acetylene triple bond (Equation (85)).



Thiazolo[5,4-*b*]pyridines can be prepared by treatment of the corresponding 3-amino-2-chloropyridine with butyllithium and subsequent cyclization with thioesters <87JHC1765>. The synthesis of isomeric thiazolo[3,2-*a*]pyridopyrimidines (**407**) and thiazolo[2,3-*b*]pteridines (**408**), and thiazolo[3,2-*a*]thieno[3,2-*d*]pyrimidines (**409**) has been reported starting from heterocyclic isothiocyanates bearing an ester group in the *ortho*-position through cyclization reactions with propargylamines <93HCA431>.



Similarly, isothiocyanates (**410**) have been employed in the preparation of thiazolo[2,3-*b*]quinazolines (**412**). Alternatively, these compounds are also accessible from amino esters (**411**) and β -chloroisothiocyanates (Scheme 100) <94BSB509>.



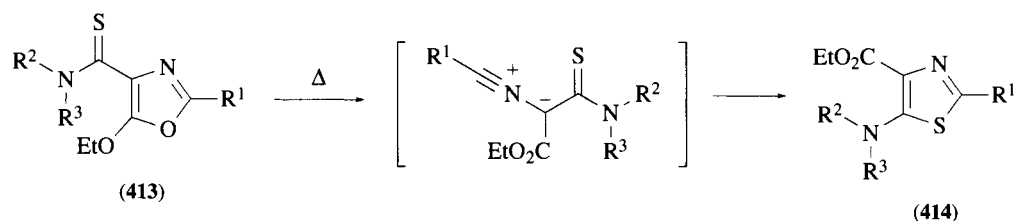
Scheme 100

3.06.10 RING SYNTHESSES BY TRANSFORMATION OF ANOTHER RING

3.06.10.1 Synthesis from Fully Conjugated Rings

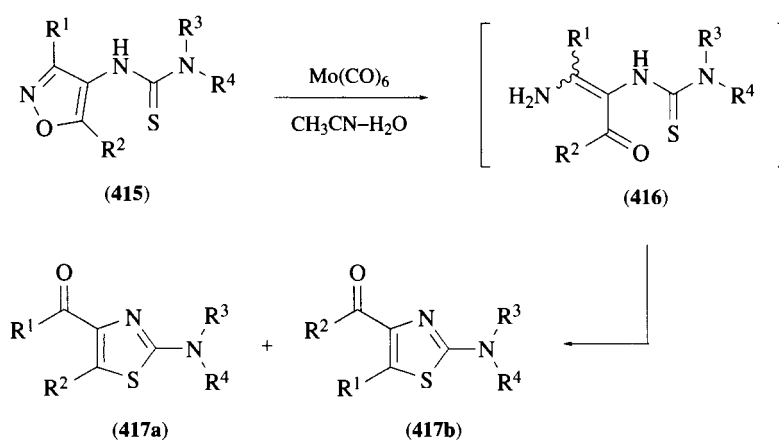
Thiazole derivatives (**414**) can be obtained by rearrangement of 4-(aminothiocabonyl)-5-ethoxyoxazoles (**413**) in refluxing toluene <90JOC4484>. The reaction should proceed via a nitrile ylide

intermediate (Scheme 101). The mechanism of this transformation has been the subject of a theoretical approach by MINDO/3MO calculations.



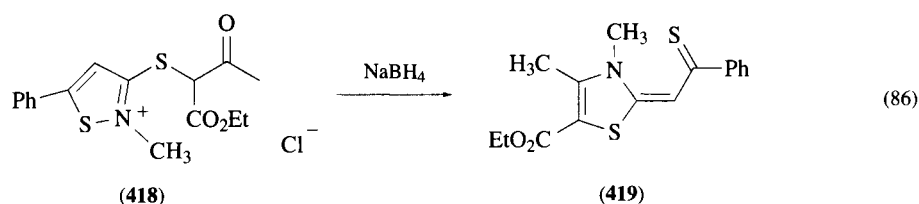
Scheme 101

2-Aminothiazoles (417) are obtained when isoxazoles (415) are treated with hexacarbonylmolybdenum in a mixture of acetonitrile–water (Scheme 102) (91HCA531).



Scheme 102

The reduction with sodium borohydride of isothiazole (418) gives rise to the thiazole derivative (419). Similar results are obtained when the same isothiazolium chloride is treated with triphenylphosphine in chloroform (Equation (86)) (93JHC929).

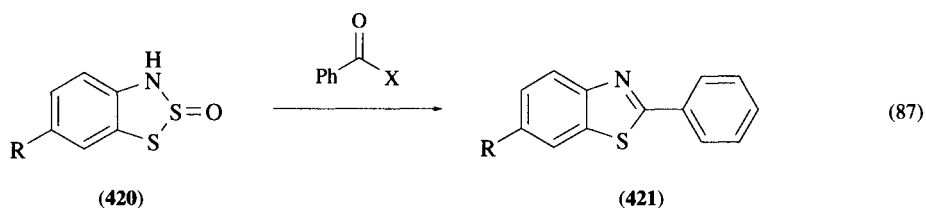


3.06.10.2 Synthesis from Di- and Tetrahydro Derivatives

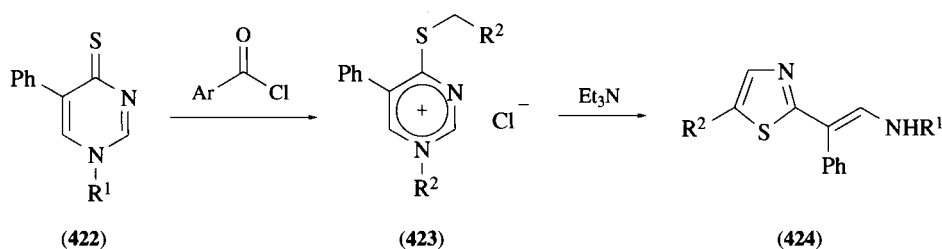
Thiazoles can be prepared by aromatization of dihydro derivatives as discussed in Section 3.06.6.2.2. In addition, dehydration of 4-hydroxy-2-thiazolines also leads to the fully conjugated derivatives. In general, the hydroxythiazolines are intermediates in various synthetic approaches to thiazoles (see Section 3.06.9).

3.06.10.3 Synthesis from Other Rings

Benzodithiazole-2-oxides (420) react with aromatic aldehydes, carboxylic acids, and their chlorides in the presence of an organic base to afford arylbenzothiazoles (421) (Equation (87)) (93SC263). No comments have been made regarding the mechanism of this process.

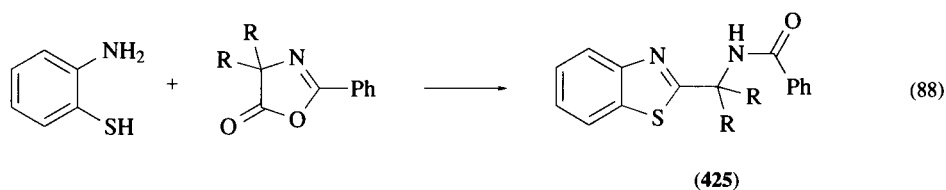


The reaction of phenacyl halides with pyrimidinethiones (422) affords the corresponding pyrimidininium salts (423) which treated with bases leads to 5-substituted 2-(2-amino-1-phenylethenyl) thiazoles (424) (Scheme 103) <87S949>.

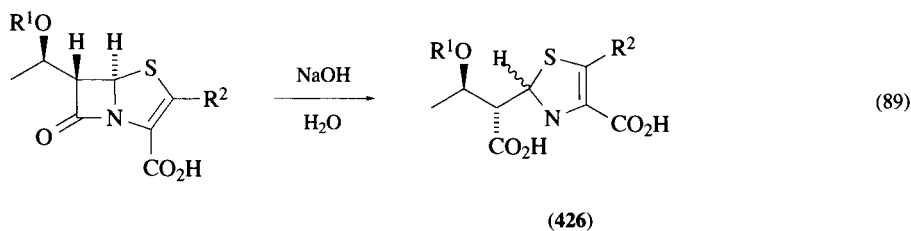


Scheme 103

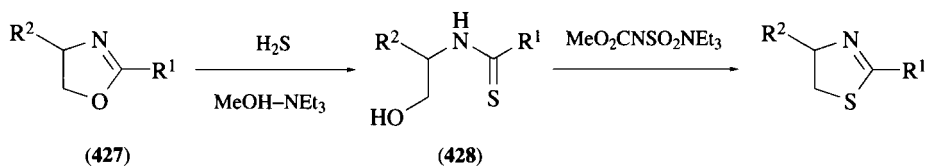
Condensation of azlactones with *o*-aminothiophenol affords benzothiazoles (425) (Equation 88) <88SC651>.



Chiral 4-thiazolines (426) can be generated upon cleavage of the β -lactam ring of penems (Equation (89)) <92H(33)859>. These compounds are unstable and degradation to a complex mixture of products occurs within a few days.



Thiolysis of oxazolines (427) with H_2S affords thioamides (428) which by subsequent cyclodehydration with the Burgess reagent ($\text{MeO}_2\text{CNSO}_2\text{NEt}_3$) lead to 2-thiazolines (Scheme 104) <95TL6395>.

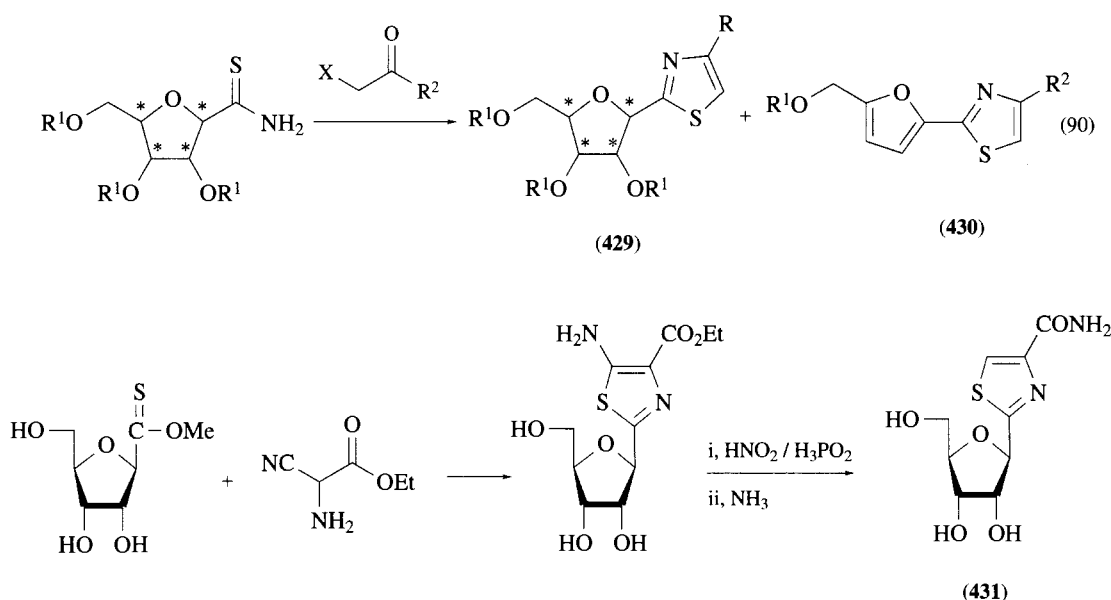


Scheme 104

3.06.11 SYNTHESIS OF PARTICULAR CLASSES OF COMPOUNDS AND COMPARISON OF THE VARIOUS ROUTES AVAILABLE

3.06.11.1 Synthesis of Thiazole-C-Nucleosides

Several C-glycosyl thiazole nucleosides exhibit antitumor and antibiotic activities (see Section 3.06.12.2). In particular, 2- β -D-ribofuranosylthiazole-4-carboxamide (**431**), currently called tiazofurin, has been shown to be an effective antitumor agent against a number of model tumor systems. The most extensively used synthetic approach for obtaining thiazole C-nucleosides is based on the construction of the thiazole ring at the selected carbon atom of a sugar moiety. To this aim, the Hantzsch reaction between a sugar thioamide or related compounds and α -halocarbonyl derivatives is the most employed method (<75HCA1507, 76JOC4074>). However, this reaction often gives low yields of the target thiazole C-nucleoside (**429**) and, by contrast, large amounts of a furylthiazole derivative (**430**) (Equation (90)). The formation of furan derivatives is a quite common side reaction in glycofuranosylthiazole chemistry (<91T5539>). A related approach involves the condensation of sugar-thioesters with 2-aminoacetonitrile (<85JOC1741>). Several ribofuranosyl thiazoles have been prepared by this method. The elaboration of the substituents in the thiazole ring allows to obtain the target C-nucleoside as illustrated for the synthesis of tiazofurin (**431**) (Scheme 105).

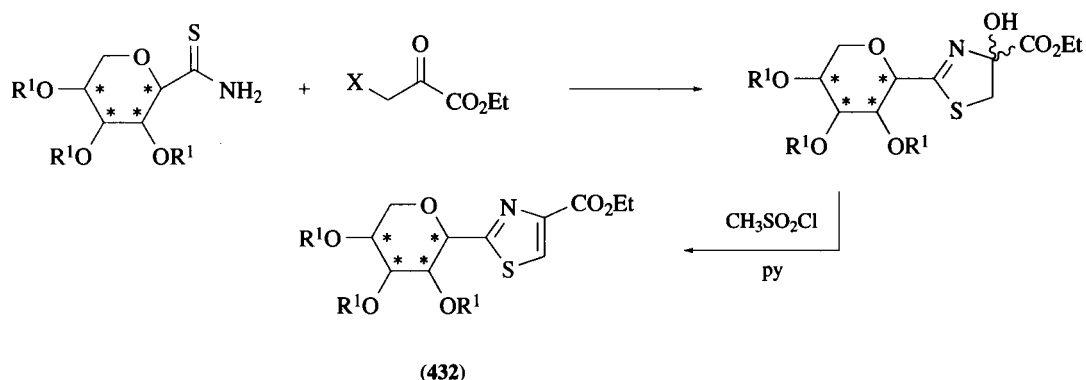


Scheme 105

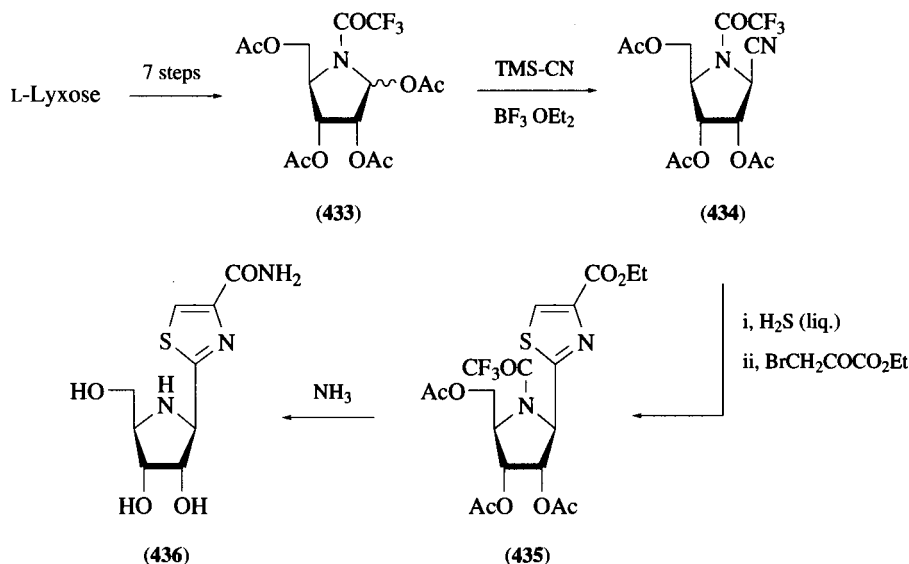
Pyranose analogues of (**431**) can be prepared by an efficient Hantzsch reaction between glyco-pyranosyl thioamides and ethyl bromopyruvate in the presence of barium carbonate. Attempted dehydration of the thiazoline ring of the resulting sugar thiazolines was accompanied by a substantial elimination reaction in the sugar moiety when the hydroxyl groups were protected as acetyl derivatives. On the other hand, hydroxyl-protected derivatives were converted to compounds (**432**) although in modest yields. (Scheme 106) (<91T5539>). These compounds are useful starting materials for the preparation of differentially functionalized derivatives (<91T5549>).

Compound (**436**), which can be looked as the aza analog of diezofurin (**431**), has been prepared starting from the pyrrolidine derivative (**433**), i.e., an azasugar, which is readily accessible from L-lyxose in several steps. The construction of the thiazole ring is achieved by reaction of the nitrile (**434**) with liquid hydrogen sulfide and the Hantzsch reaction of the resulting thioamide with ethyl bromopyruvate (Scheme 107) (<86JOC4436>).

Glycosyl cyanides have also been employed as starting materials in the synthesis of 5-glycosylthiazoles (<94JCS(P1)3029>). Direct glycosylation of thiazole under different conditions failed. An efficient method for introducing the thiazole ring at the anomeric position of sugars is the addition of 2-lithiothiazole (**219**) to sugar lactones (Scheme 54) (<93TL7319, 94JOC6404>). The resulting thiazolyl ketol is easily dehydroxylated through its acetate to give the thiazolyl glycoside (see Section



Scheme 106



Scheme 107

3.06.7.10.1). The sequence is applicable to a variety of furanoses and pyranoses leading to furanosylthiazoles (437) and pyranosylthiazoles (438), respectively.

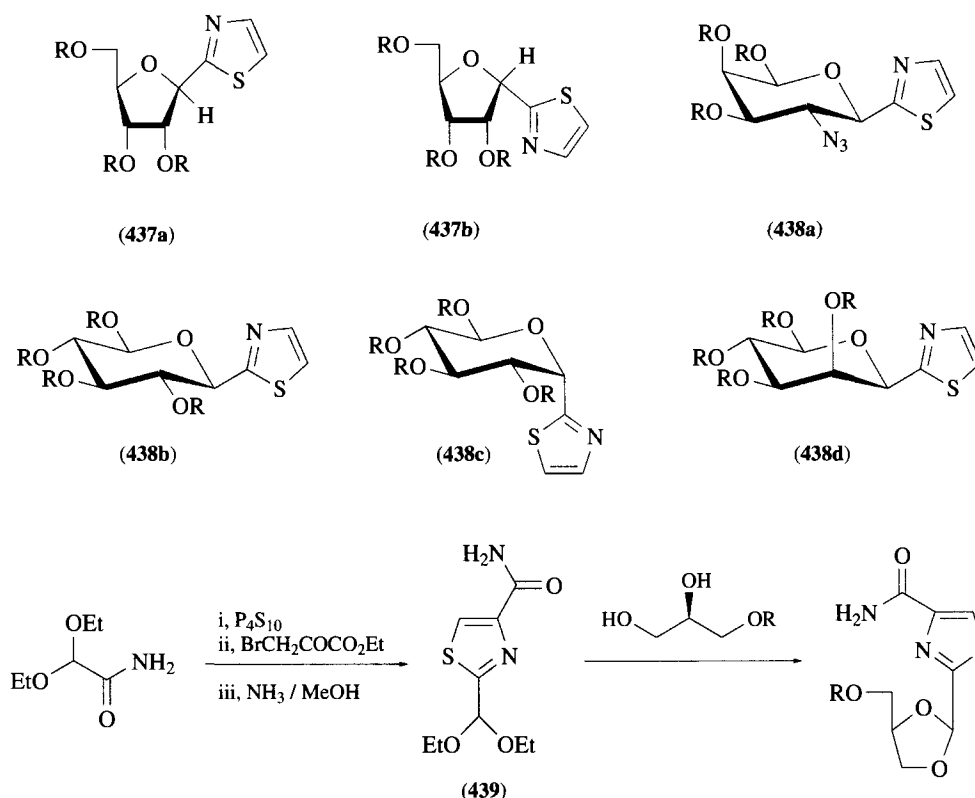
1,3-Dioxolane analogues of thiazole nucleosides have been prepared starting from the thiazole derivative (439) which in turn is readily available from 2,2-diethoxyacetamide in a one-pot reaction (Scheme 108) <95TL3781>.

3.06.11.2 Synthesis of Thiazole-containing Peptides

3.06.11.2.1 Single amino acids

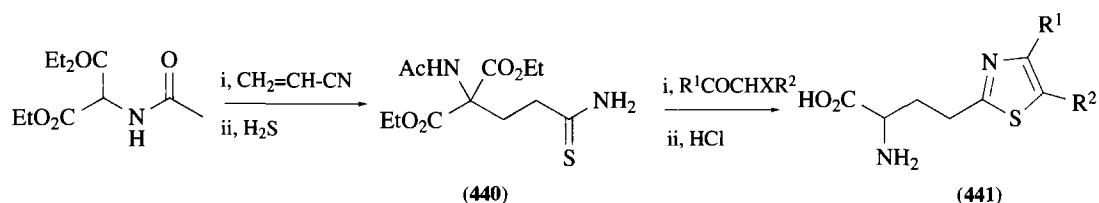
The biological interest in thiazole-containing peptides has meant that the synthesis of single thiazole amino acids has become important <93MI 306-08> since these products are the starting materials for the peptide assemblage (see Sections 3.06.11.2.2 and 3.06.11.2.3). Especially interesting is the preparation of optically active compounds such as 3-(4-thiazolyl)-L-alanine, the component of an important renin inhibitor <90SC3507, 92S1145>.

Thiazol- α -amino acids (441) can be prepared by the Hantzsch thiazole synthesis of the thioamide



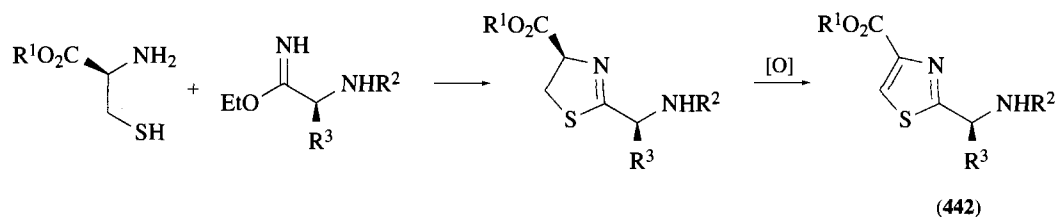
Scheme 108

(440) with suitable 2-halocarbonyl compounds (Scheme 109). In turn, the thioamide (440) is obtained through a Michael-type addition of acrylonitrile to diethyl acetamidomalonate and subsequent treatment with hydrogen sulfide. <93EJM387>.



Scheme 109

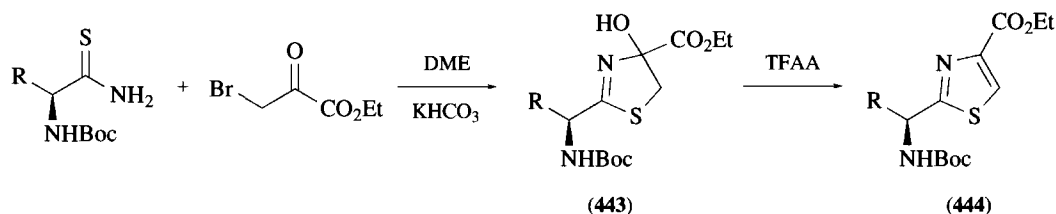
Enantiomerically pure thiazoline and thiazole amino acids can be synthesized by condensation reactions between cysteine esters and chiral imino ethers derived from amino acids (Scheme 110) <90T8267, 95SL417>.



Scheme 110

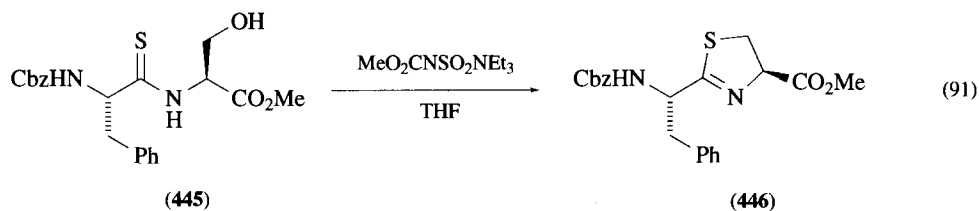
Amino acids (442) have been also prepared by the Hantzsch synthesis from thioureas and ethyl bromopyruvate <85JOC2787>. However, substantial racemization can occur in this case as well

<85JOC2323>. The preparation of a 4-hydroxythiazoline intermediate and dehydration of this compound to the target thiazole overcomes this problem. The synthesis consists of the condensation of ethyl bromopyruvate with thioamides in dimethoxyethane (DME) in the presence of potassium hydrogen carbonate to give thiazolines (**443**). Activation of the hydroxyl group and dehydration with trifluoroacetic anhydride (TFAA) leads to thiazole amino acids (**444**) <90SC2235>. Under the improved reaction conditions ($\text{KHCO}_3/\text{DME}/-15^\circ\text{C}$) outlined by Meyers <94TL2473>, compounds (**444**) are obtained in enantiomerically pure form (Scheme 111). These findings demonstrate that racemization takes place during the cyclization process and not in the dehydration step.

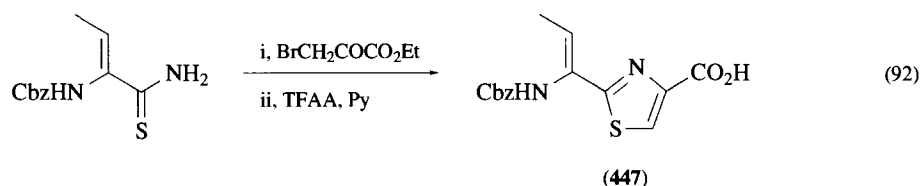


Scheme 111

Thiazoline amino acids can be prepared from β -hydroxythioamides such as (**445**) by inducing the cyclization with tosyl chloride in the presence of triethylamine or with thionyl chloride. Under both conditions, however, the complete racemization takes place. Fortunately enough, the use of the Burgess reagent ($\text{MeO}_2\text{CNSO}_2\text{NEt}_3$) induces the cyclization of (**445**) to enantiomerically pure compounds (**446**) (Equation (91)) <94TL5397>.



Thiazole α,β -dehydro amino acid (**447**) is prepared by cyclization of the corresponding thioamide with ethyl bromopyruvate (Equation (92)). The reaction occurs through the hydroxythiazoline intermediate which dehydrates in the presence of trifluoroacetic anhydride (TFAA) <92CL1005>.



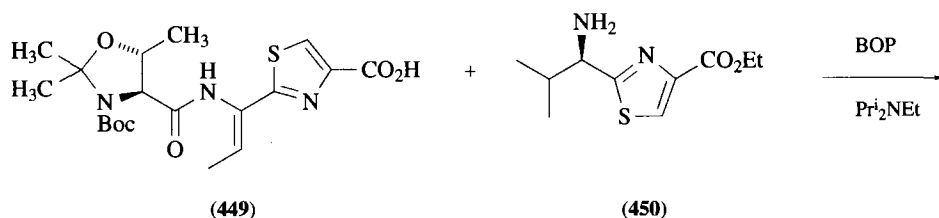
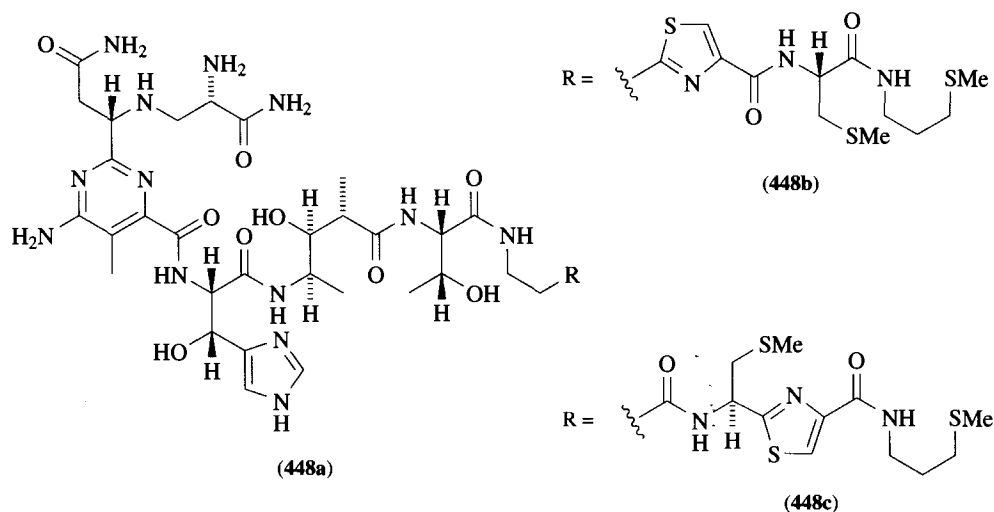
3.06.11.2.2 Linear peptides

Several thiazole-containing linear peptides such as dysidenin, isodysidenin, and dysidin have been isolated from marine invertebrates and their absolute configurations have been established <80T2133, 93JOC6336, 95TL1185>. However, the total synthesis of any of these compounds has not been reported.

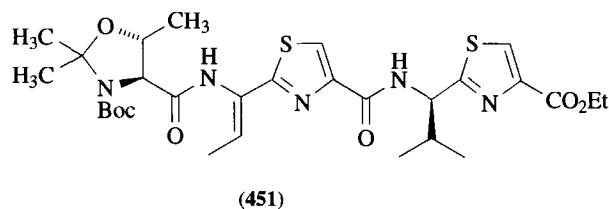
Condensation of thiazole amino acids with other α -amino acids leads to thiazole-containing linear peptides whose biological activity has been evaluated <90T8267, 93EJM387>.

Two analogues (**448b**) and (**448c**) of bleomycin A2 (**448a**) have been prepared by total synthesis <92JA6278>. These compounds have been used to obtain information on the role of individual thiazole moieties in the processes of bleomycin-mediated oxygen activation and DNA degradation. The complete synthesis of bleomycin A2 has been reported by Boger and co-workers <94JA5607, 94JA5619, 94JA5631, 94JA5647>.

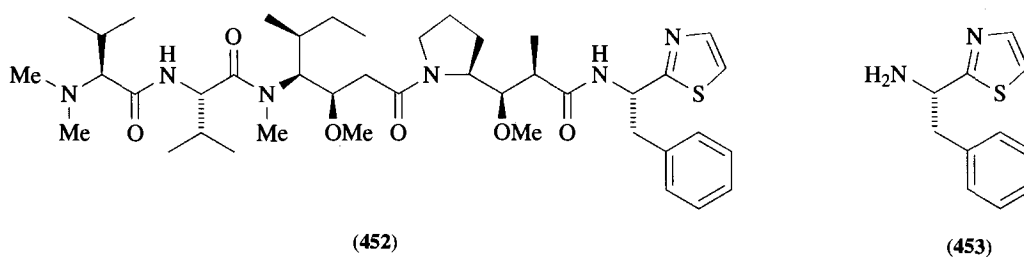
In a similar way, the dipeptide (**449**) reacts with the thiazole amino acid (**450**) in the presence of benzotriazol-1-yl-oxy-tris(dimethylamino)phosphonium hexafluorophosphate (BOP) to give the corresponding tripeptide (**451**) (Equation (93)) <92CL1005>.



(93)



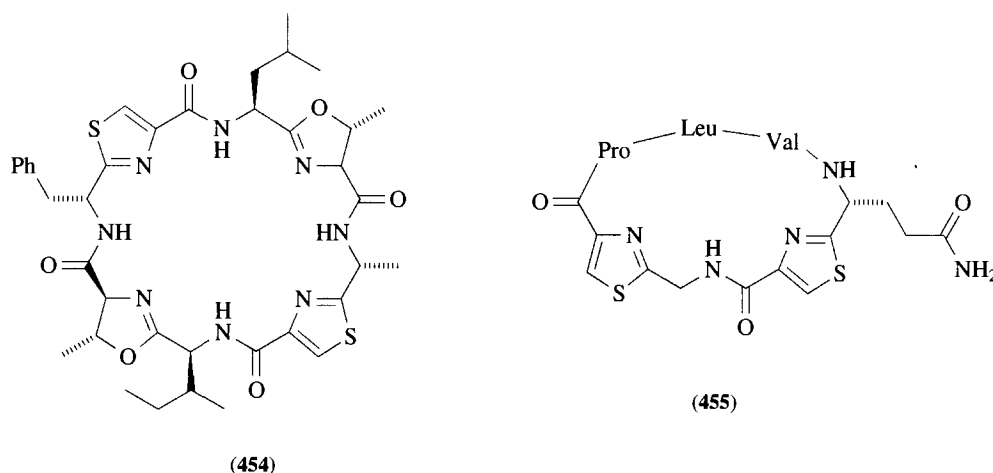
An important group of thiazole-containing linear peptides is the family of Dolastatins <93T9151> whose most representative member is Dolastatin 10 **(452)** due to its extraordinary antitumor activity. The absolute configuration of **(452)** has been confirmed by total synthesis <89JA5463>. In this context several synthetic efforts were made to achieve an expeditious synthesis of **(452)** <91TL931, 91TL2395, 93T1913, 94T5345>. Conformational studies of this compound <95T2593> and some analogs <94JOC6127> have also been carried out. Particularly interesting is the synthesis of (*S*)-Dolaphenine **(453)**, the C-terminal unit of Dolastatin 10. Preparation of **(453)** by the classical Hantzsch synthesis leads to complete racemization. Therefore, a modification of this reaction has been proposed <92SC3029>.



Convenient synthetic approaches to **(453)** and its antipode based on an asymmetric reduction of a 2-acylthiazole <92T7251> and enantioselective alkylation of 2-aminomethylthiazole <95T12731, 96S641> have been described.

3.06.11.2.3 Cyclic peptides

Numerous natural thiazole-containing cyclic peptides with interesting biological properties have been isolated and their absolute configuration established by various methods. Among these products are cyclothiazomycin <91TL217>, A10255-B, A10255-G, and A10255-J <92JOC5200>, keramamide F <92JOC5540>, nosiheptide <94SL759>, cyclodidemnamide <95TL8355>, nostocyclamide <95JOC7891>, dolastatin E <95TL5057>, and patellamides <80JA5688, 82JOC1807, 83JOC4445, 92JOC4616>. The synthesis of only a few of these compounds has been reported. Patellamide B (**454**) has been prepared by Schmidt and Griesser <86TL163>. The structure of dolastatin 3 (**455**) has been demonstrated through the synthesis of sixteen structural isomers of that compound <87S236>. The total synthesis of dolastatin E (**456**), a cyclic hexapeptide, was achieved by the sequential construction of the thiazole fragments <95TL5059>. Several thiazole fragments of nosiheptide (**457**) have been prepared <95JHC1309, 95SL1423>. Lissoclinamide (**458**) and some stereoisomers have also been synthesized <92JHC607, 94TL8271> thus showing that the earlier structure had to be modified. Bistatramide C (**459**) has been prepared by Meyers and Aguilar starting from enantiomerically pure heterocyclic amino acids <94TL2477>.



3.06.11.3 Synthesis of Linear 2,4-Disubstituted Systems

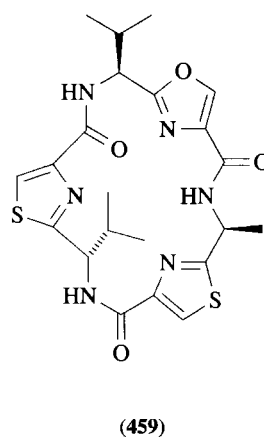
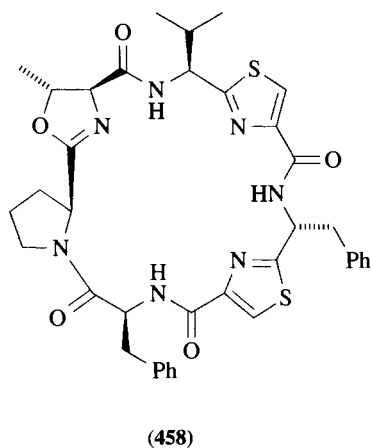
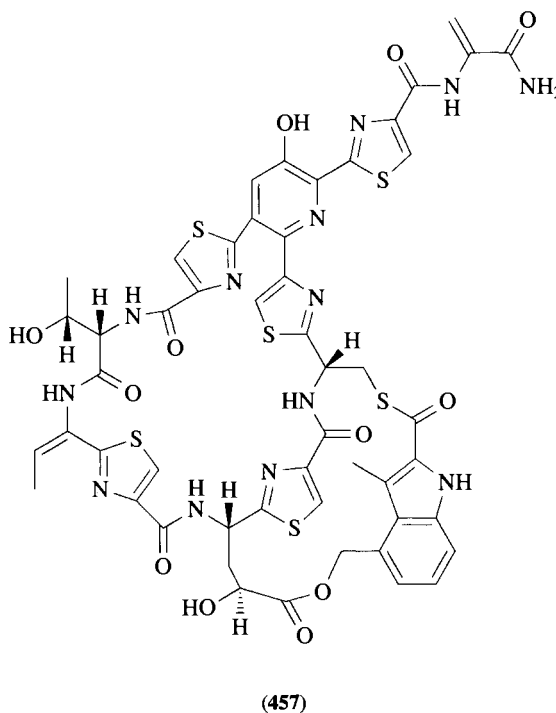
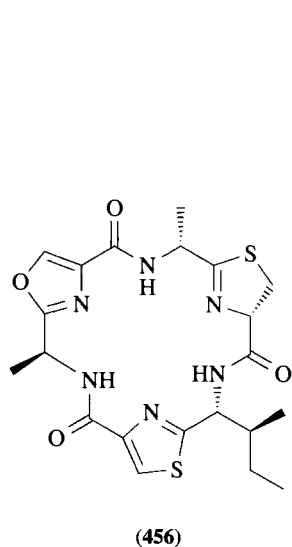
Compounds having a linear fusion of four or five successive 2,4-disubstituted thiazoline oxazole rings are important because of their antiviral activities. Among these compounds are tantazoles which exhibit an unusual cytotoxic activity <90JA8195>. The structure of tantazoles have been revised <93TL6681> and in some cases like tantazole B (**460**) the absolute configuration has been established by total synthesis <93JA8449>.

Thiangazole (**461**) is closely related to tantazoles. Three synthetic routes to (**461**) have been described and the absolute configuration has been determined by x-ray crystallography <93LA701>. One of these syntheses makes use of the stepwise formation of thiazolidine moieties <94SL702>. The second synthesis utilizes a cyclocondensation between a bithiazoline nitrile and the oxazole moiety as a key step <94TL5705, 95T7321>. The third synthesis is based on selective oxazoline-thiazoline interconversions <95JOC7224>. Mirabazoles (**462**) and (**463**) constitute another class of tantazole-related compounds <91TL2593>. Total synthesis of mirabazole B (**462b**) <94TL1383>, mirabazole C (**462c**) <94TL1379> and dehydromirabazole A (**462d**) <93JCS(P1)1629, 95T7313> have been reported.

A total synthesis of micrococcinic acid (**463**) has been achieved through the assemblage of the five heterocyclic rings from the corresponding monocyclic precursors using palladium-catalyzed coupling reactions <91TL4263>. Myxothiazol (**464**) can be prepared by a convergent synthetic process starting from easily accessible building blocks <93TL5151>.

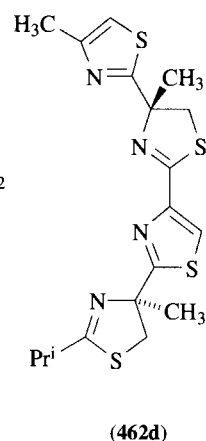
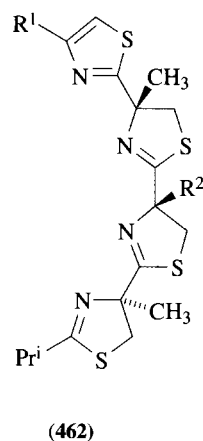
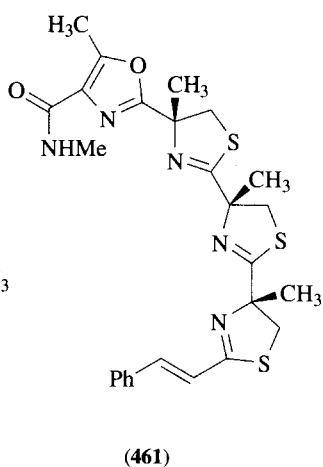
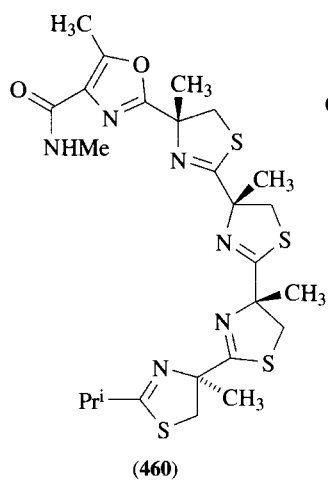
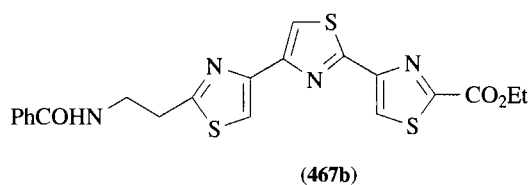
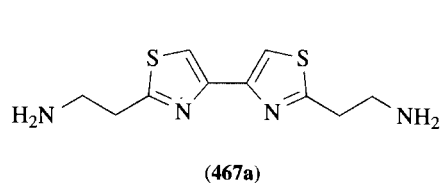
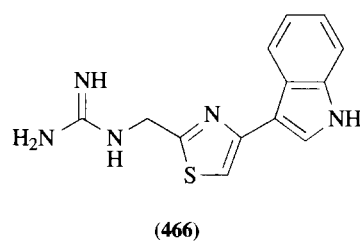
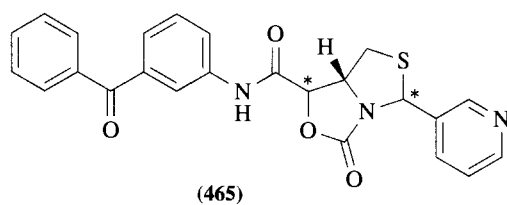
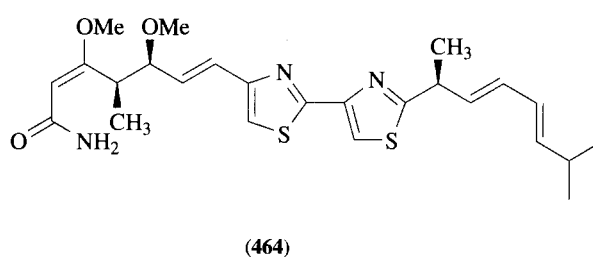
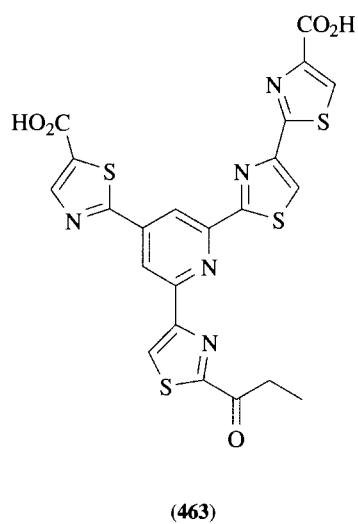
3.06.11.4 Synthesis of Other Compounds

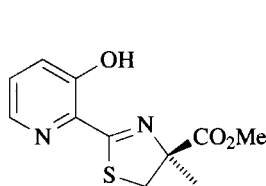
The four possible stereoisomers of the platelet activating factor antagonist (**465**) have been synthesized using a common synthetic pathway starting from L-cysteine and nicotinaldehyde <93BMC2729>.



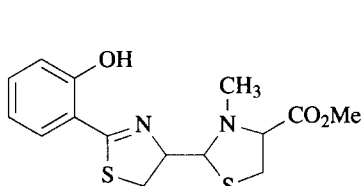
The synthesis of the 2-(guanidinomethyl)thiazole (**466**), a homologue of the important 2-guanidinothiazole (see Section 3.06.12.2), has been described starting from acetamido thioacetamide and 3-chloroacetylindole <90JHC519>. Bi- and trithiazole derivatives (**467a**) and (**467b**) are reported to be DNA cleaving agents; these systems can be prepared by repeated condensation of a bromoketone and the corresponding thioamide <92SL59> or by condensation of two equivalents of thioamide with dibromodicarbonyl compounds <94TL4401>.

The thiazoline-based siderophore (*S*)-desferrithiocin (**468**) has been prepared by a modification of the Seebach's "self-reproduction of chirality" protocol starting from (*S*)-cystein and pivalaldehyde <93T5359>. Similarly, pyochelin (**469**) has been prepared from L-cysteine and salicylonitrile <95JOC2786>. The penem thiazoline ring of ritipenems (**470**) can be constructed by the incorporation of glycolic acid into a commercially available β -lactam ring <93TL3491>. The total synthesis of leinamycin (**471**) has also been reported <93JA8451>. The structure of Dolabellin (**472**), a cytotoxic bithiazole metabolite from the sea hare *Dolabella auricularia*, has been determined by enantioselective total synthesis <95JOC4774>.

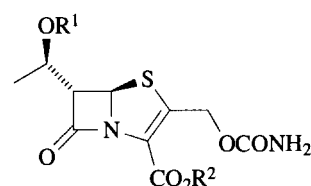
(a) $R^1 = \text{Me}$ $R^2 = \text{H}$ (b) $R^1 = \text{Me}$ $R^2 = \text{Me}$ (c) $R^1 = \text{H}$ $R^2 = \text{Me}$ 



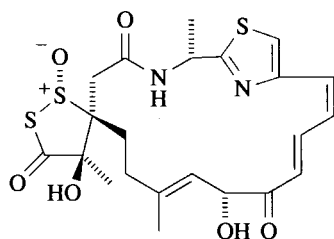
(468)



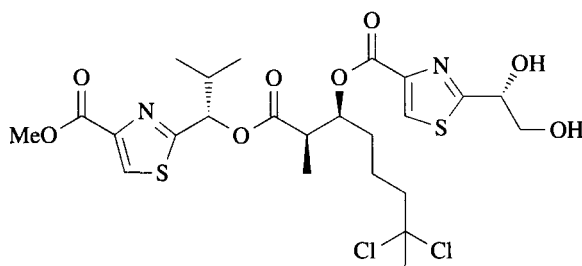
(469)



(470)



(471)



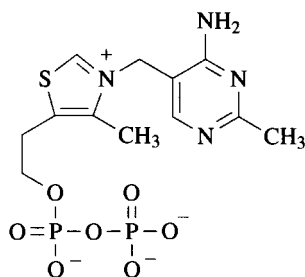
(472)

3.06.12 IMPORTANT COMPOUNDS AND SYNTHETIC APPLICATIONS

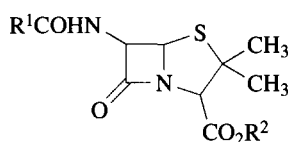
3.06.12.1 Natural Occurrence and Biological Applications

A very important naturally occurring thiazole derivative is thiamine pyrophosphate (**473**). It is the prosthetic group in a variety of enzymes which catalyze decarboxylation (decarboxylase) and aldol-type condensation (aldolase) reactions. The catalytic active site of the molecule is at C-2 of the thiazole ring <B-88MI 306-02>. The same activity of (**473**) is shown by other thiazolium salts and therefore these compounds have been widely exploited as catalysts in reactions of importance such as the benzoin condensation (see Section 3.06.12.2).

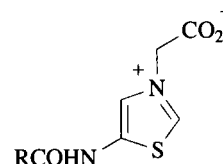
Other important naturally occurring thiazole derivatives are penicillins (**474**). These feature fused thiazolidine and β -lactam rings. A large number of penicillins are known and used as potent antibiotics <B-81MI 306-01>. Also 5-acylaminothiazolium salts (**475**) and 5-acylaminothiazolidine have been reported to exhibit antibiotic activity <91JAN844>. A wide range of thiazole-containing metabolites have been isolated and characterized from marine organisms <90T8267, 92JHC607>. Among those compounds are patellamides, a class of thiazole-containing cyclic peptides (see Section 3.06.11.2.3) which exhibit antineoplastic and antiviral activities <80JA5688, 82JOC1807, 83JOC4445, 92JOC4616>. Other thiazole-containing cyclic peptides of interest due to their antibiotic activity are keramamides <92JOC5540>, A10255 antibiotics <92JOC5200>, nosiheptide <94SL759>, and thiotipin <94TI1659>. Cyclothiazomycin is a polythiazole-containing peptide produced by *Streptomyces* sp. which exhibits an important renin inhibitory activity <91TL217, 91TL221>.



(473)



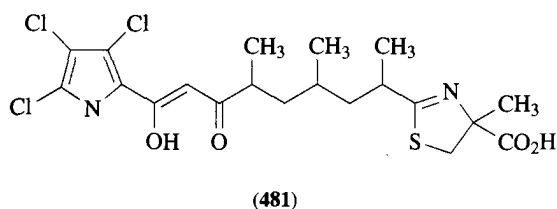
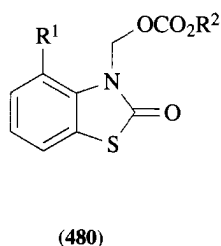
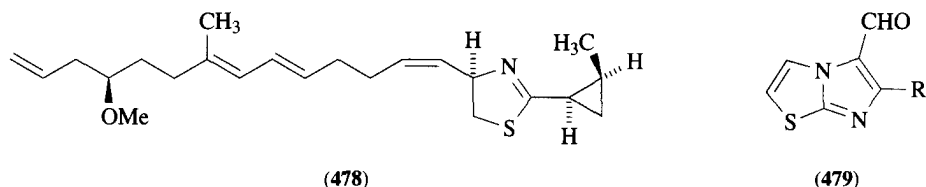
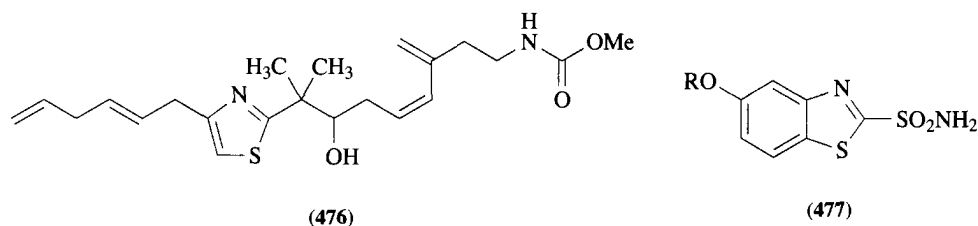
(474)



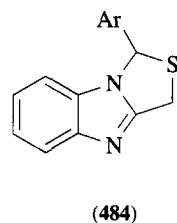
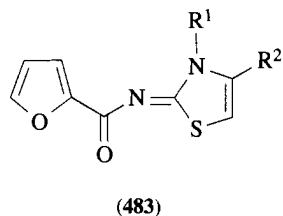
(475)

Mycothiazole (**476**) can be isolated from *Spongia mycofijiensis*, a marine sponge. This compound shows anti-helminthic activity *in vitro* while high toxicity is observed in mice <88JA4365>. *O*-Substituted

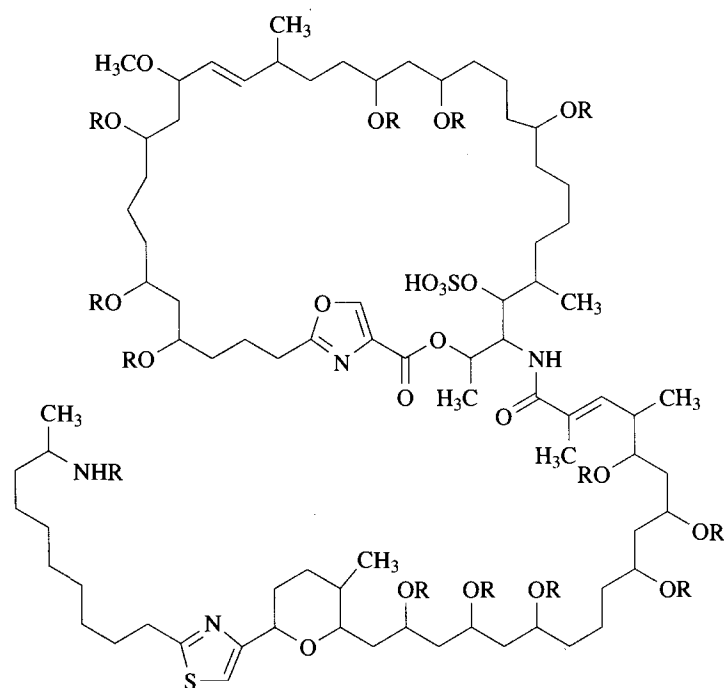
6-hydroxybenzothiazole-2-sulfonamides (**477**) are topically active carbonic anhydrase inhibitors <89JMC2486>. This activity confers to these compounds a potential utility as antiglaucoma drugs. Curacin A (**478**) is an anti-micotic which has been isolated from *Lyngbya majuscula*, a cyanobacteria <94JOC1243> and whose absolute configuration has been elucidated <95TL1189>. Formyl imidazo[2,1-*b*]thiazoles (**479**) have been proved to be effective as herbicides <91CCC2436>. Benzothiazolinones (**480**) show plant grow-stimulating effects <93MI 306-02, 93MI 306-06, 93MI 306-07, 93MI 306-09>. Some thiazolidine-2-thione derivatives showed hepatoprotective activities both *in vitro* and *in vivo* studies <93CPB876>. Thiazolohalostatin (**481**) is produced by *Actinomadura* *sp.* It prevents cell death caused by calcium overload and exhibits an inhibitory activity against lipid peroxidation <93JAN1633>. Theonezolid A (**482**) is a macrolide isolated from the marine sponge *Theonella* *sp.* which exhibits cytotoxicity against murine lymphoma and human epidermoid carcinoma <93JA6661>.



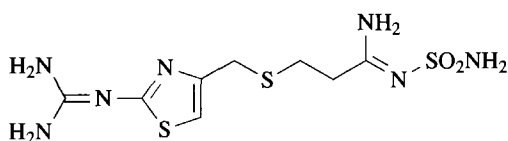
Certain 4-thiazolin derivatives (**483**) show significant activity as anti-convulsant agents <94FES133>. Thiazolo[3,4-*a*]benzimidazoles (**484**) show reproducible *in vitro* anti-HIV activity <91FES817, 91FES925>. The enantiomeric resolution of these compounds is achieved by HPLC on a chiral stationary phase <94MI 306-04>.



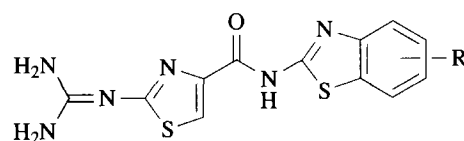
Guanidinothiazoles (**485**) such as famotidine (**485a**) are known to be inhibitors of gastric acids <88EJM97> and they have been used in the treatment of gastric ulcers <85MI 306-01, 86MI 306-03>. This class of compounds, i.e., ω -aminoalkylthiazoles, are of interest because of their analogy with histamine <94SL471>. Other guanidinothiazoles like amides (**485b**) are found to be systemically active against lung carcinomas <91JMC1975>.



(482)



(485a)



(485b)

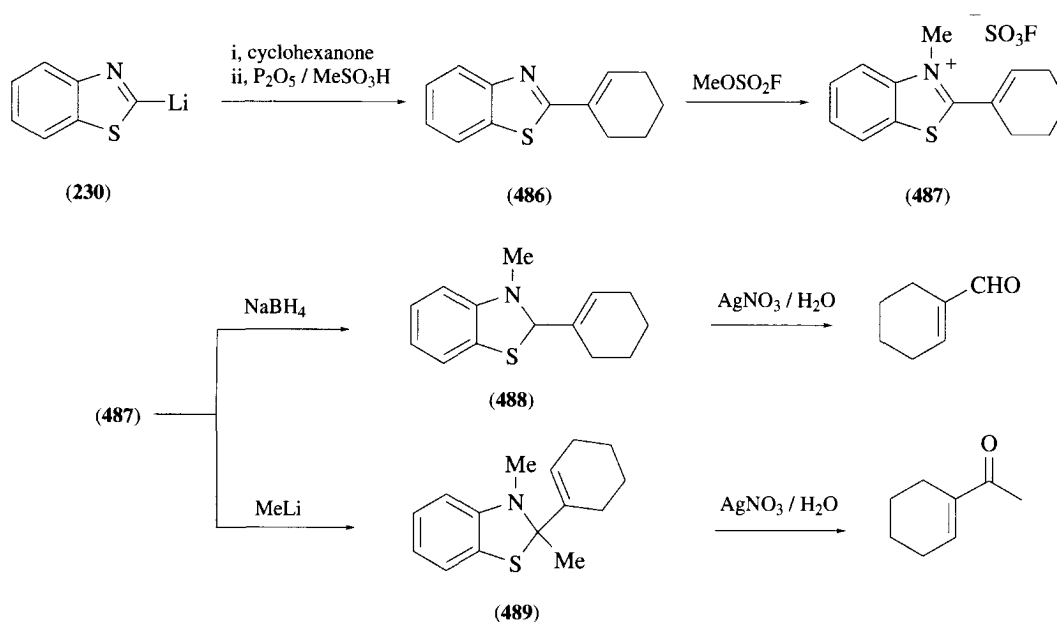
3.06.12.2 Synthetic Applications

3.06.12.2.1 Synthetic equivalence to the formyl group

Both benzothiazole and thiazole can be considered as masked carbonyl groups <B-93MI 306-10>. 2-Lithiobenzothiazole (**230**) (see Section 3.06.7.10.1) was described to be a carbonyl anion equivalent by Corey and Boger who used it for the preparation of α,β -unsaturated aldehydes and ketones <78TL5, 78TL9>. As an example, the reaction of (**230**) with cyclohexanone and dehydration leads to 2-cyclohexenylbenzothiazole (**486**); *N*-methylation of this compound with methyl triflate affords 2-cyclohexenyl *N*-methylbenzothiazolium triflate (**487**) (Scheme 112). Then, the hydride reduction of this salt and hydrolysis of the resulting benzothiazolidine (**488**) gives cyclohexene carboxaldehyde. Alternatively, methylation of (**487**) followed by the hydrolysis of the 2,2-disubstituted benzothiazolidine (**489**) gives acetyl cyclohexene.

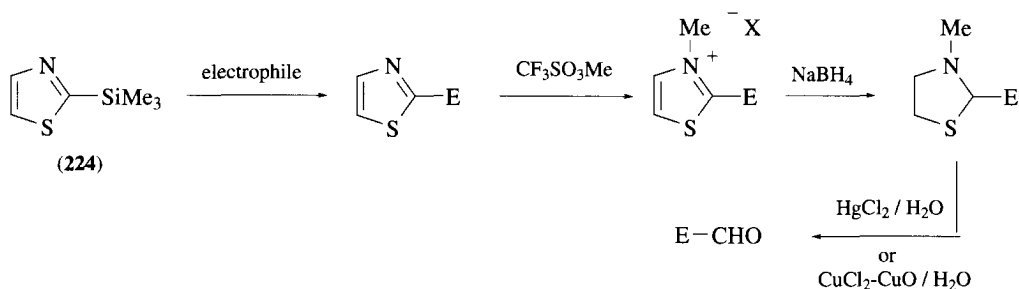
The reaction of (**230**) with a variety of electrophiles such as aldehydes, ketones, and esters, to give the corresponding 2-substituted benzothiazoles was more extensively examined later on (see Section 3.06.7.10.1) <86S375, 85H(23)2509, 88BCJ3637>. However, in most of the cases the cleavage of the benzothiazole ring to the formyl group was not carried out and therefore the actual synthetic equivalence of these products to substituted aldehydes remained unproved. In a few synthetic schemes, the benzothiazole-to-formyl equivalence has been completely exploited <90H(31)2125, 93JOC5931>.

On the other hand, the scope and synthetic potential of the thiazole-to-formyl equivalence has been amply demonstrated by Dondoni and co-workers <B-92MI 306-02, B-92MI 306-04>. 2-Trimethylsilylthiazole (**224**) (see Section 3.06.7.10.2) is the only compound which is *per se*, as a shelf reagent, a direct synthetic equivalent of the formyl anion and whose reactivity is not restricted to the range



Scheme 112

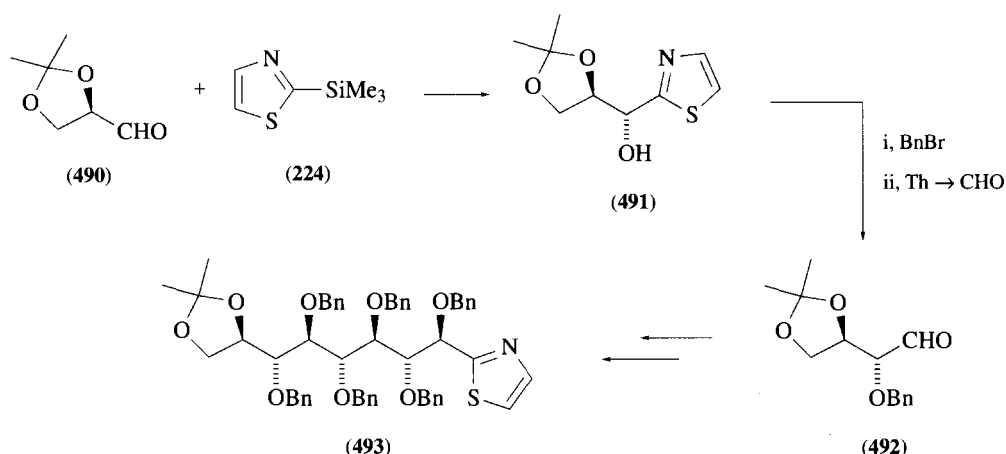
of low temperatures. The reaction of (224) with electrophiles such as aldehydes, ketones, acyl chlorides, ketenes, and heteroaryl cations occurs readily and does not require any catalyst (see Section 3.06.7.10.2). The conversion of the thiazole ring to the formyl group is carried out by *N*-methylation, reduction, and hydrolysis in a similar, but more effective way to benzothiazole. This unmasking protocol has been proved to be compatible with various protective groups and epimerizable centers (86AG(E)835, 89JOC693, 93JOC275). The neutral and mild conditions under which the whole process takes place provide considerable advantages to this successful aldehyde synthesis particularly in its chiral version (Scheme 113).



Scheme 113

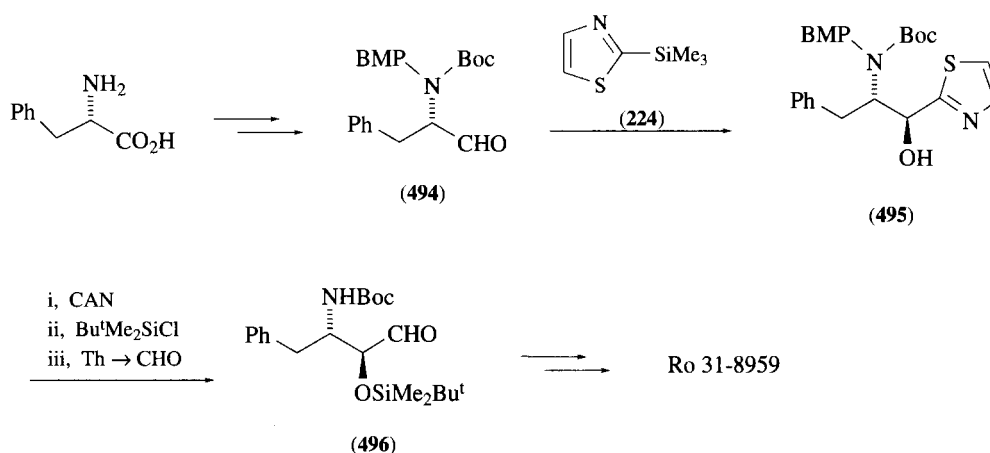
Particularly interesting is the reaction of 2-trimethylsilylthiazole (224) with chiral alkoxy-aldehydes. The addition proceeds with high levels of anti-selectivity to afford the corresponding α -hydroxyalkylthiazole which is then converted into the one-carbon homologated alkoxy aldehyde by the above thiazolyl-to-formyl conversion protocol (Th $\rightarrow$ CHO) (89PS(43)25, 90PAC643). The methodology is exemplified by the homologation of D-glyceraldehyde acetonide (490) into the protected D-erythrose (492) as shown in Scheme 114 (89JOC693, 95OS21). This homologative sequence has been employed in an iterative way to obtain a series of higher homologues of D-glyceraldehyde up to the nine carbon atom member (493) (89JOC693). The same strategy was employed for the preparation of all D-tetrose and D-pentose isomers (92SI96, 92S201) and for the chain-elongation of dialdo-furanoses and dialdopyranoses (87T3533, 90MI 306-04, 94CJC237).

2-Trimethylsilylthiazole (224) also reacts with α -amino aldehydes to give either *syn*- or *anti*-adducts depending on whether the nitrogen atom is singly or doubly protected respectively (see



Scheme 114

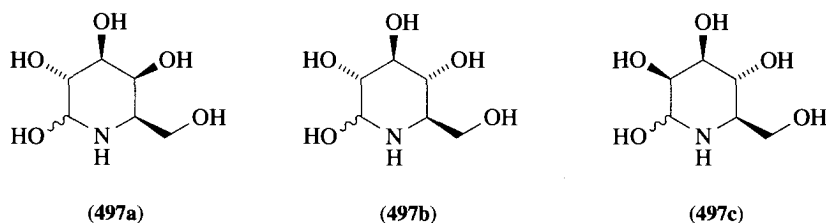
Section 3.06.7.10.2). This reactivity has been successfully utilized for the synthesis of amino sugars and sphingosines $\langle 88\text{CC}10, 90\text{JOC}1439 \rangle$, the phenylisoserine derivative side-chains of Taxol and Taxotere $\langle 95\text{S}181 \rangle$, and various dipeptide isosteres $\langle 93\text{TL}619, 94\text{JOC}3656 \rangle$. The last issue has been especially addressed by Dondoni, Perrone, and Merino for an efficient synthesis of the β -amino- α -hydroxy aldehyde (496) $\langle 95\text{JOC}8074 \rangle$, a key intermediate for the preparation of the human immunodeficiency virus proteinase inhibitor Ro 31-8959 $\langle 94\text{JOC}3656 \rangle$. The key step of the synthesis is the *anti*-stereoselective addition of 2-trimethylsilylthiazole (224) to the L-phenylalanine derived aldehyde (494) whose amino group was doubly protected with *p*-methoxybenzyl (PMB) and *t*-butoxycarbonyl (Boc) groups. The resulting major product, i.e., the *anti*-adduct (495), is readily converted into the target aldehyde (496) by selective removal of the PMB group with cerium ammonium nitrate (CAN) and thiazole to formyl conversion (Scheme 115).



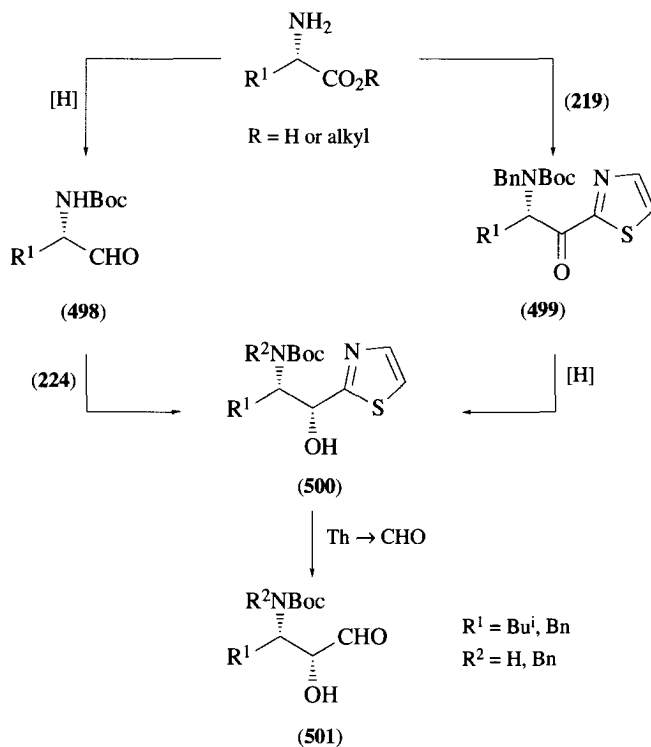
Scheme 115

In those cases in which 2-trimethylsilylthiazole (224) proved to be unreactive, 2-lithiothiazole (219) was employed as a conventional masked formyl anion. Thus, the reaction of (219) with chiral alkoxy esters affords thiazolyl ketones which have been used in the synthesis of natural products like L-rhodinose $\langle 89\text{T}5141 \rangle$. The addition to sugar lactones leads to C-glycosyl aldehydes $\langle 93\text{TL}7319, 94\text{JOC}6404, 94\text{JOC}7517 \rangle$. This is very likely the most efficient and wide scope method for the stereoselective formylation of furanoses and pyranoses at the anomeric center. The reaction of (219) with chiral α -amino esters provides another viable route to β -amino- α -hydroxy aldehydes $\langle 93\text{S}1162 \rangle$. Suitable elaborations of these products lead to various classes of compounds of biological relevance $\langle 92\text{BSB}433, \text{B-92MI } 306\text{-02} \rangle$. Among these compounds are the azasugars galactostatin (497a) $\langle 91\text{CC}1576,$

95JOC4749), nojirimycin (**497b**) and mannojinimycin (**497c**) (93T2939), various dipeptide isomers (92TL7259), and unusual amino acids (91CC1313, 93S1162, 95S181).



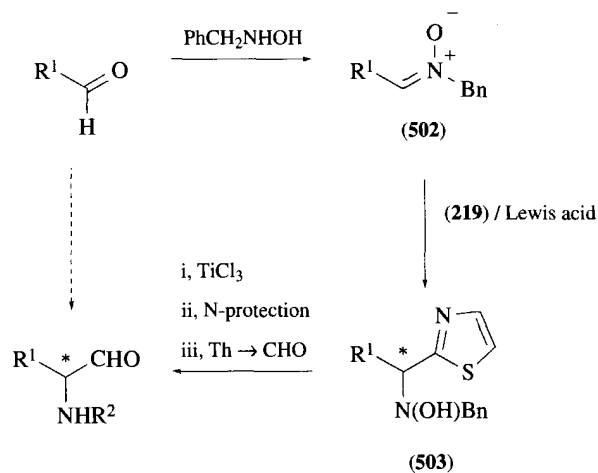
One of the latest significant achievements of the above thiazole-based complementary routes to β -amino- α -hydroxy aldehydes is the preparation of the key intermediates to leucine and phenylalanine hydroxyethylene dipeptide isostere inhibitors of renin and HIV-1 aspartic protease (95JOC7927) (see Scheme 116). Suitable protection of the amino group is employed to achieve the correct *syn* relationship between the amino and hydroxy groups in the target aldehydes. In one route the α -amino acid (L-leucine, $R = \text{Bu}^i$; L-phenylalanine, $R = \text{Bn}$) is reduced to an α -amino aldehyde (**498**) containing a singly-protected nitrogen. In the other route the α -amino acid containing a doubly protected nitrogen is converted through the ester into the α -amino ketone (**499**). Both the addition of (**224**) to the aldehyde (**498**) and the hydride reduction of the ketone (**499**) lead to the *syn* amino alcohol (**500**). The aldehyde (**501**) is then revealed from this compound by the conventional thiazole-to-formyl unmasking protocol ($\text{Th} \rightarrow \text{CHO}$).



Scheme 116

2-Lithiothiazole (**219**) has also been employed to convert aldehydes into one-carbon homologated α -amino aldehydes (aminohomologation) (92TL4221, 93SL78, 93TL5475, 94CC1731, 95MI 306-01). In this case the key reaction is the stereoselective addition of (**219**) to the chiral aldehyde nitron (**502**), an equivalent of an iminium ion, to give the thiazolyl hydroxylamine (**503**) (see Section 3.06.7.10.1). The stereoselectivity of this reaction can be controlled by the appropriate choice of a Lewis acid (93TL5475, 95MI 306-01). The hydroxylamine (**503**) is then converted into the corresponding amino aldehyde by reductive dehydroxylation and thiazole to formyl conversion (Scheme 117). The *syn*-

thetic utility of this reaction scheme is substantiated by the formal total synthesis of lincosamine and destomic acid, and the total synthesis of D-mannosamine and D-nojirimycin <95MI 306-01>.

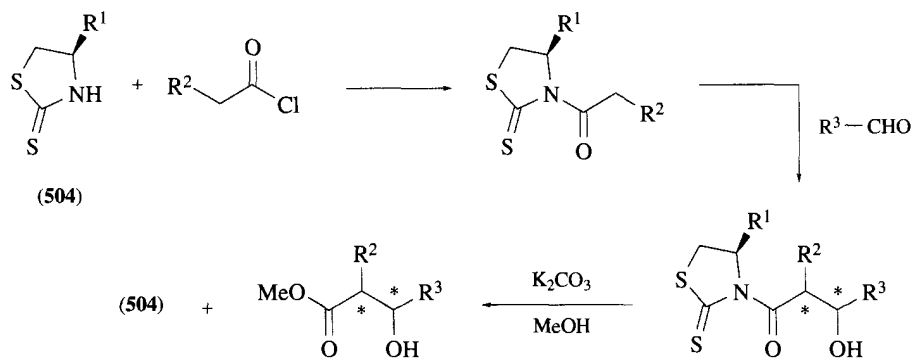


Scheme 117

Several thiazole-armed reagents have been developed and their synthetic utility amply demonstrated <88FES1119, 89PS(43)25, B-92MI 306-04>. Among those reagents are phosphoranes (134) and (143) (see Sections 3.06.7.3.2 and 3.06.7.4.3, respectively) which have been employed in the synthesis of amino sugars <88T3215, 90T6167>, C-glycosides <93TL7327>, higher sugars <94JCS(P1)1231>, and sialic acids <93SL256, 94TA2209>. Another reagent of importance is 2-acetylthiazole (see Section 3.06.7.4.3) which has been employed as a lactaldehyde equivalent in the synthesis of polyol chains <93S903> and as a masked pyruvate in the stereoselective construction of higher sugars <94JCS(P1)1231>, ulosonic acids <90TL4513, 91JOC5294>, and aza sugars <90CC854, 93T2939>.

3.06.12.2.2 Chiral auxiliaries

1,3-Thiazolidine-2-thiones (504) have been used as chiral auxiliaries for aldol type reactions <86JOC2391>. The diastereoselectivities are good and the chiral auxiliary is easily recoverable <87JOC2201>. A number of highly selective syntheses have been described using this method (Scheme 118) <85MI 306-02>.

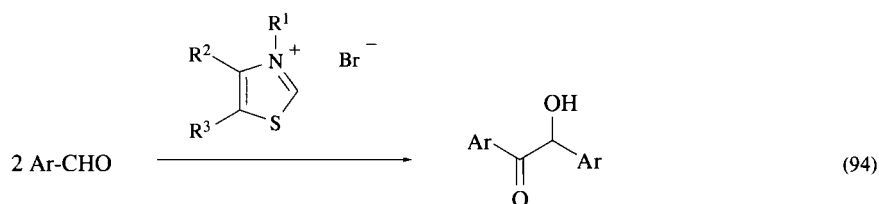


Scheme 118

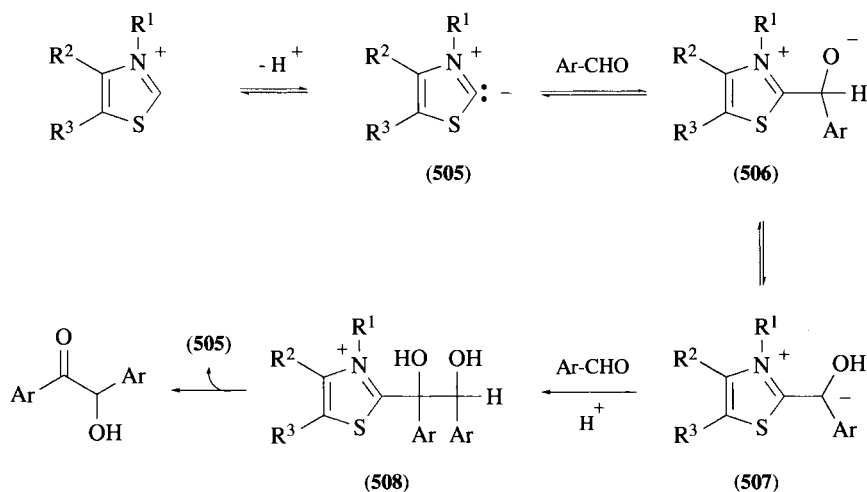
Chiral intermediates based on a thiazolidine ring prepared from L-cysteine have been used in enantioselective synthesis of biotin <95JOC321>.

3.06.12.2.3 Thiazolium salts as catalysts

Since the catalytic action of thiamine pyrophosphate (**473**) (see Section 3.06.12.1) was found to be due to the thiazolium ring, the catalytic activity of thiazolium salts have been widely studied. A reaction of interest which is catalyzed by thiazolium salts is the benzoin condensation (Equation (94)) <58JA3719>. An asymmetric version of this reaction has been described by the use of chiral thiazolium salts <74JOC1196>. Cross acyloin-condensations between formaldehyde and another aldehyde have also been described to be catalyzed by thiazolium salts <85JOC603>. The regioselectivity of the interaction of the thiazolium salt with differentially substituted aromatic aldehydes can be controlled with an appropriate design of the catalyst <94CL1417>. Hetaryl aldehydes also give similar condensations when they are treated with a thiazolium salt <93MI 306-11>.

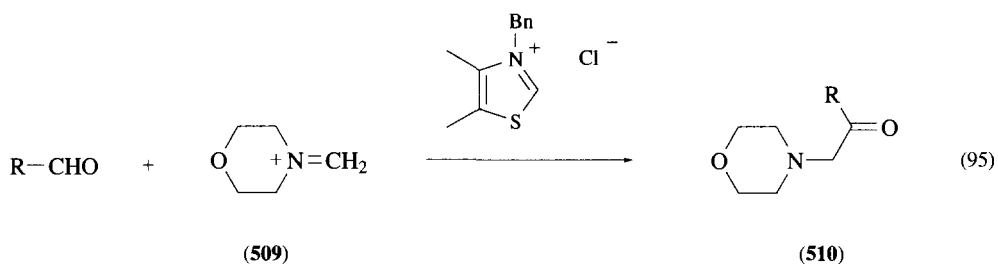


The mechanism of the reaction proposed by Breslow <58JA3719> is outlined in Scheme 119. The thiazolium salt operates through the ylide (**505**) which essentially serves to invert the polarity of the aldehyde carbonyl. The resulting dipolar intermediate (**507**) then reacts with another molecule of aldehyde to give (**508**) which leads to the benzoin and regenerates the ylide (**505**). Another mechanism has been proposed wherein bis(thiazolin-2-ylidene)s are the catalytic species for this reaction <88JOC4433, 93TL517>. However, the identification by NMR of the intermediate (**506**) <94TL699> and kinetic measurements <94JOC7714> confirmed the Breslow mechanism.



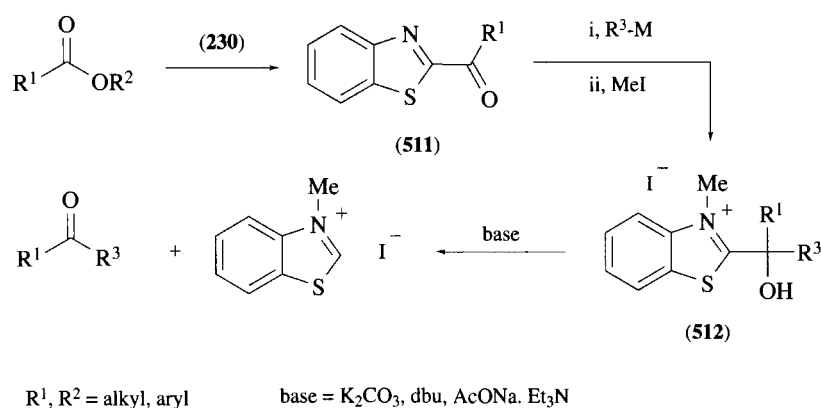
Scheme 119

Thiazolium salts also catalyze several reactions related to the benzoin condensation. An example is the reaction of aldehydes and imminium salts (**509**) to form α -amino ketones (**510**) (Equation (95)) <88S314>. The oxidation of aromatic aldehydes to carboxylic acid is also catalyzed by thiazolium salts <77TL205, 89TL2759>.



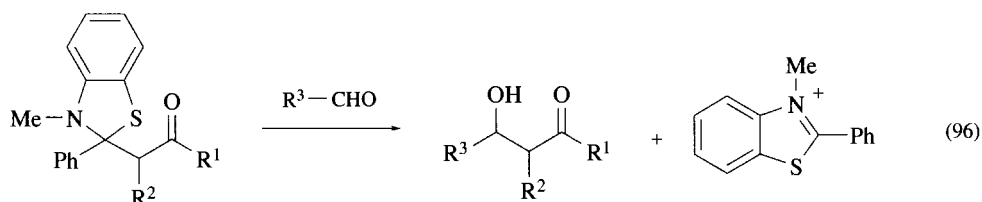
3.06.12.2.4 Other synthetic applications

Ketones can be prepared starting from esters via the intermediate 2-acylbenzothiazoles (**511**) which are easily obtained by condensation with 2-lithiobenzothiazole (**230**). The reaction of these compounds with an organometallic reagent and subsequent quaternization of the heterocyclic ring affords the *N*-methylbenzothiazolium salts (**512**) which upon treatment with a base yield the corresponding ketones (Scheme 120) <91BCJ3256>.



Scheme 120

2-(2-Oxoalkyl)benzothiazolines (prepared by the reaction of 3-methyl-2-phenylbenzothiazolim fluorosulfate with lithium enolates of ketones) act as enolate-transferring reagents in Lewis acid promoted cross aldol reactions of aldehydes with ketones (Equation (96)) <90BCJ497>.

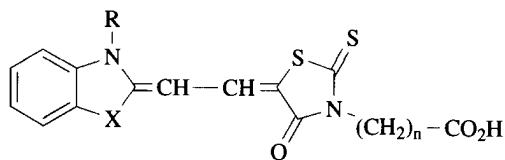


3.06.12.3 Other Applications

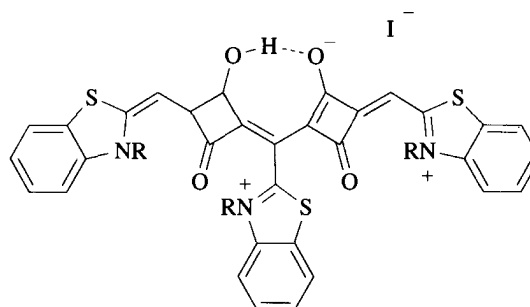
It is well-known that benzothiazoles are used as accelerators in the vulcanization process <84CHEC-1(6)330>. Because of the toxicity of the benzothiazole-containing by-products produced in rubber manufacture, it is of interest in the isolation of bacteria which degrade those by-products <93MI 306-12>. The one mainly responsible for the toxicity of rubber chemical waste water is 2-thiobenzothiazole <93MI 306-13>.

Cyanine dyes (**513**) containing a benzothiazole ring form aggregates in mixed monolayers with methyl arachidate and *n*-hexadecane <86JPC6144>. The changes in the orientation of that type of

dyes have been studied by UV spectroscopy <95TL559>. New cationic squarylium dyes (**514**) have been prepared and their structure determined by x-ray analysis <94AG(E)1001>.



(513)

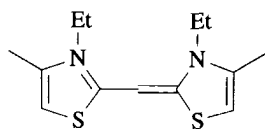


(514)

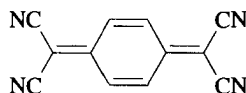
Thiazolium salts are employed in the determination of selenium in biological samples by flow injection analysis, the limit being 0.63 pmol <91MI 306-05, 91MI 306-06>.

Thiazolocyanine (**515**) forms an organic anion radical salt with TCNQ (**516**). The magnetic susceptibility of the complex shows a maximum near 265 K and steeply decreases below 50 K with decreasing temperature <93MI 306-05, 94MI 306-01>.

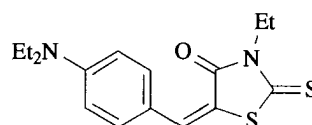
In a similar way the rhodanine derivative (**517**) and related compounds show second order nonlinear optical properties of interest <94TL3849>.



(515)

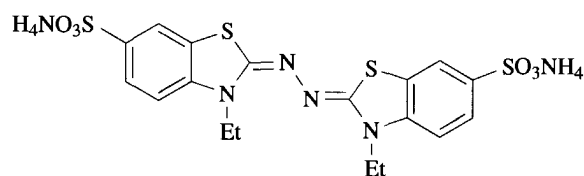


(516)



(517)

2,2'-Azinobis(3-ethylbenzothiazoline-6-sulfonic acid), namely ABTS-(NH₄)₂ (**518**), is found to be an adequate cosubstrate (or mediator) in the enzymatic oxidation of methyl groups on aromatic rings. The mediator (**518**) acts as a single-electron donor and activator of the enzyme (laccase) but does not function as oxidant of the substrate <95JOC4320>.



(518)

3.07

1,2-Selenazoles

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3.07.1 INTRODUCTION

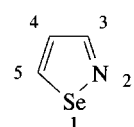
The first report of a synthesis of an isoselenazole was in 1936. It was not until 1975 that the first general synthesis of the ring structure was published using a bromine/ammonia addition to a β -methylselenoacrolein (B-86MI 307-01). This approach continues to be the method most used, with various adaptations, to prepare isoselenazoles and benzoselenazoles. The benzoselenazol-3-one was first reported in 1924 and was prepared by the addition of ammonia to the *o*-chloroselenobenzoyl

chloride. This overall methodology of adding ammonia to a 1-haloseleno-2-carbonyl moiety is still used predominately to prepare these heterocycles.

The chapter on the isoselenazoles in the first edition of *Comprehensive Heterocyclic Chemistry* (CHEC-I) was concise <84CHEC-I(6)333> but gave a good overview of the reactions, syntheses, and structural determinations of isoselenazoles and benzoselenazoles. There was, however, no mention of the benzoselenazol-3-ones; a great deal of the literature on isoselenazoles since 1982 has been concerned with this class of compound.

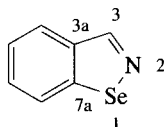
A number of reviews on isoselenazoles has been published. In *Advances in Heterocyclic Chemistry*, Shafiee covered the literature to 1976 <79AHC(24)109>. The book *Organic Selenium Compounds; Their Chemistry and Biology*, edited by Klayman and Gunther, contains a section written by Bulka devoted to selenium heterocycles <B-73MI 307-01>. One chapter in volume I of *The Chemistry of Organic Selenium and Tellurium Compounds*, part of the Patai series "The Chemistry of Functional Groups," covers selenium heterocycles <B-86MI 307-01>; a list of earlier reviews is also provided. The annual review in *Progress in Heterocyclic Chemistry* <B-94MI 307-01> under the section "Five-membered heterocycles containing one nitrogen and one heteroatom" continues to summarize the current literature.

The literature is mainly concerned with three ring structures: isoselenazoles (1), benzoselenazoles (2), and the benzoselenazol-3-ones (3). No publications on the hydro forms of the monocyclic system were found in the literature. Reports on the dihydro form of the benzoselenazole actually concern the 3-one derivative (3).



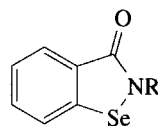
1,2-Selenazole
isoselenazole

(1)



1,2-Benzisoselenazole

(2)



1,2-Benzisoselenazol-3(2H)-one

(3)

3.07.2 THEORETICAL METHODS

No information on the computational studies and molecular mechanics of the isoselenazole ring system was found in the literature.

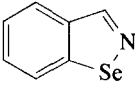
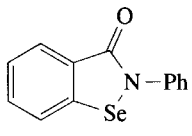
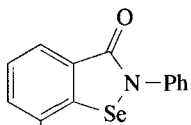
3.07.3 EXPERIMENTAL STRUCTURAL METHODS

3.07.3.1 X-ray Diffraction

The crystal structure of benzoselenazole (2) <81JCS(P1)607> and the benzoselenazol-3-one ebselen (3a) were reported <90AX(C)484>. The most notable feature of these compounds is the bonding to selenium. The bonds are quite long compared to the other ring bonds (Table 1). The longer bonding constricts the N—Se—C bond angle to 85.8–91°, as compared to the other ring bond angles of 109–116.6°. An interesting contrast between the benzoselenazole and benzoselenazol-3-one rings is the decreased bond angle at the selenium atom of the latter. This is probably due to the decreased bond angle of the carbonyl carbon, which squeezes both ends of the 5-membered ring.

In ebselen there is a 33.5° dihedral angle between the phenyl and isoselenazole rings. Significantly, the crystal packing shows a Se···O intermolecular nonbonding interaction with an intermolecular distance of 256.9 pm. The crystal structure of the 7-nitroebbselen analogue (4a) was also published <88AX(C)2159>. Here the Se···O intermolecular nonbonding interaction is blocked; instead, the alternative Se···O intramolecular nonbonding interaction between the selenium and 7-nitro group was detected with a nonbonding length of 257.3 pm. The bond lengths and angles of the heterocycle were on the same order as those in ebselen. The dihedral angle (13.2°) between the phenyl and heterocyclic rings was smaller.

Table 1 X-ray data for benzoselenazoles.

			
	(2)	(3a)	(4a)
Bond length (pm)			
Se-1—N-2	189.3	189.6	189.6
N-2—C-3	129.2	135.9	138.1
C-3—C-3a	147.7	146.5	145.8
C-7a—C-3a	142.4	141.3	138.5
C-7a—Se-1	184.5	189.3	184.6
Bond angle (deg)			
C-7a—Se-1—N-2	91.0	85.8	85.5
Se-1—N-2—C-3	109.6	116.1	114.7
N-2—C-3—C-3a	119.8	110.8	110.8
C-3—C-3a—C-7a	110.3	116.6	115.2
C-3a—C-7a—Se-1	109.2	110.7	113.7

3.07.3.2 NMR Spectroscopy

3.07.3.2.1 Proton NMR spectroscopy

Three hydrogens are available for NMR analysis of isoselenazoles (**5**) (Table 2). The signals for H-3 and H-5 being next to the heteroatoms are more downfield than H-4. The $J_{4,5}$ coupling constant is larger (5.2 Hz) than $J_{3,4}$ (1.6 Hz). The H-4 position will couple with the protons of a C-5 methyl group, whereas no such coupling is observed with a C-3 methyl group. The presence of a nitro group shifts the signal downfield. For the benz- or heterofused isoselenazole only an H-3 proton is available. The H-3 proton of benzoselenazole quaternary salt (**6**) is at 10.2 ppm. For the fused heterocycles the H-3 proton resonates between 9.0 ppm for the selenoloisoselenazole (**7**) and ~9.3 ppm for the benzothieno- and benzoselenolo-fused isoselenazoles (**8a**) and (**8b**).

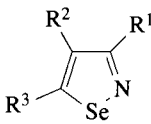
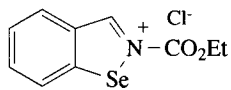
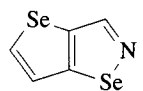
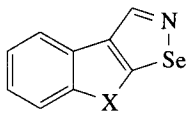
3.07.3.2.2 Carbon-13 NMR spectroscopy

The three carbons of the isoselenazole ring, generally, move downfield from C-4 to C-5 to C-3, except when substituted as in (**7**) and (**9**) (Table 3). A useful method for distinguishing the proximity of a carbon to the selenium is to measure the $^1J(\text{C}-^{77}\text{Se})$ coupling constants present as a result of the ^{77}Se satellites. Since ^{77}Se has a natural abundance of 7.5%, this is easily accomplished in a proton-decoupled spectrum <B-86MI 307-01>. Even $^2J(\text{C}-^{77}\text{Se})$ values can be measured, as observed with the C-3 of (**10**); the hetero-ring carbon atoms of the 3-substituted isoselenazole (**10**) were assigned with this information. The C-3a and C-6a carbon atoms are shifted downfield when the benzoselenazole selenium atom of (**3b**) is oxidized (**11a**).

3.07.3.2.3 Selenium-77 NMR spectroscopy

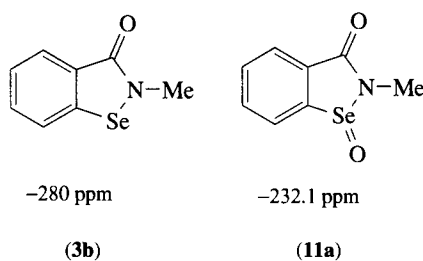
Selenium-77 NMR is more useful than the ^1H technique for studying isoselenazoles because the selenium signals can be spread over 1000 ppm. Being attached to a nitrogen, the selenium of an isoselenazole is further downfield than in a selenophene. Much can be learned of the selenium atom of a benzoselenazole-3-one; for example, the ring-opened diselenide of (**3b**) resonates at 453.6 ppm. Upon cyclization to (**3b**) and oxidation to (**11a**) it shifts to 888 ppm and 1142 ppm, respectively (Table 4). Making use of this, a ^1H and ^{77}Se NMR study of the mode of action of ebselen was reported and a mechanism for the *in vivo* catalytic reduction of hydroperoxides was proposed <87BSB757>.

Table 2 Proton NMR data for isoselenazoles.

Compound	¹ H chemical shift (CDCl ₃ , ppm), (coupling constant (Hz))			Ref.
	H-3	H-4	H-5	
 (5)				
(5a) R ¹ = H, R ² = H, R ³ = H	9.17 (1.6)	7.38 (5.2, 1.6)	9.38 (5.2)	84T931
(5b) R ¹ = Me, R ² = H, R ³ = H		7.22 (5.1)	9.22 (5.1)	84T931
(5c) R ¹ = H, R ² = H, R ³ = Me	8.86	7.09 (1.8, 1.2 ^a)		84T931
(5d) R ¹ = Me, R ² = H, R ³ = Me		6.89 (1.1 ^a)		84T931
(5e) R ¹ = Me, R ² = NO ₂ , R ³ = H			10.31	88H(27)2431
(5f) R ¹ = H, R ² = NO ₂ , R ³ = Me	9.64			88H(27)2431
(5g) R ¹ = Me, R ² = H, R ³ = CO ₂ Me		7.86		85H(23)127
 (6)	10.1			89BSB395
 (7)			9.0	87BSB407
 (8a) X = S (8b) X = Se			9.36 9.31	83BSB53 83BSB53

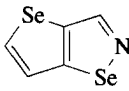
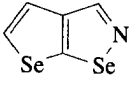
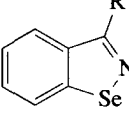
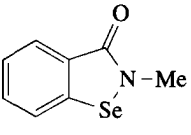
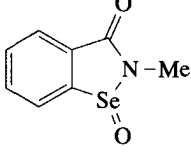
^aCoupling with protons of C-5 Me group.**3.07.3.2.4 Nitrogen-15 NMR spectroscopy**

Very little research of the ¹⁵N signals of isoselenazoles has been reported. Along with the ¹H, ¹³C, and ⁷⁷Se signals reported in the ebselen study above, the ¹⁵N signals were also measured ((**3b**) and (**11a**)). The signals are referenced to nitromethane.

**3.07.3.3 Mass Spectrometry**

There are six stable isotopes of selenium, which can be diagnostic in the mass spectrum; however, owing to the loss of a proton or presence of ¹³C, the situation can be confused. Only two isotopes are present at > 10%: ⁷⁸Se at 23.61% and ⁸⁰Se at 49.61%. To avoid confusion in reporting mass

Table 3 Carbon-13 NMR data for isoselenazoles.

Compound	Carbon-13 chemical shifts (ppm)			Ref.
	C-3	C-3a	C-6a(C-7a)	
 (7)	155.2	139.4	159.4	82OMR(19)74
 (9)	155.7	151.8	155.3	82OMR(19)74
 (10)^a	162.6 (² J(C-3— ⁷⁷ Se) = 11 Hz)	137.7	(152.0) (¹ J(C-6a— ⁷⁷ Se) = 129 Hz)	81JCS(P1)607
 (3b)	166.6	127.6	(139.0)	92JST(268)311
 (11a)	168.3	130.5	(147.2)	92JST(268)311

^aR = 5-(2-*trans*, 4-*trans*-3,4-dimethylpentadienonitrile).

spectral data, most authors report the mass spectra of isoselenazoles based on ⁸⁰Se, the most abundant isotope of selenium <B-86MI 307-01>. The mass peak of isoselenazoles is generally the most intense, with the (M⁺ - HCN), (M⁺ - Se), and (M⁺ - HCN - Se) peaks present at moderate intensity <80BSB773, B-86MI 307-01, 87BSB407>.

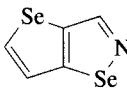
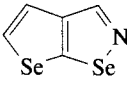
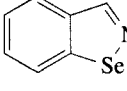
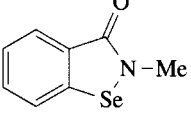
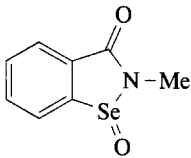
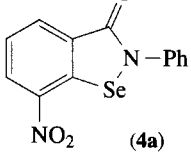
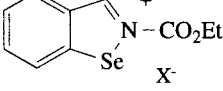
3.07.3.4 Infrared Spectroscopy

Infrared spectroscopy is not very diagnostic for simple isoselenazoles (Table 5). It is better used for attached functionality, particularly for carbonyl groups.

3.07.3.5 Ultraviolet Spectroscopy

As discussed in CHEC-I, the UV spectral data for isoselenazoles and isothiazoles are similar except for a slight bathochromic shift. A summary of the UV spectra of representative isoselenazoles is collected in Table 6.

Table 4 Selenium-77 NMR data for isoselenazoles.

Compound	⁷⁷ Se chemical shift (ppm)	Solvent (reference)	Ref.
 (7)	Se-1: 1023.1 Se-4: 555.2	CDCl ₃ (Me ₂ Se)	82OMR(19)74
 (9)	Se-1: 1050.1 Se-6: 595.6	CDCl ₃ (Me ₂ Se)	82OMR(19)74
 (2)	1013	CDCl ₃ (Me ₂ Se)	80BSB773
 (3b)	888.1	DMSO (Ph ₂ Se ₂ : 460 ppm, relative to Me ₂ Se)	92JSTS(268)311
 (11a)	1142.7	DMSO (Ph ₂ Se ₂ : 460 ppm, relative to Me ₂ Se)	92JSTS(268)311
 (4a)	951	CDCl ₃ (Me ₂ Se)	91T9053
 (6)			
X = Cl	945.6	Me ₂ Se	89BSB395
X = Br	1030.3	Me ₂ Se	89BSB395

3.07.4 THERMODYNAMIC ASPECTS

Isoselenazole is a solid melting at 125–126°C. Interestingly, a methyl group at the C-3 position causes the heterocycle to become a liquid: e.g., 3-methylisoselenazole (b.p. 50–51°C/14 torr) and 3,5-dimethylisoselenazole (b.p. 80°C/22 torr). In contrast, 5-methylisoselenazole is a solid (m.p. 92–93°C) <84T931>. Blocking of the intermolecular interactions of the lone pair on nitrogen may be responsible. Adding a bromo substituent at the 4-position of 3,5-dimethylisoselenazole increases the boiling point (82–83°C/7 torr). With the 4-nitro group, the heterocycle is a solid (m.p. 85–86°C) <88H(27)2431>. The thieno- and selenoloisosenazoles are solids. The ebselen series offers interesting insights into intermolecular interactions (Table 7). The unsubstituted amide (3c) is the highest melting, with substitution lowering the melting point; for example, the *N*-3,7,11-trimethyldodeca-

Table 5 Infrared data for isoselenazoles.

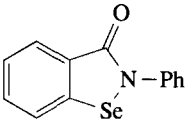
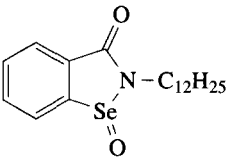
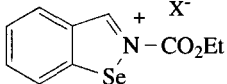
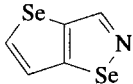
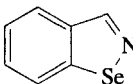
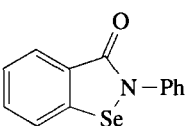
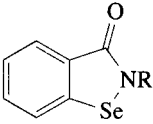
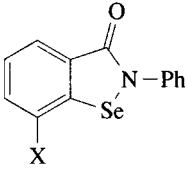
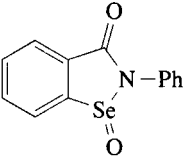
Compound	ν (cm ⁻¹)	Ref.
 (1)	1504, 1396, 402	84T931
 (3a)	1600 (C=O)	86BCJ2179
 (11b)	1680 (C=O), 800, 810 (Se=O)	93LA1239
 (6)	1745 (C=O) X = Br, Cl	89BSB395

Table 6 UV spectral data for 1,2-selenazoles and analogues.

Compound	$\lambda_{\max}$ (nm) (log ϵ)	Solvent	Ref.
 (1)	265 (3.75)	Isooctane	84T931
 (7)	204 (3.36); 235 (3.09); 270 (3.50); 316 (3.65)	Ethanol	87BSB407
 (2)	203 (4.15); 228 (4.30); 318 (3.67)	Ethanol	78JHC865
 (3a)	260 (3.37); 325 (3.30)	Methanol	86BCJ2179

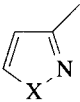
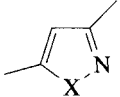
2,6,10-trienyl derivative is an oil. The crystal structure of ebselen shows a $\text{Se} \cdots \text{O}$ nonbonding interaction. With C-7 substitution (**4a**)–(**4c**) this bonding is not observed and the melting point drops. The 7-nitro derivative (**4a**) is the highest melting of the three derivatives probably owing to the $\text{Se} \cdots \text{O}$ nonbonding interaction of the nitro group as well as polarity (see Section 3.07.3.1). The selenium oxide (**11c**) increases the melting point slightly.

Table 7 Substituent effects on melting point of ebselen derivatives.

Compound	<i>m.p.</i> (°C)	Ref.
		
(3a) R = Ph	182–183	91CZ135
(3c) R = H	234–235	91CZ135
(3d) R = allyl	121–122	91CZ135
(3e) R = 3,7-dimethyl octadi-2,6-ene	68	91CZ135
		
(4a) X = NO ₂	160–163	91T9053
(4b) X = Cl	101–103	91SC85
(4c) X = OMe	139–140	91SC85
 (11c)	189–190	86SUL1

The $\text{p}K_{\text{a}}$ of isoselenazoles was measured by spectrophotometric methods. The values were compared to isothiazoles and isoxazoles (Table 8). The basicity increases from oxygen to sulfur to selenium, being enhanced by the dimethyl groups $\langle 88\text{H}(27)2431 \rangle$.

Table 8 The $\text{p}K_{\text{a}}$ of azole derivatives.

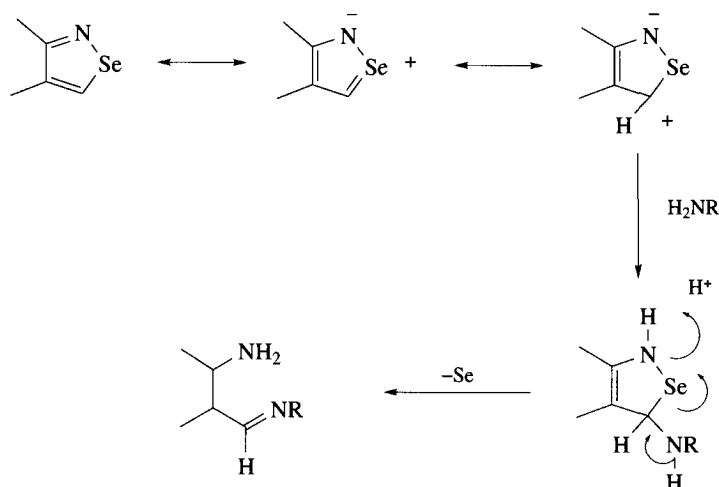
Compound		$\text{p}K_{\text{a}}^{\text{a}}$
	X = O	–1.62
	X = S	+0.48
	X = Se (5b)	+2.99
	X = O	–1.61
	X = S	+1.12
	X = Se (5d)	+3.39

^a(25°C), 1.6% aqueous methanol ($\mu = 0.1$).

The isoselenazoles can be purified by silica gel chromatography using solvents ranging from cyclohexane to ethyl acetate.

A study of the electrochemical behavior of derivatives of ebselen was carried out. The presence of a substituent at the C-7 position, adjacent to the selenium atom, enhances the glutathione peroxidase-like activity. A Hammett relationship was observed between the oxidation potential and the Hammett constant values of the C-7 substituent $\langle 90\text{MI } 307\text{--}01, 91\text{MI } 307\text{--}01 \rangle$.

The reactivity of the 5-position to nucleophilic addition by amines was attributed to the canonical forms of the heterocycle (Scheme 1) <87CPB398>.

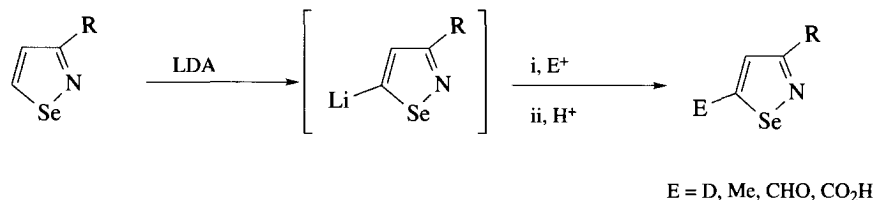


Scheme 1

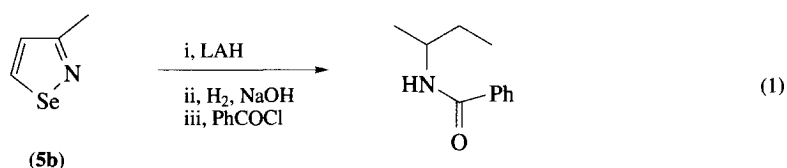
3.07.5 REACTIVITY OF FULLY CONJUGATED RINGS

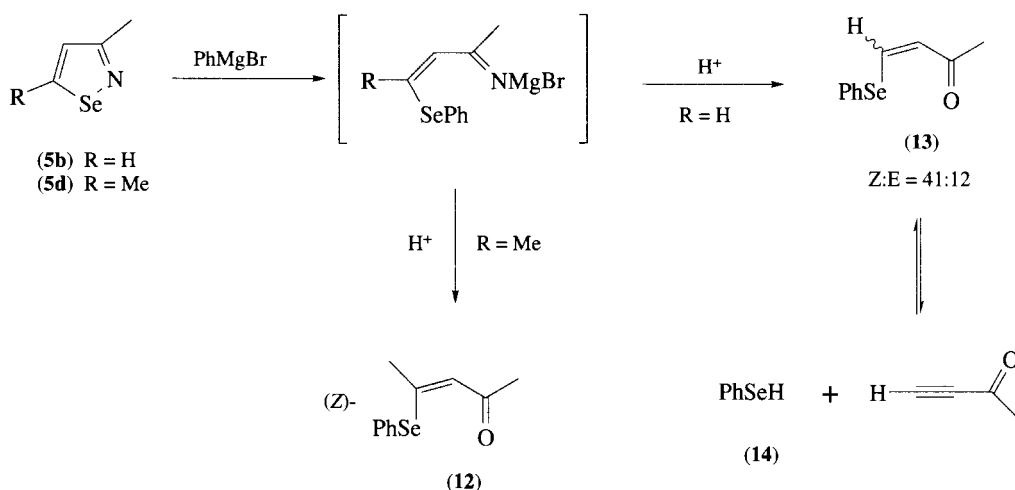
3.07.5.1 1,2-Selenazoles

Isoselenazoles have two reactive sites with nucleophiles depending on the type of reaction. LDA provides metalation at the 5-position. The resultant anion can undergo substitution with electrophiles (Scheme 2). Other nucleophiles such as carbanionic nucleophiles give ring opening by attack at the chalcogen atom; the selenium atom is electrophilic, leading to facile ring cleavage (Scheme 3). The yield and (*Z*):(*E*) ratio of the ring opening depend on the substitution of the resultant β -phenylselenoenone. In the case of the dimethyl analogue (**5d**) the elimination is not as facile and pure (*Z*)-isomer (**12**) is obtained in high yield; in contrast, the 3-methyl derivative (**5b**) forms a 3:1 (*Z*):(*E*) mixture (**13**) from the reversibility of the alkyne phenylselenenol elimination. The yield is also lower since the eliminated phenylselenenol (**14**) can undergo oxidation to diphenylselenide, thereby no longer being available for the reversible reaction. The LAH reduction of (**5b**) starts with Se—N bond cleavage followed by complete reduction (Equation (1)) <89H(29)349>. Reaction of amines with the fused isoselenazole (**15**) gave ring cleavage (Scheme 4) to the Schiff base (**16**) followed by hydrolysis to the aldehyde (**17**). This reaction is proposed to occur through the canonical forms of the heterocycle (Scheme 1) <87CPB398>. Similarly, the [4,3]isoselenazole (**15**) was converted to the pyridine derivative (**18**) with active methylene compounds (Scheme 5) <85CPB3065>.

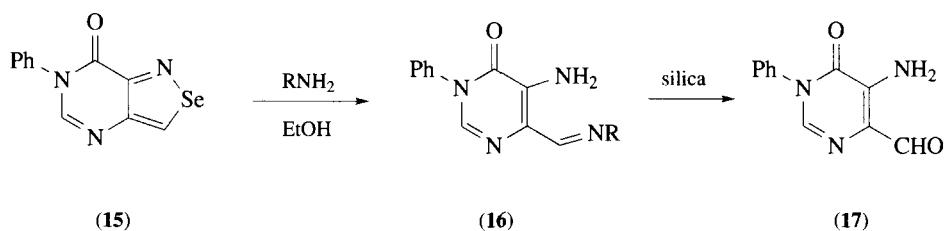


Scheme 2

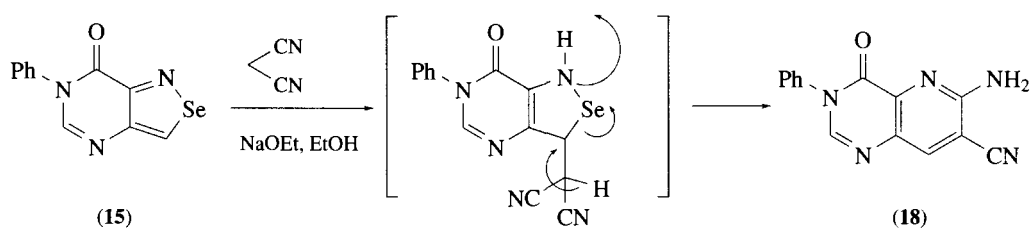




Scheme 3

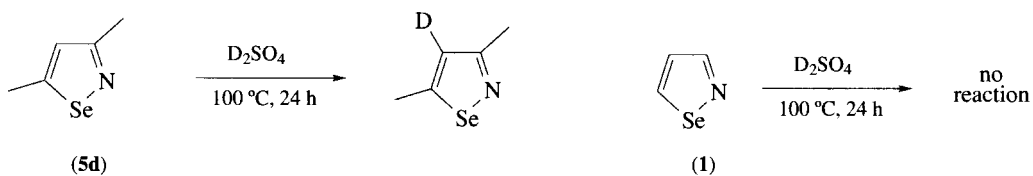


Scheme 4

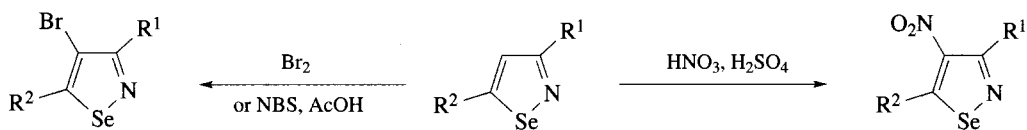


Scheme 5

Electrophiles react at the 4-position. With two methyl groups the 4-position is more reactive, as evidenced by the H–D exchange of 3,5-dimethylisosenazoles after 24 h at 100 °C (Scheme 6); in contrast, isosenazole fails to exchange. Bromination and nitration both occur at the 4-position. In the case of the 3-phenylisosenazoles, the phenyl group is more reactive towards nitration and less reactive towards bromination than the C-4 position of the isosenazole ($R^1 = \text{Ph}$, Scheme 7). Upon nitration or bromination the parent isosenazole underwent complete decomposition <88H(27)2431>.



Scheme 6



Scheme 7

3.07.5.2 Benziselenazoles

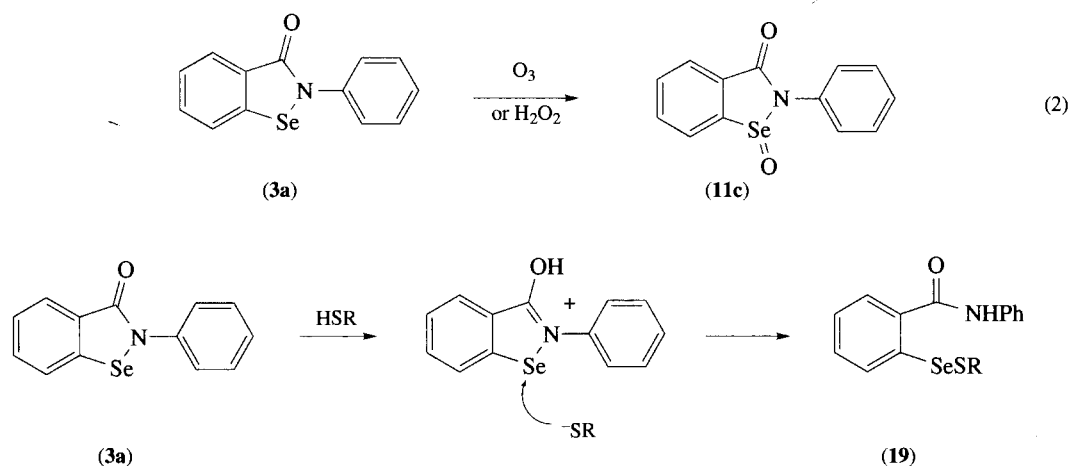
Many of the existing reactions of benziselenazoles were covered in CHEC-I (84CHEC-I(6)333) as well as the review in *Advances in Heterocyclic Chemistry* (79AHC(24)109). For the most part, electrophiles react with the benzene ring; for example, nitration and bromination give mixtures of C-5 and C-7 substitution. Nucleophiles, on the other hand, react at the heterocycle by substitution at the 3-position or cleavage of the ring (79AHC(24)109). For example, potassium amide affords the 3-amino derivative. Metalation leads to ring cleavage by deprotonation of the 3-position followed by formation of the cyano group with ejection of the selenium anion.

3.07.5.3 Quaternary Salts

The quaternary salts of 1,2-benziselenazoles can be converted to other rings by virtue of the lability of the ring to nucleophiles (79AHC(24)109).

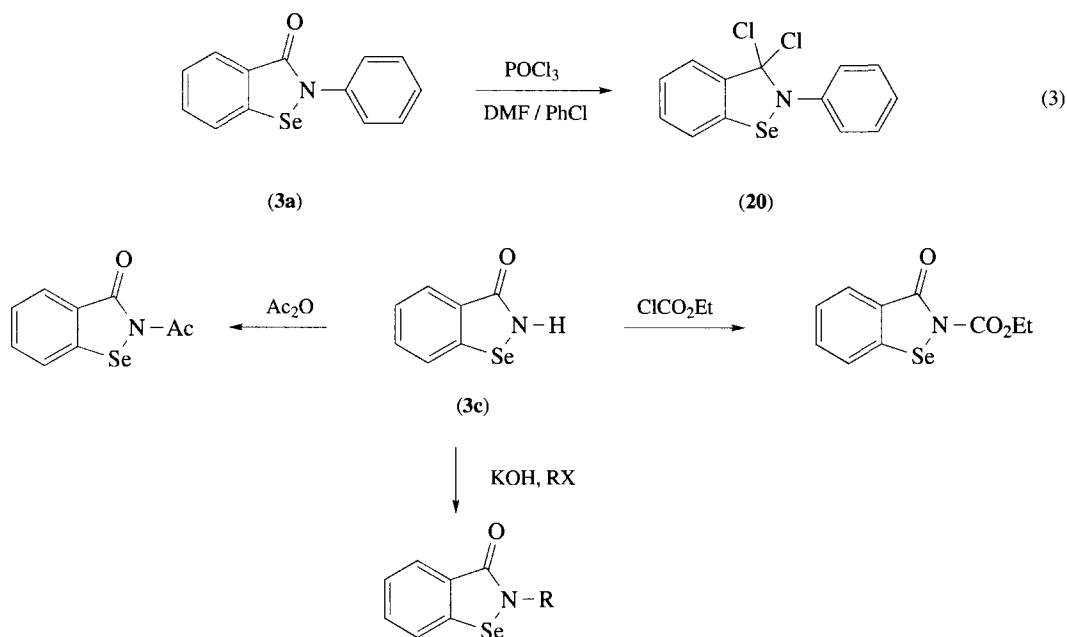
3.07.6 REACTIVITY OF NONCONJUGATED RINGS

The reactivity of nonconjugated rings is mostly concerned with the benziselenazol-3-ones. The selenium atom is nucleophilic or electrophilic depending on the reactant. The heteroatom of ebselen (3a) can be oxidized with ozone to the selenoxide (11c) (Equation (2)); other oxidants that will oxidize selenides failed or provided low yields (86SUL1). A later report showed that hydrogen peroxide can effectively oxidize the selenium atom (91PS(59)267). Attack of sulfur at the selenium atom of ebselen forms the selenium-sulfide bond (19) with ring cleavage (Scheme 8) (86H(23)3027).



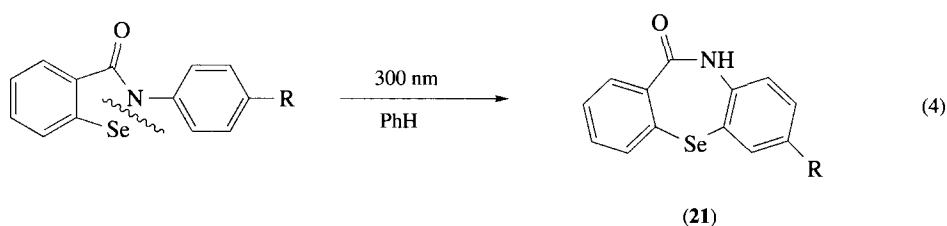
Scheme 8

The amide carbonyl can be converted to the geminal dichloro derivative (20) (Equation (3)) (91CZ169). The nitrogen of the secondary amide (3c) can be acylated (Scheme 9) (89BSB395), or alkylated with KOH and the alkyl halide (91CZ135).



Scheme 9

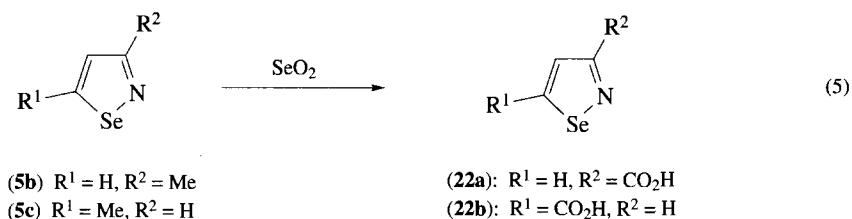
The heterocycle undergoes photochemical ring rearrangement to **(21)** (Equation (4)) by cleavage of the weakest bond (Se—N) in the molecule and attack of the resultant selenium radical on the aromatic ring <86BCJ2179>.

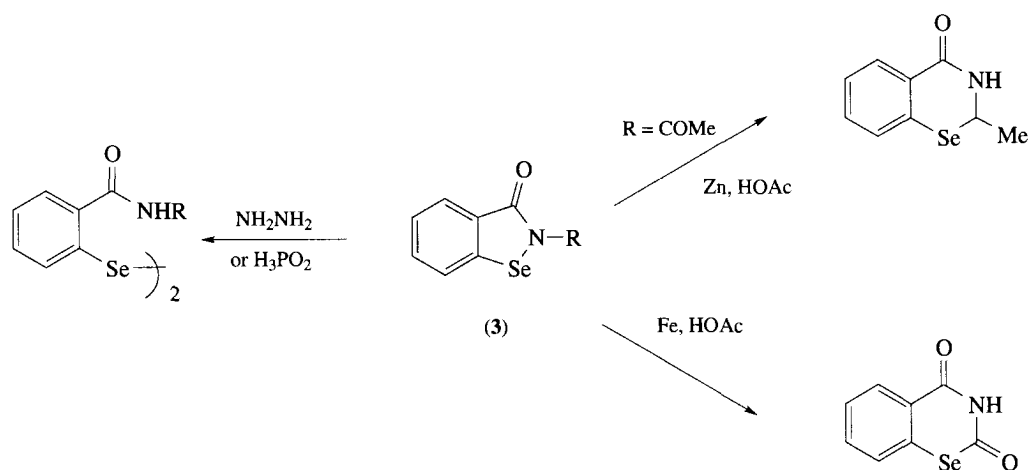


The benzoselenazol-3-one can be converted to the ring-opened diselenide by treatment with hydrazine (Scheme 10). Other ring-opening schemes were also reported <89BSB395>. The 2-prenyl or geranyl derivative undergoes ring expansion to the 1,5-benzoselenoazepinen upon heating in methanol (Scheme 11). Reaction of the *N*-2-substituted compounds with various nucleophiles and electrophiles causes ring opening <91CZ169>. The 7-nitro derivative of ebselen was prepared to test its interference in the formation of the intermediates typical of those with glutathione peroxidase-like activity. The stabilizing effect of the *o*-nitro group on the selenium atom towards reaction is due to the selenium–oxygen dipole interaction <91T9053>.

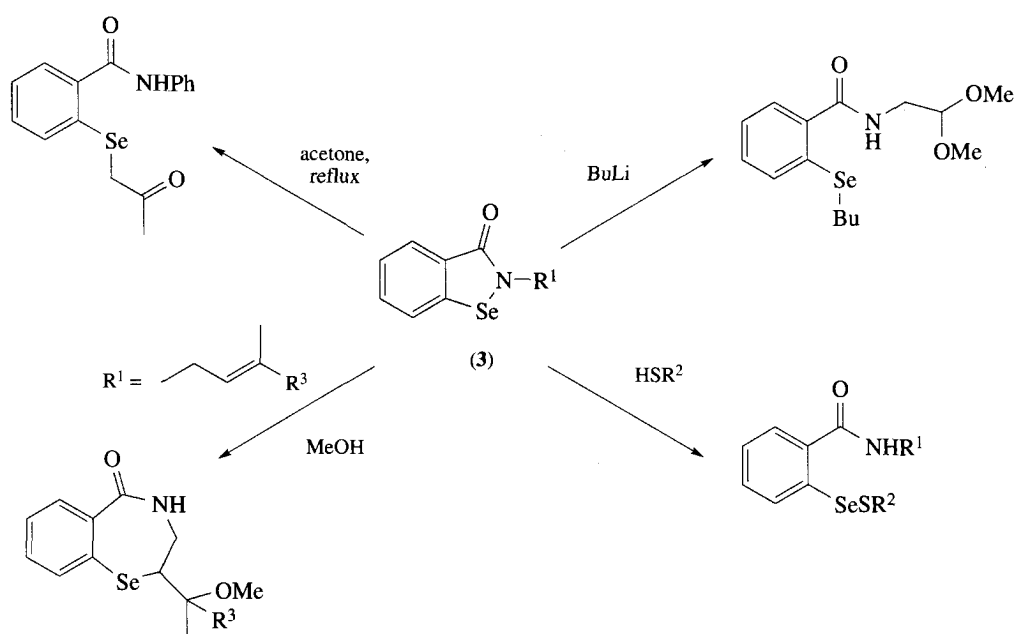
3.07.7 REACTIVITY OF SUBSTITUENTS ATTACHED TO RING CARBON ATOMS

The oxidation of alkyl groups attached to the isoselenazole with SeO_2 provides the carboxylic acid derivatives **(22)** (Equation (5)). The dimethyl analogue provides a mixture of the mono-carboxylic isomers and the dicarboxylic compound. Other oxidants, such as potassium permanganate or chromic anhydride, fail <85H(23)127>.



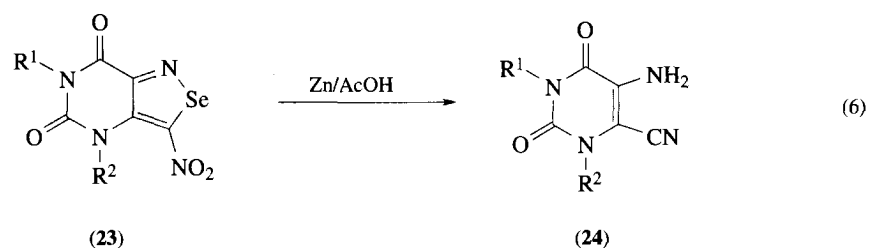


Scheme 10



Scheme 11

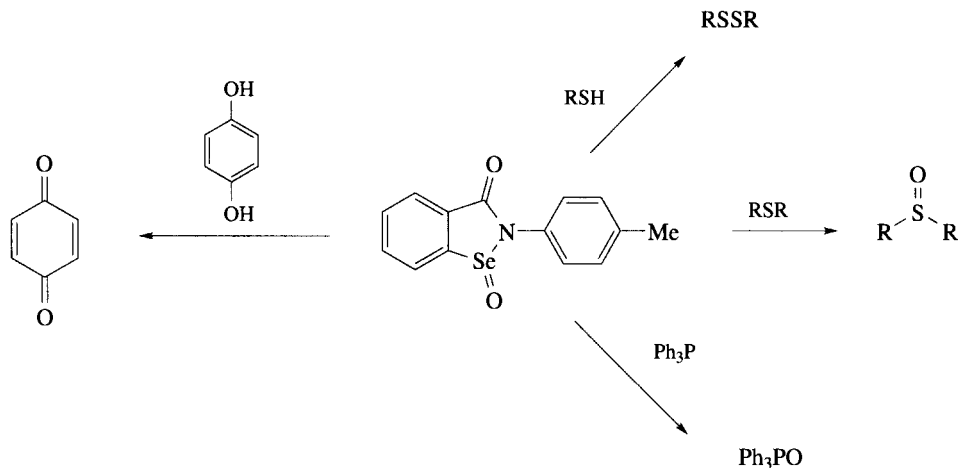
Reduction of the nitrated isoselenazole (**23**) affords ring cleavage to the nitrile (**24**) with extrusion of the selenium atom (Equation (6)) <87TL4579>.



3.07.8 REACTIVITY OF SUBSTITUENTS ATTACHED TO RING HETEROATOMS

The oxygen attached to the selenium atom of ebselen derivatives can cause oxidation of a sulfide or phosphine to the sulfoxide or phosphine oxide, respectively (Scheme 12). Thiols are converted to

the disulfide, and hydroquinones are oxidized to the hydroquinone. The atom transfer is not by direct oxygen transfer; rather, it proceeds by attack at the selenium atom with opening of the selenazole ring. Rearrangement transfers the oxygen to the heteroatom or oxidizes the substrate with reformation of the isoselenazolinone $\langle 86\text{SUL1} \rangle$.



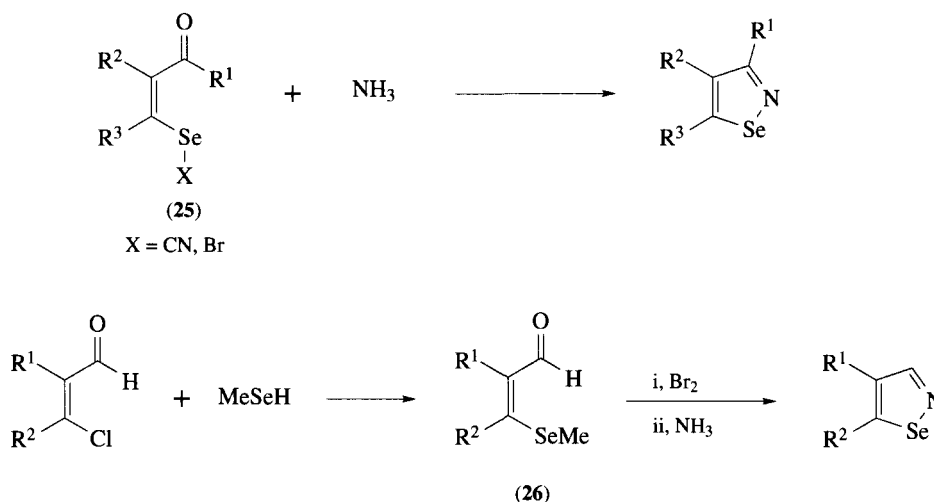
Scheme 12

3.07.9 RING SYNTHESSES CLASSIFIED BY NUMBER OF RING ATOMS IN EACH COMPONENT

The $[4 + 1]$ and $[3 + 1 + 1]$ routes are basically the same. Which is designated depends on, respectively, whether the β -selenoenone derivative is considered the starting material or the addition of the selenium atom is part of the sequence (Scheme 13). In both cases, ammonia addition completes the ring synthesis.

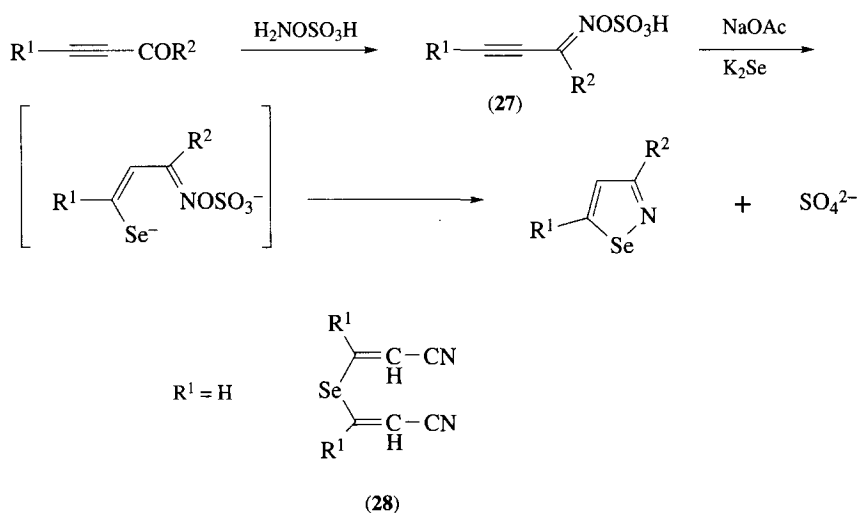
3.07.9.1 1,2-Selenazoles

The addition of ammonia to a 3-selenoacrolein (**25**), where X is a leaving group, is the most commonly used method (Scheme 13). The bromine leaving group can be introduced by bromination of the methyl selenide derivative (**26**). The parent isoselenazole (**1**) and its methyl derivative were prepared in this manner. In contrast to 1,3-selenazoles, the parent compound is stable $\langle 79\text{AHC}(24)109 \rangle$.



Scheme 13

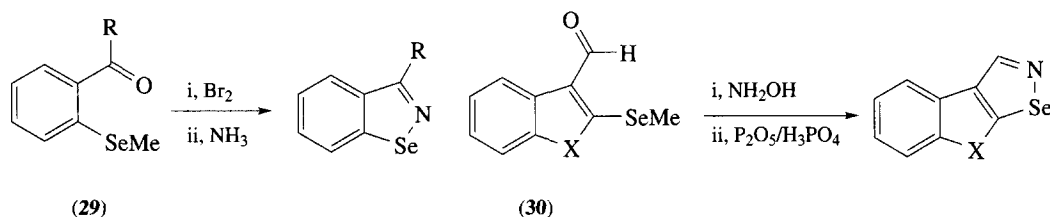
A new synthesis of 3- and 5-substituted isoselenazoles was reported (Scheme 14). Conversion of alkynic aldehydes or ketones to the oxime sulfonates (27) is followed by conjugate addition of buffered potassium selenide. Ring closure yields the isoselenazole (84T931, 87H(26)1587). This process has the advantage that substituted bifunctional selenium reagents containing an appropriate leaving group for cyclization with ammonia are not needed; only potassium selenide is required. The aldehydes do not provide as good a yield since the oxime can eliminate sulfonate to generate the alkynic nitrile. This allows a second conjugate addition to form the dialkynic selenide (28).



Scheme 14

3.07.9.2 Benz- and Heterofused Isoselenazoles

The benzoselenazoles are prepared through a similar procedure to the isoselenazoles (Scheme 15). The *ortho*-selenophenone (29) is activated by treatment with bromine and the ring closure is brought about by addition of ammonia (79AHC(24)109). Alternatively, the *ortho*-carbaldehydic methylselenide (30) can be converted to the oxime. Elimination of the oxime to the cyano group with P₂O₅ brings about ring closure (83BSB53).

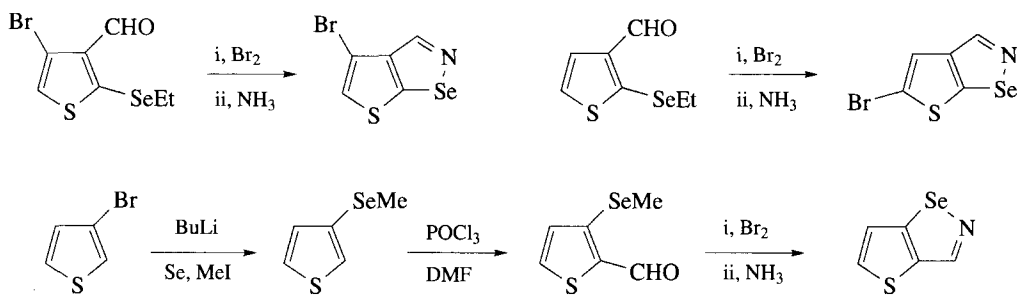


Scheme 15

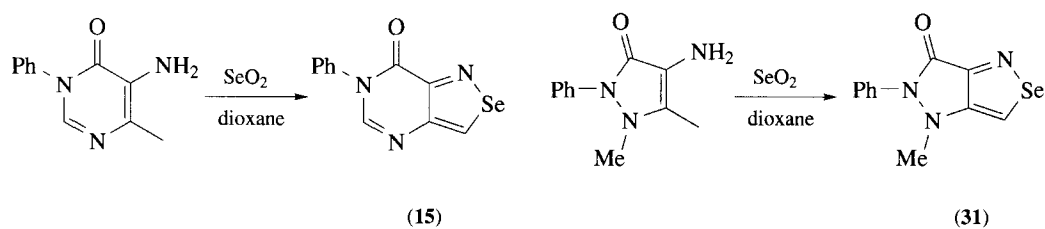
The thienoisoselenazole ring structure is prepared by treatment of the 3-formyl-2-ethylselenothiophene with bromine followed by ammonia (Scheme 16). In the case where there is no bromo substitution, bromination will take place at that 5-position (82OMR(19)74). The selenoloisosenazole is similarly prepared from the 2-formyl-3-methylselenide (87BSB407).

The condensed pyrimidone- and antipyrene[4,3]isoselenazoles (15) and (31), respectively, can be prepared by oxidation of the methyl group with selenium dioxide and cyclization to the selenazoles (Scheme 17) (85S695). The ring of either can be converted to diazepines (85MI 307-01, 88CPB2902).

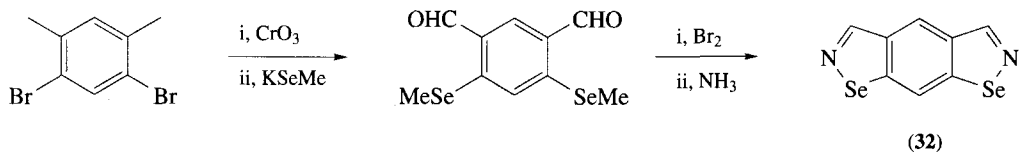
The benzodiisosenazole (32) was prepared (Scheme 18) for comparison with it to the biologically active psoralens and benzodifurans (91BSB1).



Scheme 16



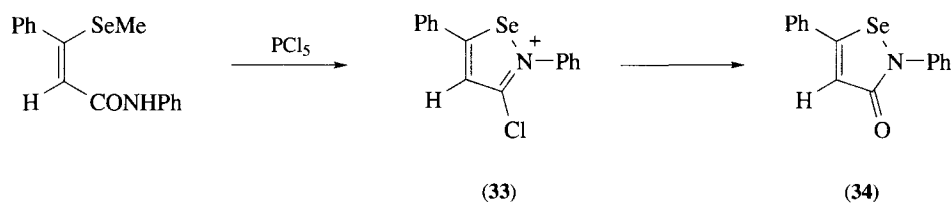
Scheme 17



Scheme 18

3.07.9.3 Quaternary Salts

The quaternary salt (33) can be formed by treatment of the amide (Scheme 19) with PCl_5 (93SUL55). The salt can undergo hydrolysis to the 1,2-isoselenazol-3-one (34).



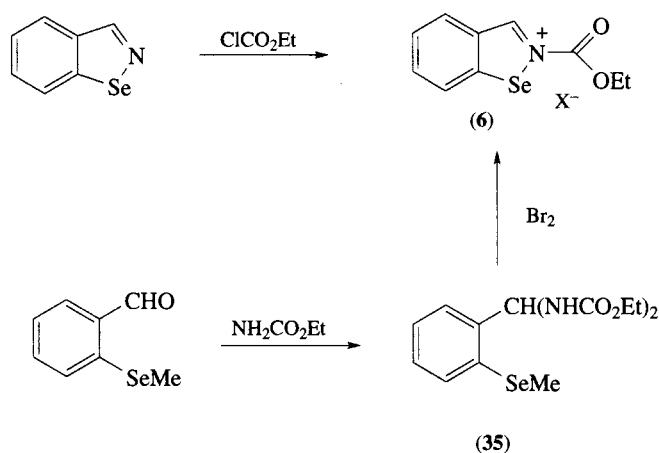
Scheme 19

The acyl quaternary salt (6) can be prepared by acylation of benzoselenazole or reaction of a carbamate with the aldehyde and treatment of the methyl selenide (35) with bromine (Scheme 20). Interestingly, only the diamino species (35) is involved and not the iminocarbamate (89BSB395).

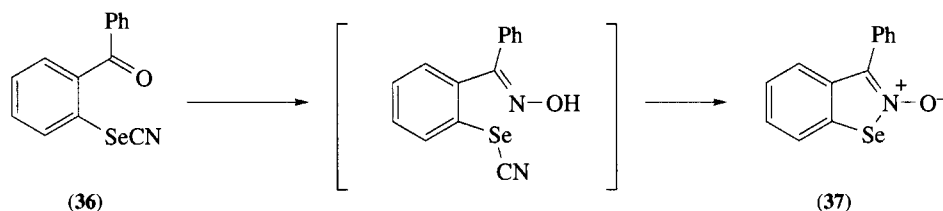
The *o*-selenocyanatobenzophenone (36), when treated with hydroxylamine, cyclizes (Scheme 21) through nitrogen displacement of the cyanide leaving group to yield the mesoionic isoselenazole (37) (83T831).

3.07.9.4 Benzoselenazolinone

Ebselen derivatives (3) can be prepared by any of three routes from *ortho*-selenobenzoic acid derivatives (Scheme 22) (90MI 307-02; 91MI 307-01). Introduction of diselenide by conversion of the *ortho*-amino carboxylic acid to the diazo derivative followed by addition of sodium selenide results in a Sandmeyer reaction. The diselenide is converted to the selenenyl chloride (38) and ring closure

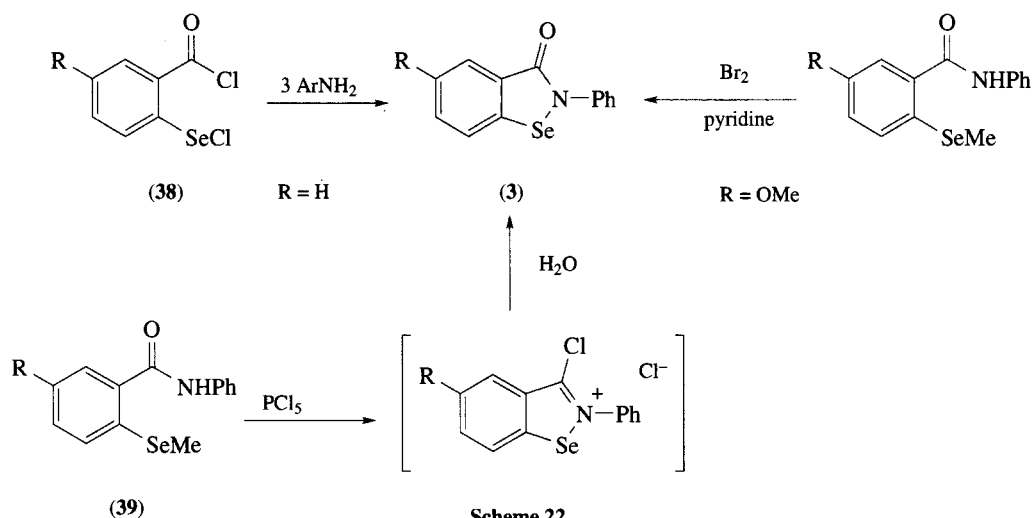


Scheme 20



Scheme 21

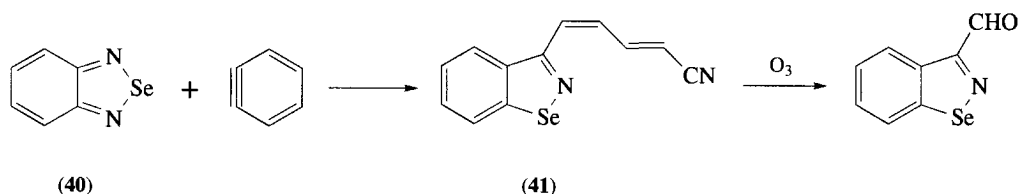
is carried out by addition of the aniline. This approach was used to introduce ^{75}Se into the ebselen system $\langle 86\text{MI } 307\text{-}02 \rangle$. The methylselenide can be used as a handle for cyclization to ebselen; the *ortho*-methylselenide group can be introduced by directed *ortho* metalation or halogen-metal exchange $\langle 91\text{SC}85 \rangle$. Treatment of the methylselenide (39) with PCl_5 brings about cyclization via the chloroimidate with concomitant loss of the methyl group. Hydrolysis yields the benzoselenazolinone. Alternatively, bromine treatment gives direct ring closure.



Scheme 22

3.07.10 RING SYNTHESIS BY TRANSFORMATION OF ANOTHER RING

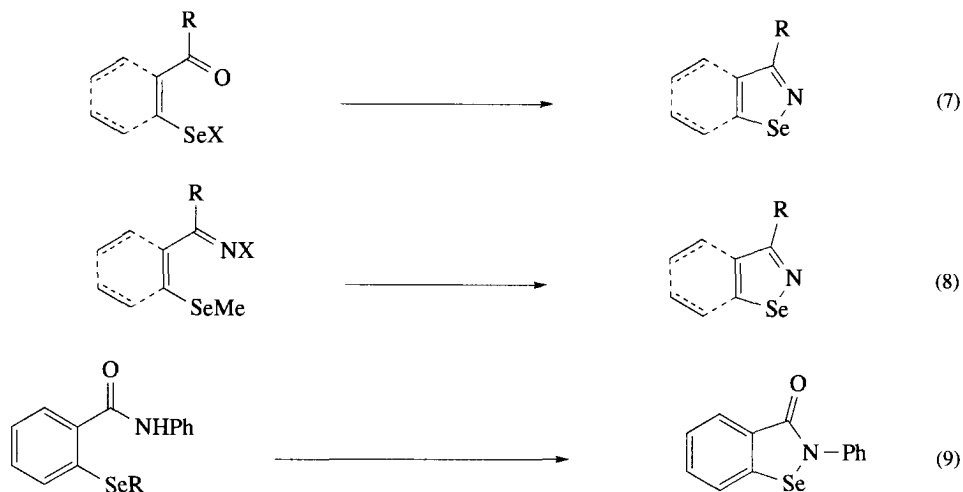
Cycloaddition of 2,1,3-benzoselenadiazole (40) with benzyne (Scheme 23) is followed by rearrangement to provide the benzoselenazole (41) $\langle 83\text{T}835 \rangle$. The cycloaddition of dimethyl- or diphenylselenadiazole with benzyne gives the 3-methyl- or 3-phenylbenzoselenazole, respectively, refuting a previous report of rearranged structure as the 1,3-benzoselenazole $\langle 88\text{JCS(P1)2141} \rangle$.



Scheme 23

3.07.11 SYNTHESIS OF PARTICULAR CLASSES OF COMPOUNDS AND CRITICAL COMPARISON OF THE VARIOUS ROUTES AVAILABLE

The major entry into the 1,2-selenazole ring system is by addition of ammonia to an enone system (Equation (7)) containing a 3-seleno derivative. Alternatively, activation of an amine brings about ring closure with the loss of the methyl group (Equation (8)). Either method can be used for the monocyclic or condensed heterocycles. The very important benzoselenazolinone ring system is prepared by conversion of an *ortho*-selenobenzoic acid derivative to the amide. Suitable activation of the selenium atom or amide group brings about ring closure (Equation (9)).



3.07.12 IMPORTANT COMPOUNDS AND APPLICATIONS

Ebselen (**3a**), a benzoselenazolinone (BISA), displays anti-inflammatory activity and antioxidant capabilities by catalytically reducing hydroperoxides in the presence of thiols, akin to the enzyme glutathione peroxidase <84BP3235, 84BP3241, 84BP3247>. A study of the metabolism and structure-activity relationships was reported <90MI 307-02>. The 2-pyridyl analogue RP61605 showed greater activity with less toxicity and the 7-nitro analogue showed similar activity with less toxicity <89MI 307-01>. Ebselen has also been tested as an anti-methicillin-resistant *Staphylococcus aureus* (anti-MRSA) antibiotic <89MI 307-02>. Analogues of ebselen and related compounds have also been tested as immunomodulators <93LA1239>. A discussion of the mode of bioactivity is presented. A comparison study of the 1,3-benzoselenazolinone shows these to be completely inactive, confirming the importance of the 1,2-relationship of the selenium-nitrogen bond to activity <94JMC2903>. Metabolites of ebselen were prepared <87BSB383>.

Some heterofused isoselenazoles (**15**) and (**31**) have found activity as antitumor agents <85MI 307-01, 88CPB2902, 90MI 307-03>.

3.08

1,3-Selenazoles

ROBERT D. LARSEN

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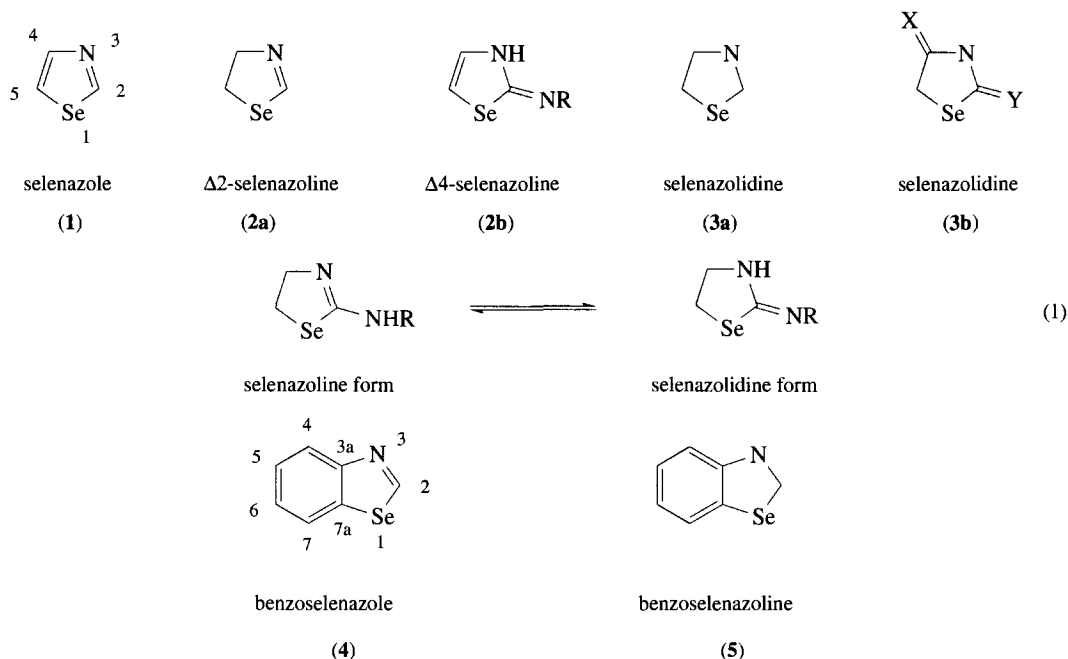
3.08.1 INTRODUCTION

Selenazoles were first prepared in 1889, but intensive research did not begin in this area until 1940 <79AHC(24)109>. For the most part the Hantzsch approach has been used as the method of choice to prepare analogues of selenazole. The majority of the literature is concerned with applications and improvements in this basic methodology. Reactions of selenazole systems involve substitution of the ring and manipulation of attached functionality. The chemistry of the benzo- and hetero-fused ring systems has continued to develop with new analogues and uses reported.

The original review on selenazoles in the first edition of *Comprehensive Heterocyclic Chemistry* <84CHEC-I(6)333> was divided into three sections: structure, reactivity, and synthesis. In the structural section a discussion of ^1H and ^{13}C NMR concerned only benzoselenazole. No mention of ^{77}Se NMR was made; unfortunately, little has been done in this area since. More information concerning fragmentation patterns of selenazoles in the mass spectrum has been reported. The chapter did not mention IR, UV, and other less-used analytical methods. The reactivity discussion was limited to electrophilic additions at the 5-position and reactions of 2-methylbenzoselenazoles. The synthesis section was more extensive.

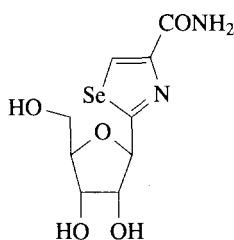
A number of reviews have been written concerning the chemistry of the 1,3-selenazoles. The *Advances in Heterocyclic Chemistry* series has not updated the chemistry of the 1,3-selenazoles for some time <79AHC(24)109>. The Weissberger and Taylor series *The Chemistry of Heterocyclic Compounds* reviewed the chemistry of selenazoles as part of the three-volume work on thiazoles <79HC(34)217>. The single chapter offered little discussion of benzo- and hetero-fused systems. The annual review in the *Progress in Heterocyclic Chemistry* <B-94MI 308-01> under the section of "Five-membered Heterocycles Containing One Nitrogen and One Heteroatom" continues to summarize the current literature. The Patai series *The Organic Chemistry of Functional Groups* contains a two-volume set entitled "The Chemistry of Organic Selenium and Tellurium Compounds" <B-86MI 308-01>. This is a general treatment of the area and the coverage of the selenazole system is cursory, but a good overall background is presented.

Selenazole (1) is a five-membered heterocycle containing a selenium and nitrogen atom in the 1- and 3-positions, respectively, with the numbering system beginning with the selenium. The reduced rings are designated as the selenazoline (dihydro) (2) and the selenazolidine (tetrahydro) (3). The dihydro form is generally the Δ -2 isomer (2a). The Δ -4 isomer (2b) is less common and in many cases is the *exo*-tautomer of a 2-substituted selenazole; for example, the acylated amine predominates as the acylated imino group. The tetrahydro form contains oxo and/or thio groups in the 2- and/or 4-positions or an imino group in the 2-position (3b); when R = H the amino form is predominate, whereas, when R = alkyl the imino form is the major isomer (Equation (1)). The benzoselenazoles (4) are numbered differently than the monocyclic compounds with the ring junctions designated 3a and 7a. The benzoselenazoline ring (5) is generally oxidized in the 2-position.



3.08.2 THEORETICAL METHODS

Computational studies were performed on the isolated selenazole ring and nucleoside fragments of selenazofurin (**6**) <92JA2313>. The purpose was to evaluate the electron distribution of the atoms and the resultant electrostatic environments to explain the $\text{Se}\cdots\text{O}$ nonbonding interaction observed in selenazole nucleosides. A population analysis using STO-3G basis set was used. The Mulliken population analyses show that the lone pair of the selenium participates in π -bonding with adjacent carbon atoms producing a net positive charge on the heteroatom. This information was used to explain the electrostatic nonbonding interaction observed between the selenium of the selenazole and oxygen of the furan in selenazofurin. The nitrogen in contrast carries a net negative charge. In the sulfur analogue, tiazofurin, the energy barrier to rotation of the heterocycle is $\sim 4 \text{ kcal mol}^{-1}$ ($16.74 \text{ kJ mol}^{-1}$) due to the nonbonded electrostatic interaction as well as the repulsion between the negatively charged nitrogen and oxygen atoms; no measurement was made for the selenium case, but this is expected to be similar.



(6)

The cycloaddition of mesoionic thiazoles and selenazoles was explained using second-order perturbation theory, limited to frontier orbitals. Only a detailed study of the sulfur case was reported, but an understanding of the selenium model may be gained <82T2129>.

3.08.3 EXPERIMENTAL STRUCTURAL METHODS

3.08.3.1 X-ray Diffraction

The results of the x-ray diffraction of the 2,2'-biselenazole (**7**) was reported <82CB2516>. The selenazole ring is planar. The C—C bond distance between the two rings is $1.44 \text{ \AA}$ with the bond angle relative to the selenium and nitrogen essentially equivalent (121° and 123° , respectively). The C—Se—C bond angle is 84° as compared to the other ring bond angles that range from 111° to 116° . The C—Se bond distances are $1.87 \text{ \AA}$ and $1.88 \text{ \AA}$ as compared to $1.28\text{--}1.39 \text{ \AA}$ for the remaining bonds. The greater bonding distance of selenium is responsible for the constricted bond angle.

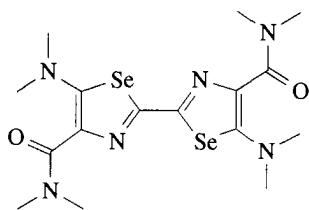
The crystal and molecular crystal structure of 2-styrylselenazole (**8**) was determined <92MI 308-01>. The molecule is almost planar with a dihedral angle of 4.8° between the heterocycle and the phenyl ring. The C—Se—C bond angle is 84.6° , far less than the other bond angles of the selenazole ($110\text{--}116^\circ$) due to the greater bond length for C(1)—Se ($1.9 \text{ \AA}$) and C(2)—Se ($1.86 \text{ \AA}$) as compared to the $1.3\text{--}1.4 \text{ \AA}$ range of the other bonds. A comparison of the bond lengths and angles of the analogous azoles (O and S) was made. The bond lengths decrease from Se to O and the bond angles correspondingly increase. Interestingly, the other bond lengths and angles of the azole rings are similar over the whole series. The relative bond angles from the selenium and nitrogen atoms to the vinyl group are roughly equivalent (122.2° and 123.4° , respectively).

The crystal and molecular structures of platinum complexes of the 2-styrylselenazole (**8**) were also determined by x-ray diffraction techniques. The platinum was found to be bound to the nitrogen atom <93MI 308-01>.

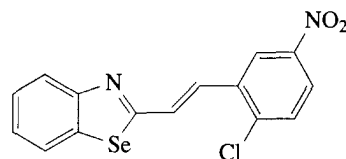
3.08.3.2 NMR Spectroscopy

3.08.3.2.1 ^1H NMR spectroscopy

The ^1H NMR spectra of selenazoles have the H-4 and H-5 signals when unsubstituted (Table 1). These can range from 7.0 with an electron-donating group in the 2-position (**9**) to ~ 9.0 with an



(7)



(8)

adjacent electron-withdrawing group (**10**). When both positions are unsubstituted (**11a–e**), the two protons, generally, are not resolved or coupled, except for the *o*-chlorophenyl analogue (**11e**) where two doublets are observed. Alkyl groups attached to the C-4 or C-5 position have signals in the same range expected of aromatics (2–3 ppm) and those substituted with a heteroatom are similarly shifted downfield. The selenazolidine (**12**) has one signal from the ring at 3.28 ppm. The H-4 and H-5 protons of the quaternary selenazolinium (**13**) are shifted downfield.

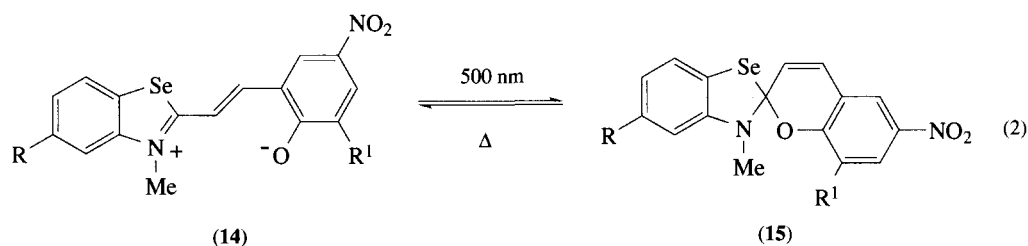
Table 1 ^1H NMR data for selenazoles.

Compound	^1H chemical shifts (ppm)			Ref.
	Solvent	4	5 Coupling constants (Hz)	
 (9)	DMSO- d_6		7.00	93JMC3843
 (10)	CDCl_3	8.70		90MI 308-01
 (11a): R = H (11b): R = <i>p</i> -MeO (11c): R = <i>p</i> -Cl (11d): R = <i>p</i> -NO ₂ (11e): R = <i>o</i> -Cl	CDCl_3	7.76 7.81 7.76 8.11 7.93	7.76 7.81 7.76 8.11 7.93 4	90MI 308-01 90MI 308-01 90MI 308-01 90MI 308-01 90MI 308-01
 (12)	CCl_4		3.28	88MI 170-01
 (13)	DMSO- d_6	5.96 ^a	3.93–4.26 ^a	87KGS690

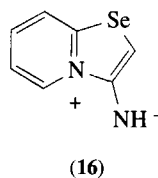
^aBased on numbering of selenazoline ring.

The chemical shift of H-2 of benzoselenazole (**4**) was discussed in *CHEC-I* (9.85 ppm in CCl_4) and the C–H coupling constant (3.56 Hz) was reported $\langle 67\text{JHC139} \rangle$. The $J^{13}\text{C}-^1\text{H}$ coupling constant of methyl azolium cations has been correlated to the acidity of the H-2 position and stability of the ylide. The *N*-methylbenzoselenazolium cation coupling constant (211 Hz) is the same as that of methylbenzothiazolium implying comparable stability of the ylide $\langle 88\text{SC181} \rangle$.

The methyl signals of the *N*-methylbenzoselenazolium cation (**14**) and the spiro derivative (**15**) resonate at 4.06 and 3.01 ppm, respectively, providing a useful tool in assigning the active structure (Equation (2)) of these photochromic molecules (see Section 3.08.12) $\langle 91\text{CL1873} \rangle$.



The mesomeric pyridinium selenazole (**16**) has a proton signal at 8.45 ppm for the imine and the adjacent position $\langle 83\text{IJC(B)328} \rangle$.



3.08.3.2.2 ^{13}C NMR spectroscopy

The C-2 signal in the ^{13}C NMR of the selenazoles is generally the furthest downfield (Table 2). The C-4 and C-5 carbons depend on substitution as is exemplified by (**17**) and (**18**). The C(3a) signal of benzoselenazole (**4**) being next to nitrogen is further downfield than the C(7a) signal; the $^{13}\text{C}(2a)-^{77}\text{Se}$ coupling constant is -136.7 Hz. Although $^{13}\text{C}-^{77}\text{Se}$ coupling constant as measured from the ^{77}Se satellites (natural abundance of ^{77}Se is 7.5%) can be useful for assigning carbons adjacent to selenium, its application in the selenazole literature is scant.

3.08.3.2.3 ^{77}Se and ^{15}N NMR spectroscopy

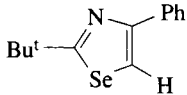
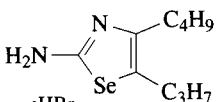
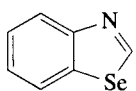
No discussions on the use of ^{77}Se or ^{15}N NMR with selenazoles were found in the literature.

3.08.3.3 Mass Spectrometry

Fragmentation of a 2-phenylselenazole with $\text{R} = \text{H}$, alkyl, or aryl releases benzonitrile or phenyl-selenoaldehyde. An episelenide is also formed with subsequent selenium extrusion. Depending on the R group the resultant alkyne can further fragment. The phenyl group also fragments or ethylene is extruded to form a selenaziridine $\langle 90\text{MI 308-01, 79S66} \rangle$.

The mass spectrum of benzoselenazole (**4**) shows loss of HCN to give $[\text{C}_6\text{H}_4\text{Se}]^{+\cdot}$ which extrudes Se to give the phenyl cation $[\text{C}_6\text{H}_5]^{+\cdot}$ $\langle \text{B-86MI 308-01} \rangle$. In the Patai series a number of other fragmentation patterns of selenazole derivatives is discussed.

Table 2 ^{13}C NMR data for selenazoles.

Compound	¹³ C chemical shift δ (ppm)				Ref.
	Solvent	C-2	C-4 (C-3a)	C-5 (C-7a)	
 (17)	CDCl ₃	180.0	155.0	117.1	93S870
 (18)	CDCl ₃	172.4	133.4	123.2	92BMC1603
 (4)	DMSO- <i>d</i> ₆	160.6	(154.8)	(137.3)	77JOC3725

3.08.3.4 Infrared Spectroscopy

The IR absorption spectra of the aminoselenazoles contain the diagnostic NH and $\text{C}=\text{N}$ stretches. The 4-(2-thienyl)-2-aminoselenazole has the NH stretches at 3460 cm^{-1} and 3300 cm^{-1} and the $\text{C}=\text{N}$ stretch at 1625 cm^{-1} [88PS243]. The IR spectra of selenazoles have two stretches attributed to the $\text{C}=\text{N}$ group. The first band at $1650\text{--}1680\text{ cm}^{-1}$ is due to the $\text{C}=\text{N}$ stretch. The second at $1537\text{--}1570\text{ cm}^{-1}$ is due to the $\text{N}=\text{C}-\text{Se}$ [B-73MI 308-01]. A complete analysis of the IR and Raman spectra of benzoselenazole was reported [84PS21].

The IR of 4-thioxo-5-arylidene-selenazolid-2-ones contain absorption bands at $1680\text{--}1720\text{ cm}^{-1}$ ($\text{C}=\text{O}$), $1150\text{--}1200\text{ cm}^{-1}$ ($\text{C}=\text{S}$), and $1580\text{--}1615\text{ cm}^{-1}$, related to the aromatic ring $\text{C}=\text{C}$ vibrations [83KGS338]. The IR of the 5-arylidene-2-acetylaminoselenazolin-4-ones (19) and the 2,4-dioxo analogues (20) are listed in Table 3. The $\text{C}=\text{C}$ vibration ranges from 1610 cm^{-1} to 1585 cm^{-1} . The $\text{C}=\text{Se}$ stretch of 2-selenoselenazoline is at 1520 cm^{-1} [80SA371].

3.08.3.5 Ultraviolet Spectroscopy

Comparison of the UV spectra of selenazoles and thiazoles shows little difference in spectra except for a slight bathochromic shift from the heteroatom [79HC(34)217]. The ultraviolet spectra of 2-arylselenazoles (11) will shift depending on the electron density of the aryl group (Table 4). The UV spectra of arylidene selenazolidinone systems have three bands; and a fourth if substituted with a *p*-methoxy- or *p*-dimethylaminophenyl moiety. The band between $400\text{--}500\text{ nm}$ is due to the $\pi\text{--}\pi^*$ transitions of the electrons of the conjugated and arylidene substituents of the thioxo group. This is confirmed by the lack of the intense absorption in the 5-unsubstituted parent compound; a low-intensity band is present at 440 nm due to the n to π^* transition of the thiocarbonyl [83KGS338]. The three bands shift to higher wavelengths with an increased electron-withdrawing effect on the aryl group.

3.08.3.6 Polarography

The polarographic aspects of 1,3-selenazolium salts were investigated [84ZOB617]. The reactivity of the ring was found to be dependent on the second heteroatom when the oxazole and thiazole analogues were compared. The electrophilicity of the rings follows the order: oxazoles are the most stable with the thiazole and selenazoles being similarly more electrophilic.

Table 3 IR absorption spectra for selenazolidines.

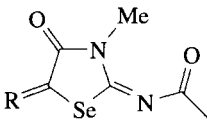
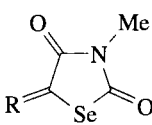
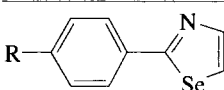
Compound	IR absorption frequency, ν (cm^{-1})			Ref.
	C(2)=O	C=N	C(4)=O	
				
(19a): R = PhCH	1652	1520	1708	85ZOR641
(19b): R = <i>p</i> -NO ₂ PhCH	1661	1520	1706	85ZOR641
(19c): R = <i>p</i> -MeOPhCH	1650	1517	1708	85ZOR641
				
(20a): R = H ₂	1723		1670	83ZOR654
(20b): R = PhCH	1725		1679	83ZOR654
(20c): R = <i>p</i> -NO ₂ PhCH	1740		1684	83ZOR654
(20d): R = <i>p</i> -MeOPhCH	1729		1680	83ZOR654

Table 4 UV spectral data for 2-arylselenazoles
<90MI 308-01>.

Compound	λ_{max} (nm)	$\log \epsilon$
		
(11a): R = H	290	3.32
(11b): R = MeO	304	4.4
(11c): R = Cl	304	4.29
(11d): R = NO ₂	334	4.18
(11f): R = NH ₂	334	4.55
(11g): R = AcNH	307	4.44

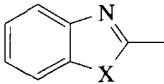
3.08.4 THERMODYNAMIC ASPECTS

The comparison of the basicities of benzazoles over group 16 was measured (Table 5). The basicity increased over X = O, S, Se, and Te. The contribution in basicity is determined by the π -conjugation and the inductive effect of the metal. There is a large jump from X = O to X = S and from X = Se to X = Te, even though the electronegativity of Se and Te are similar. The substantial decrease in the inductive effects of the heteroatoms X on passing from O to Te leads to the observed regularities <91KGS836>.

The aromaticity of the selenazole is less than that of thiazole and in turn less than pyridine. The metallic character of the Se atom weakens the C—Se bond rendering the heterocycle susceptible to ring opening. The stability of the heteroaromatics is in the order: selenazole < thiazole < pyridine <79HC(34)217>.

The elucidation of the two-dimensional arrangement of merocyanine dyes as *J* aggregates was reported <86JPC6144>.

Table 5 Comparison basicity of benzazoles over group 16.

Compound	pK_{BH^+}
	
X = O	7.30
X = S	8.63
X = Se	8.87
X = Te	10.10

The acidity of the N—H bond of 5-benzylideneselenazolidinedione is less with the selenium atom than the sulfur analogue ($pK_a = 10.7$ vs. 9.34). The thermodynamic parameters of the equilibrium were calculated. The substitution of the arylidene moiety and the selenium atom participation were correlated with the pK_a and reactivity of the NH bond <83ZOR216>.

The tautomerism of 2-acylamino-selenazolinone was studied. Alkylation takes place on the ring nitrogen with an equimolar amount of alkylating agent, whereas, alkylation at the *N*-acyl group will occur with a 10-fold increase in the concentration of the alkylating agent <85ZOR641>. With the dioxo system reactivity is increasingly at the oxygen atom with more polar solvents and stronger alkylating agents <83ZOR654>.

Alkylselenazoles, for example, 2,4-dimethylselenazole (b.p. 163–4°C/760 mm), are generally liquids. Aryl or carboxylic acid derivatives, such as 2-methyl-4-phenylselenazole (m.p. 63°C) are solids, except for some 2-phenylselenazoles which are liquids. 2-Amino and 2-hydrazino-selenazoles are almost always solids with the melting point increasing as the molecular weight increases <79HC(34)217>. Benzoselenazolones are solids <93SC621>.

Selenazoles have been purified by chromatography on silica gel with CHCl_3 -methanol <90MI 308-01> or benzene/hexane <93S870>. Benzoselenazolinones can be chromatographed on alumina with acetone, toluene, and cyclohexane as eluents <93SC621>. Some 5-arylideneselenazolidinediones were eluted from alumina with oxalic acid in acetone/hexane <83ZOR654> or Silufol with DMF, dioxane, and ethanol <85ZOR641>.

3.08.5 REACTIVITY OF FULLY CONJUGATED RINGS

3.08.5.1 Electrophilic Attack

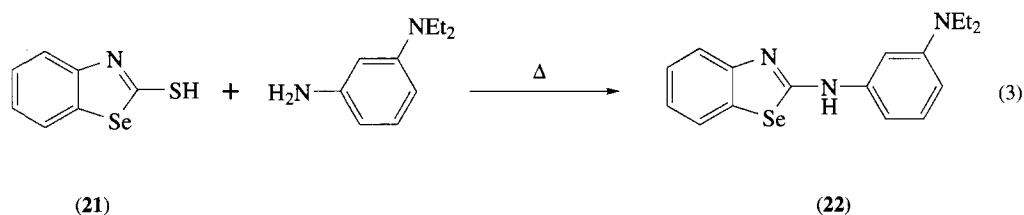
The equilibrium of benzoselenazole (**4**) with gold(III) <91JCS(D)307>, zinc, cadmium, and mercury was studied <81ZAAC(478)233>. The nitrogen of benzoselenazoles reacts with platinum bromide to form the platinum complex (see Section 3.08.12).

Nitration, nitrosation, diazotization, halogenation, and electrophilic reactions of 2-phenyl, 2-amino, or 2-amido selenazoles take place at the 5-position. In cases where the 5-position is blocked or the group in the 2-position is reactive, side reactions, and by-products can be formed <79HC(34)217>. For example, nitration of 2-benzamido-1,3-selenazole provides a mixture of 2-(3-nitrobenzamido)-1,3-selenazole and 2-benzamido-5-nitroselenazole <90MI 308-01>. Azo coupling also occurs in the 5-position <88PS243>.

3.08.5.2 Nucleophilic Attack

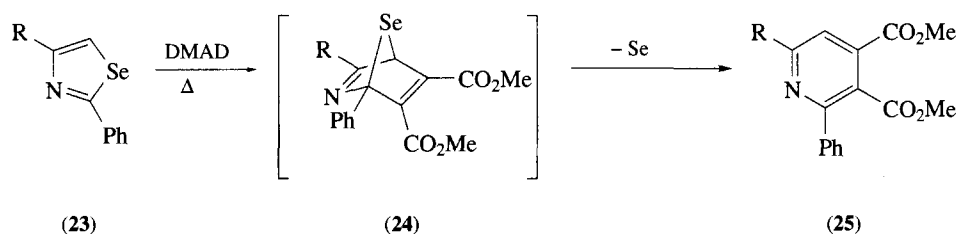
Displacement of the 2-thiol group of 2-thiolbenzoselenazole (**21**) to prepare the 2-anilino derivative (**22**) (Equation (3)) is carried out by heating the mixture at 180°C <88HCA33>. The amino group can be displaced by diazotization. Addition of nitrosonium tetrafluoroborate in the presence of sodium fluoride and tetrafluoroboric acid gave a mixture of the 2-hydroxy- and 2-fluoroselenazole <82JHC1245>. This is the first successful example of the Sandmeyer–Schiemann-type reaction on a 2-

aminoselenazole (see Scheme 5). The quaternary salt of benzoselenazole will undergo addition at the 2-position (see Scheme 2).



3.08.5.3 Cycloaddition

Cycloaddition of 2,4-disubstituted-selenazoles (**23**) with DMAD forms a bicyclo intermediate (**24**) (Scheme 1) that undergoes extrusion of elemental selenium liberating the pyridine product (**25**) <91CL2043>.



Scheme 1

3.08.5.4 Mesoionic Selenazoles

Cycloaddition of a mesoionic selenazole with an alkyne forms a bicyclic intermediate that undergoes deselenization to form pyridones. This is in contrast to the analogous thiazole which can undergo a retro-Diels-Alder to liberate the thiophene <82T2129>. The reaction was also discussed in CHEC-I <75CC617, 77JOC1644>.

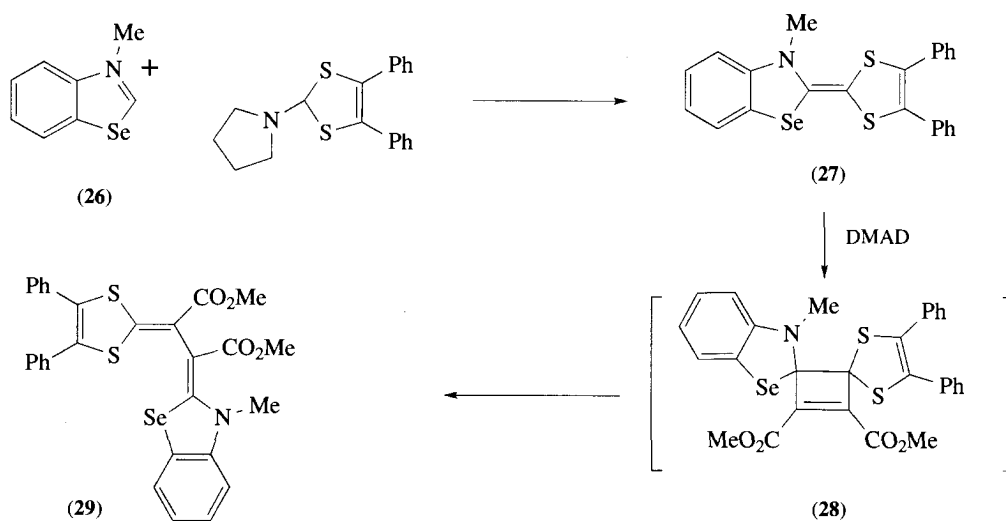
3.08.6 REACTIVITY OF NONCONJUGATED RINGS

3.08.6.1 Selenazolines

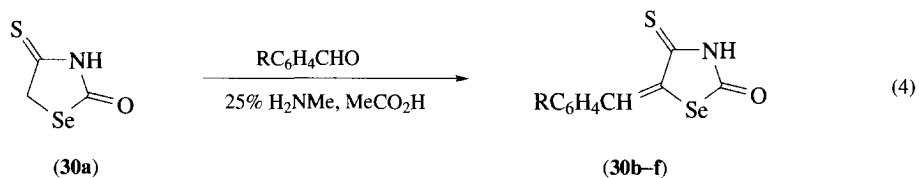
The quaternary salt (**26**) of benzoselenazole is converted to the benzoselenazoline (**27**) with the 1,3-dithiole. The electron-rich alkene in turn undergoes cycloaddition (Scheme 2) to the cyclobutene intermediate (**28**) which spontaneously isomerizes by electrocyclic ring opening to the 1,3-butadiene (**29**) <84ZN(B)1806>.

3.08.6.2 Selenazolidines

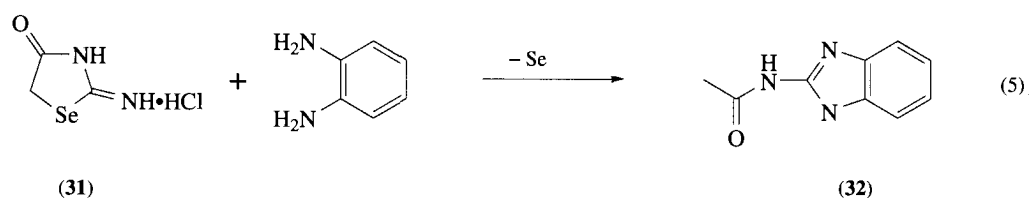
Aldol condensation of 4-thio-2-oxoselenazolidine (**30a**) occurs at the 5-position (Equation (4)) to yield the arylidene derivatives (**30b-f**) using a catalytic amount of 25% aqueous methylamine in acetic acid <83KGS338>. Similarly, 2-thio-4-oxoselenazolidines undergo the aldol reaction at the 5-position <88MI 308-01>. In contrast, alkylation of 2-aminoselenazolidin-4-one and the 2,4-dione analogue occurs at the nitrogen position with concomitant hydrolysis of the imino group to the oxo group <84KGS266, 83ZOR654, 85ZOR641>. In the case of the 2-oxo species no methylation on oxygen takes place; with the 2-imino substrate the methylated amine undergoes hydrolysis to the 2-oxo species (**20**).



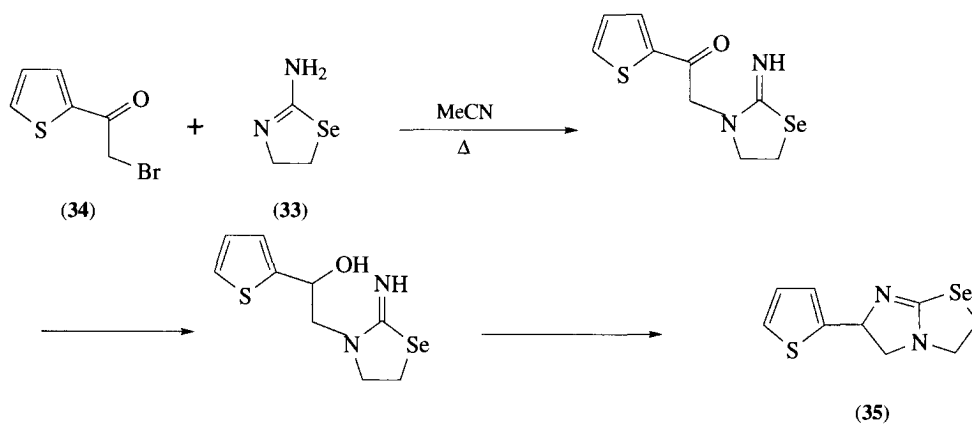
Scheme 2



The 2-imino group of selenazolidine (31) will undergo exchange (Equation (5)). For example, reaction with *o*-phenylenediamine causes cleavage of the ring with extrusion of selenium to provide the imidazole (32) <85KGS1135>.



Alkylation of 2-aminoselenazoline (33) with thiopheneacetyl bromide (34) occurs on the ring nitrogen (Scheme 3). Ring closure is then carried out by reduction and alkylation of the imino group to prepare the selenoisostere (35) of levamisole <83JHC523>.

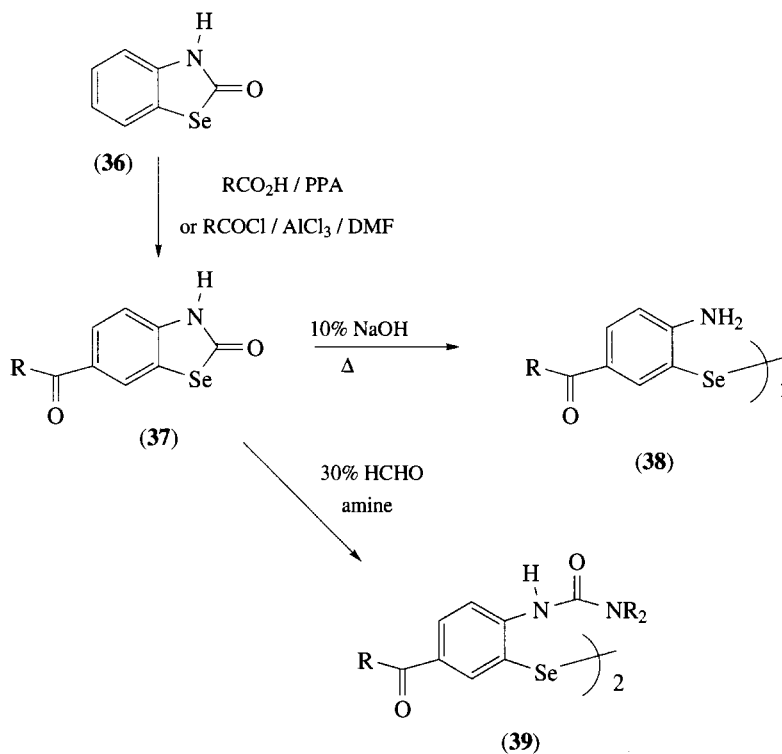


Scheme 3

Methylation of 2-phenylselenazolidine does not take place on nitrogen; instead, on selenium causing ring opening <79HC(34)217>.

3.08.6.3 Reaction of Benzo- and Heterofused Selenazolinones

The electrophilic character of the benzoselenazol-2-one ring (**36**) was ascertained. Friedel–Crafts acylation of benzoselenazolinone is regioselective at the C-6 position following the same trend as the sulfur and oxygen azoles (Scheme 4) <93SC621>. The resultant acylated benzoselenazolinone (**37**) can be methylated with methyl iodide and sodium ethoxide or with an alkyl chloride in K_2CO_3 /DMF. A comparison of the ring cleavage of the azolines under alkaline conditions was made: the order of reactivity follows $Se > S > O$ for these heterocycles. In the case of the selenazoles the diselenide (**38**) is formed due to oxidation of the product. The benzoselenazoline can be cleaved to the urea derivative (**39**) by treatment with formaldehyde and an amine <94JMC2903>.



Scheme 4

3.08.7 REACTIVITY OF SUBSTITUENTS ATTACHED TO RING CARBON ATOMS

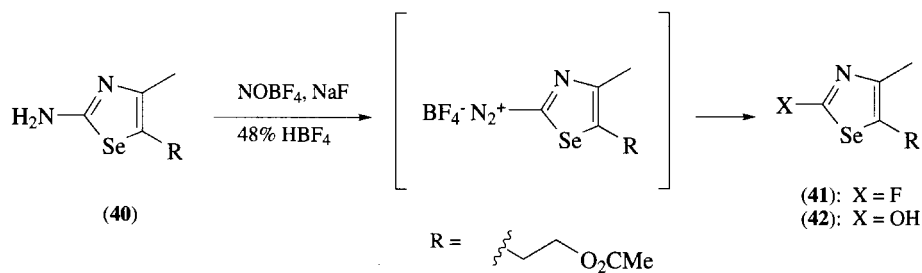
Oxidation of a 2-hydrazino-1,3-selenazole with H_2O_2 can give either of two products depending on the conditions. Oxidation with H_2O_2 in AcOH gives a diazo coupled product whereas in ethanol with HCl a diselenazole selenide is formed <89ZC205>. The hydrazine moiety is oxidized when treated with mercuric oxide, copper(II) salts or silver oxide yielding the difficult-to-prepare 2-unsubstituted selenazoles <79HC(34)217>. The first successful example of a Sandmeyer–Schiemann-type reaction (Scheme 5) was carried out on the 2-aminoselenazole (**40**) with nitroso tetrafluoroborate in the presence of sodium fluoride to give the 2-fluoro compound (**41**) contaminated with some of the 2-hydroxy by-product (**42**) <82JHC1245>.

The methyl group at the 4-position of selenazoles can be further functionalized by free-radical bromination to the bromomethyl intermediate (Scheme 6) <89JHC709>; this provides an alternative to incorporating the halomethyl group as part of the ring synthesis <81JHC789, 86JHC861>.

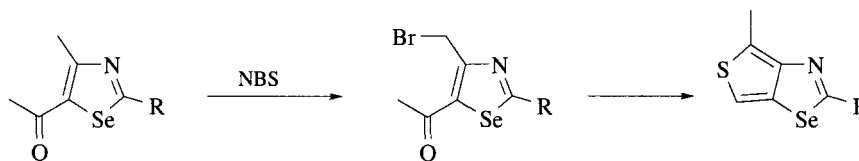
The 2-methyl group of selenazoles and benzoselenazoles, as well as the selenazolium derivatives (see Section 3.08.12) undergoes condensation with aldehydes to give the unsaturated product <92MI 308-01>. The 2-methylselenazoles are also oxidized to the carboxylic acid with SeO_2 <79HC(34)217>.

3.08.8 REACTIVITY OF SUBSTITUENTS ATTACHED TO RING HETEROATOMS

No examples of this reaction class were found.



Scheme 5



Scheme 6

3.08.9 RING SYNTHESSES CLASSIFIED BY NUMBER OF RING ATOMS IN EACH COMPONENT

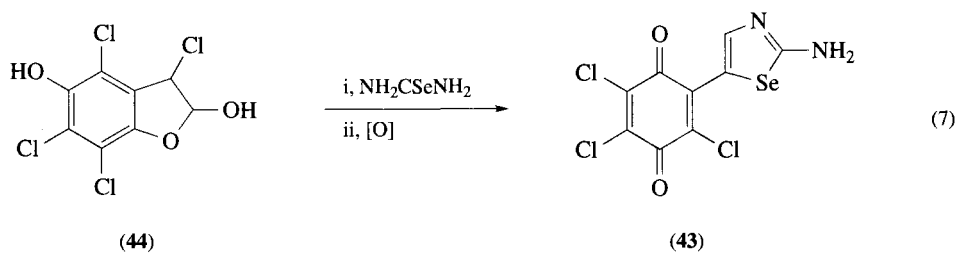
3.08.9.1 Selenazoles

Few reliable methods relative to the preparation of oxazole and thiazole systems have been reported. Generally, the 2-substituted products are prepared through the use of selenoamide derivatives. The synthesis of 2-unsubstituted selenazoles is made more difficult by the instability of the product. For example, the parent compound has never been isolated. The simplest 2-unsubstituted selenazole that has been reported is 4-methylselenazole <79HC(34)217>.

The modified Hantzsch synthesis first described by Hofmann <1889LA(250)294> has remained the general method for preparing 1,3-selenazoles. Depending on the substitution required in the selenazole the requisite selenocarboxamide and α -halocarbonyl derivatives are coupled (Scheme 7) <79HC(34)217>. Since a chlorooxirane is isomeric with an α -chlorocarbonyl, 2-aminoselenazoles are also formed with selenourea (Equation (6)) <81T2607>. The synthesis of a 5-quinonyl-1,3-selenazole (43) from the α -chlorolactol (44) was also carried out with this approach providing a substrate with electron donor and acceptor moieties connected by one bond; the product is of interest as a charge transfer complex (Equation (7)) <89KGS1430>.

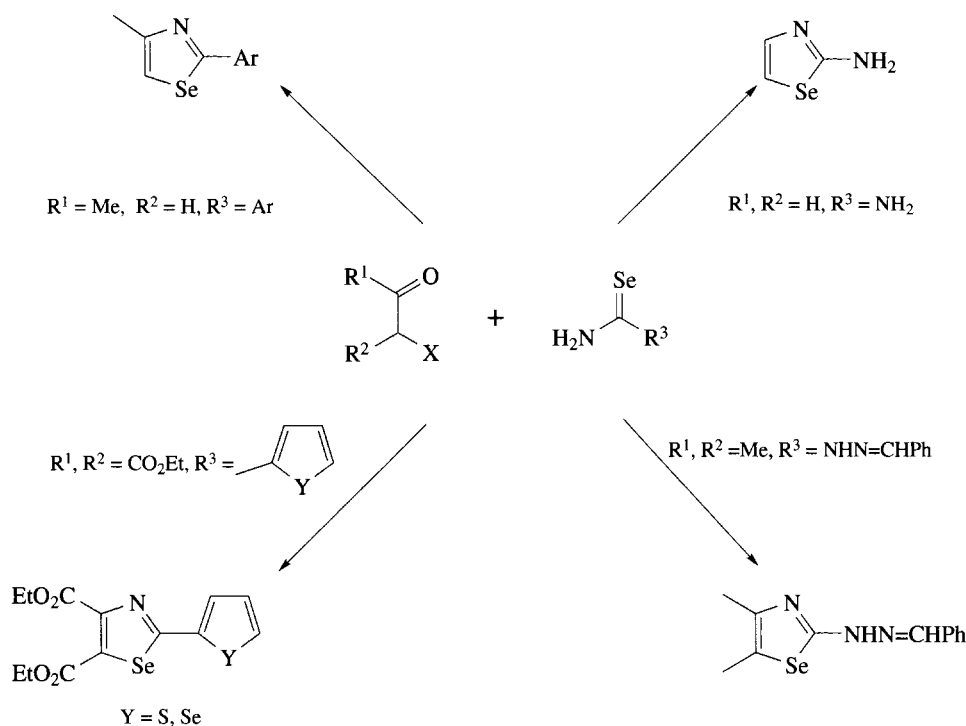


(6)



(7)

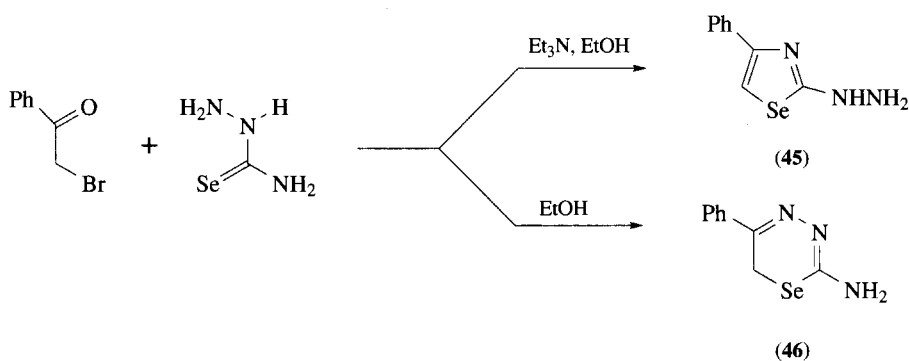
Advancements in the Hantzsch method have appeared in the literature since 1982. An improved synthesis of the aryl- and alkylselenoamide precursors by reaction of the nitrile with aluminum selenide <85JOC384> or NaHSe prepared *in situ* from NaBH_4 and selenium <93S870> has been reported. In particular the latter method aids in the synthesis of 2-alkylselenazoles because of the instability



Scheme 7

of the requisite starting alkyl selenoamides. Similarly the styryl analogue, previously unavailable by the Hantzsch method, was prepared in 14% yield.

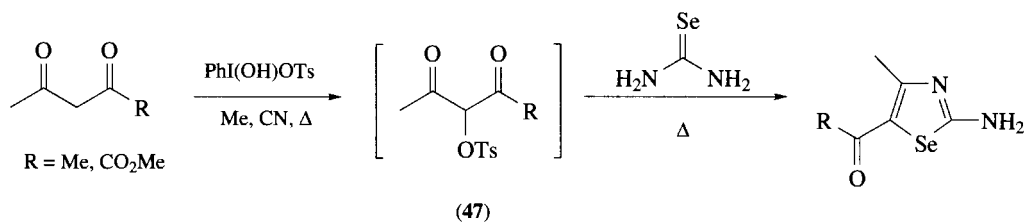
The 2-hydrazino-1,3-selenazoles are prepared from the selenosemicarbazide. Since any of the three nitrogen atoms can react, the hydrazine is protected as the selenosemicarbazone allowing selective formation of the selenazole (Scheme 8). Better control of the formation of the 2-hydrazinoselenazole (**45**) vs. the 1,3,4-selenadiazine (**46**) is offered without protection of the hydrazine moiety (Scheme 7) by adding triethylamine to neutralize the generated hydrogen bromide; no deprotection is required. Without the triethylamine the selenadiazine is formed preferentially [91CZ361].



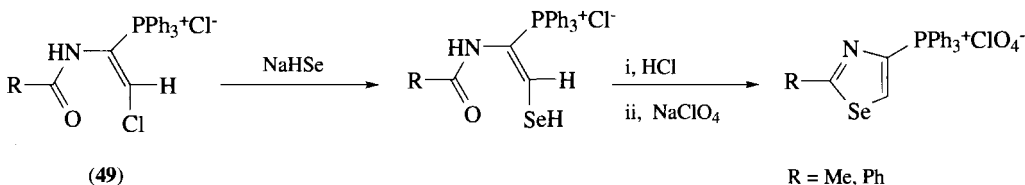
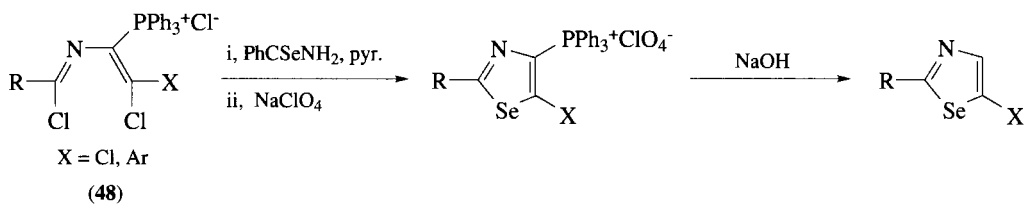
Scheme 8

One problem in the synthesis of some selenazoles has been the lack of availability of the α -halocarbonyl. Another means to activate the carbonyl is through oxidation. Pentanedione or methyl 2,5-dioxopentanoate is converted to the tosylate (**47**) in the presence of [hydroxy(tosyloxy)-iodo]benzene (Scheme 9). Reaction with selenourea provides the 2-aminoselenazole [92S845].

Vinylphosphonium salts (**48**) and (**49**) when treated with phenyl selenoamide [93ZOB87, 93ZOB1053] or sodium hydrogen selenium [86ZOB321], respectively, close to form the 4-phosphonium salts of the 2-substituted benzoselenazoles (Scheme 10). The phosphonium group can then be removed with sodium hydroxide.



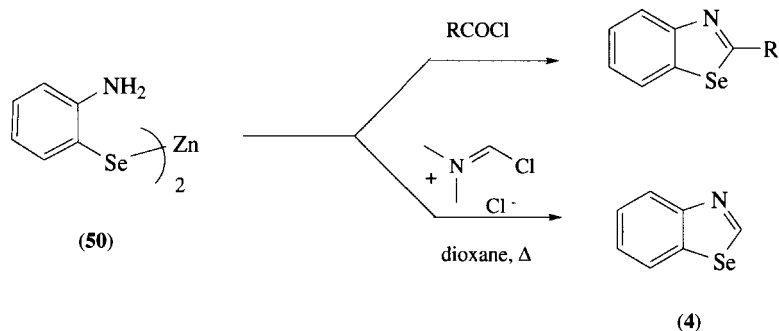
Scheme 9



Scheme 10

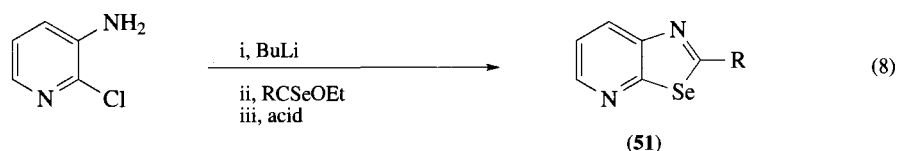
3.08.9.2 Benzo- and Heterofused Selenazoles

The traditional approach to preparing benzoselenazoles has been to react the *o*-amino-phenylselenate as the zinc salt (**50**) with an acid chloride $\langle 79\text{HC}(34)217 \rangle$. The synthesis of the parent benzoselenazole (**4**) from formic acid, however, has been more difficult. By using the *N,N*-dimethylchloroiminium chloride (Scheme 11) a 66% yield of benzoselenazole (**4**) was obtained $\langle 88\text{SC}181 \rangle$.



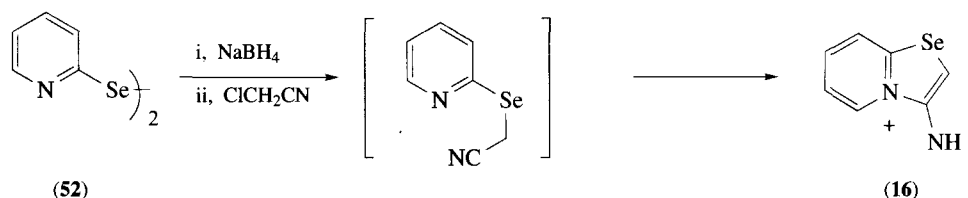
Scheme 11

In many cases a 1-chloro-2-amino derivative is used as a starting material. The 2-aryl-selenazolopyridine (**51**) can be prepared directly from the 1-chloro-2-amino intermediate without prior selenation by reaction of the lithium amide with the arylselenoester (Equation (8)) $\langle 87\text{S}363, 94\text{H}(37)323 \rangle$.



3.08.9.3 Selenazolium Salts

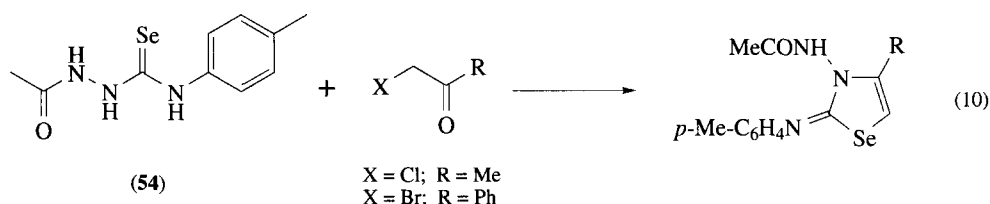
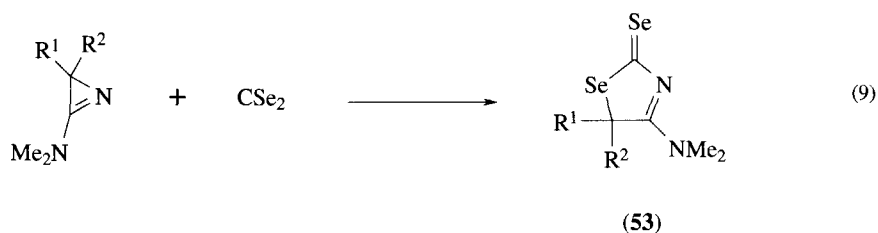
Synthesis of condensed mesoionic selenazoles (Scheme 12) can be carried out by cyclization of a pyridine moiety with a nitrile. Reduction of diselenide (**52**) was followed by alkylation with chloroacetonitrile. The ring closes directly to form the 3-aminoselenazolo[3,2-a]pyridinium hydroxide inner salt (**16**) <83IJC(B)328>.



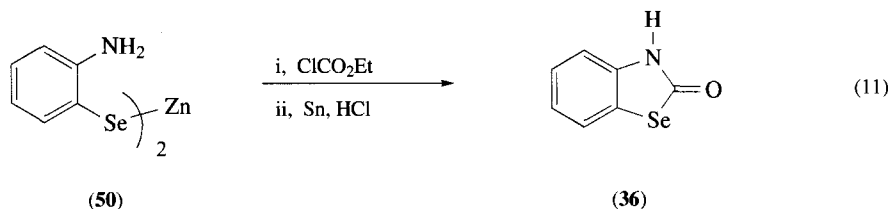
Scheme 12

3.08.9.4 Selenazolines

Few improvements have been made in the synthesis of Δ^2 -selenazolines. They are often prepared by reaction of a selenoamide with a β -haloamine or by treatment of bis(2-acetamidoethyl)diselenide with PCl₅ to form the methyl selenazoline <79HC(34)217>. Azirines undergo ring opening with carbonyl diselenide (Equation (9)) and subsequent cyclization to the 2-selenoselenazoline (**53**) <82CB2516>. Reaction of selenosemicarbazides (**54**) with chloroacetone <89MI 308-01> or bromoacetophenone <89MI 308-02> yields the 2-iminoselenazolines (Equation (10)).



The synthesis of benzoselenazolidinones (**36**) still follows the 1912 method of Bauer. Studies of the medicinal properties of the ring system has recently utilized this approach (Equation (11)) <93SC621, 94JMC2903>.

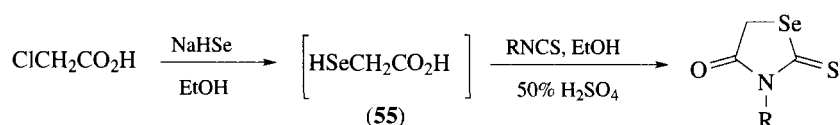


3.08.9.5 Selenazolidines

The selenazolidines are divided into two classes: the tetrahydro form of selenazole and the 2,4-oxidized selenazolidines. No improvements in the synthesis of the former class of selenazoles has

been reported since the publication of CHEC-I. The tetrahydro forms are most commonly prepared by reaction of an aziridine with hydroselenide generating the β -selenoamine that in the presence of an aldehyde or ketone ketalizes to form the 2,2'-disubstituted selenazolidine. Transketalization can yield other derivatives <79HC(34)217> although these compounds can be quite unstable.

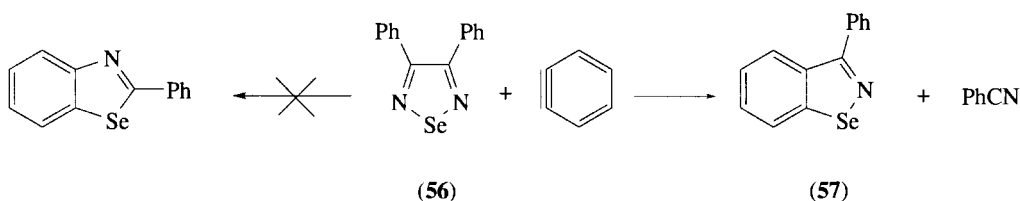
The latter class of selenazolidines have the 2 and/or 4 positions in the oxidized form. The combination of oxo, thio, and imino forms have been reported previously <79HC(34)217>. For the 2-imino compounds the appropriately substituted selenourea derivative is reacted with an α -halo-carboxylic acid. Depending on the substitution of the amine the product can also exist as the 2-aminoselenazolinone. The 2-oxo derivative is often obtained by hydrolysis of the 2-imino substrate. The 2-thio derivatives are prepared by reacting hydrogen selenide with an α -chloroisothiocyanate <78CCC2298> or the α -selenocarboxylic acid with an isothiocyanate. An improved approach to the 2-thio-4-selenazolidones traps ethylthiocyanate with *in situ* prepared selenoglycolic acid (**55**) (Scheme 13) <88MI 308-01>. The 2-thio compounds can also be obtained from the dioxo analogue by treatment with P_2S_5 in refluxing dioxane <83KGS338>.



Scheme 13

3.08.10 RING SYNTHESIS BY TRANSFORMATION OF ANOTHER RING

The original report on the cycloaddition of diphenylselenadiazole (**56**) with benzyne and rearrangement of the cycloadduct to a 1,3-benzoselenazole was not confirmed <82CC299>. The reaction was readdressed <88JCS(P1)2141>. A 3-substituted benzoselenazole (**57**) was the actual product, as confirmed by mass spectrometry and the detection of benzonitrile (Scheme 14).



Scheme 14

3.08.11 SYNTHESIS OF PARTICULAR CLASSES OF COMPOUNDS AND CRITICAL COMPARISON OF THE VARIOUS ROUTES AVAILABLE

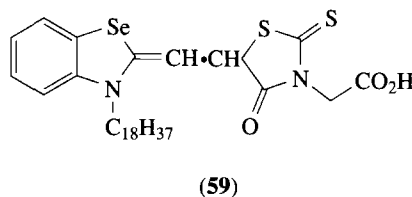
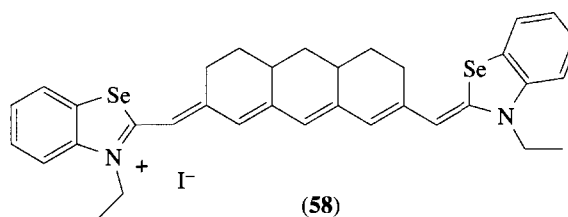
Selenazoles are generally prepared via the [3 + 2] route using the Hantzsch method. An exception is the [4 + 1] route using the phosphonium intermediate (Scheme 10). Benzoselenazoles are formed by the [4 + 1] route through the reaction of the *o*-selenoaniline compound with acylating agents. The selenazoline and selenazolidine rings are usually prepared by the [3 + 2] route through reaction of an α -selenoacetic acid with an isocyanate derivative or reaction of an α -haloacetic acid with a selenoamide, similar to the Hantzsch method. Very few improvements in the basic approach to the selenazoles have been made since the publication of CHEC-I. The major improvements that have been reported are in the preparation of the substrates for ring synthesis; for example, the *in situ* generation of the selenoamides. The ring syntheses still tend to be low-to-moderately yielding.

3.08.12 IMPORTANT COMPOUNDS AND APPLICATIONS

3.08.12.1 Conjugated Benzoselenazoles

3.08.12.1.1 Dyes

N-Octadecylsquarylium <85NKK1516, 87NKK714, 89DP21> and cyanine dyes containing the benzoselenazoline or benzoselenazolium moiety(ies) (**58**) conjugated to another heterocycle through methine(s) <86ZOR163, 86CB3102, 87HCA1583> or aza units <84HCA765, 85HCA1394, 85HCA1401> continue to be of interest in the manufacture of dyes. Because of their extended conjugation other potential applications for these unique structures have been pursued. For example, the merocyanine dye, BSeER (**59**), is a promising organic electronic material. Its application as a sensitizer or utility as part of a solar battery has been investigated <89MI 308-03>. These cyanine dyes are prepared by base-induced alkylation/condensation of the 2-methyl-*N*-alkylbenzoselenazolium salt with the appropriate carbonyl derivative.

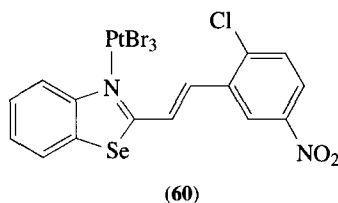


3.08.12.1.2 Photochromic properties

A series of photochromic spirobenzoselenazoles have been studied for their potential application in photo-information memory devices <93CLI3, 91CLI873, 93CE93>. Again, the compounds are easily prepared by base-induced condensation of the 2-methylbenzoselenazolium ion with the benzaldehyde. The compounds undergo a reversible ring opening of the spirobenzopyran (**15**) by heating to the highly colored conjugated benzoselenazolium phenoxide (**14**). Irradiation of the purple solution of the zwitterion causes bleaching by inducing ring closure to the colorless spirobenzopyran (see Equation (2)). As many as 1000 cycles have been carried out with only 50% reduction in the activity of the substrate.

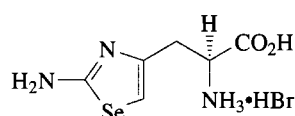
3.08.12.2 Medicinal Agents

The platinum complex (**60**) of the styrylbenzoselenazole (**8**) has potential as an antitumor agent. X-ray data has shown that the Pt is bonded through the nitrogen atom <93MI 308-01>. Again the styryl moiety is prepared by condensation of 2-methylbenzoselenazole with a benzaldehyde.

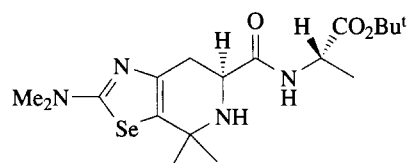


Selenazofurin (CI-935) (**6**) is a selenium analogue of the IMPD inhibitor tiazofurin (CI-909). The selenazole nucleoside has antitumor activity and broad spectrum *in vitro* antiviral activity <88MI 308-02, 86JHC155, 85JOC1741, 83JMC445, 83BBR(115)544, 83BBR(115)971>. The heterocycle is prepared by conversion of a cyano glycoside intermediate to the selenoamide and subsequent ring formation with the Hantzsch synthesis.

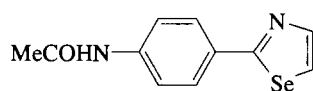
A selenium analogue (**61**) of histidine was prepared and compared to the sulfur-containing analogue. These amino acids were discussed in CHEC-I <81JHC205>. The synthesis of (**61**) was racemic however. In 1992, an enantioselective synthesis using aspartic acid as the chiral starting material was reported <92S1145>. The bicyclo analogue (**62**) was prepared from (**61**). The antimicrobial activity of 2-phenylbenzoselenazole (**11g**) was studied <90MI 308-01>. The isothiocyanatomethyl substituted selenazole (**63**) has activity as an antifilarial and antitumor agent <93JMC3843, 93JMC3849>. The 4,5-dialkylselenazole (**18**) has affinity for odorant-binding proteins acting as an aid in the study of the binding site <92BMC1603>.



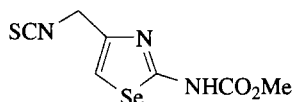
(61)



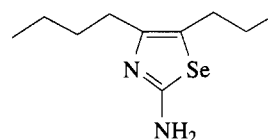
(62)



(11g)



(63)



(18)

3.09

1,2-Dioxoles and 1,2-Oxathioles

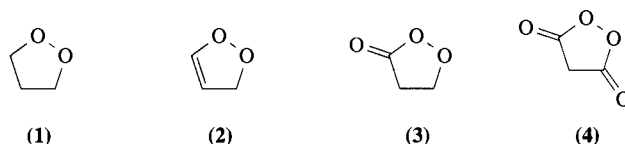
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University of St. Andrews, UK

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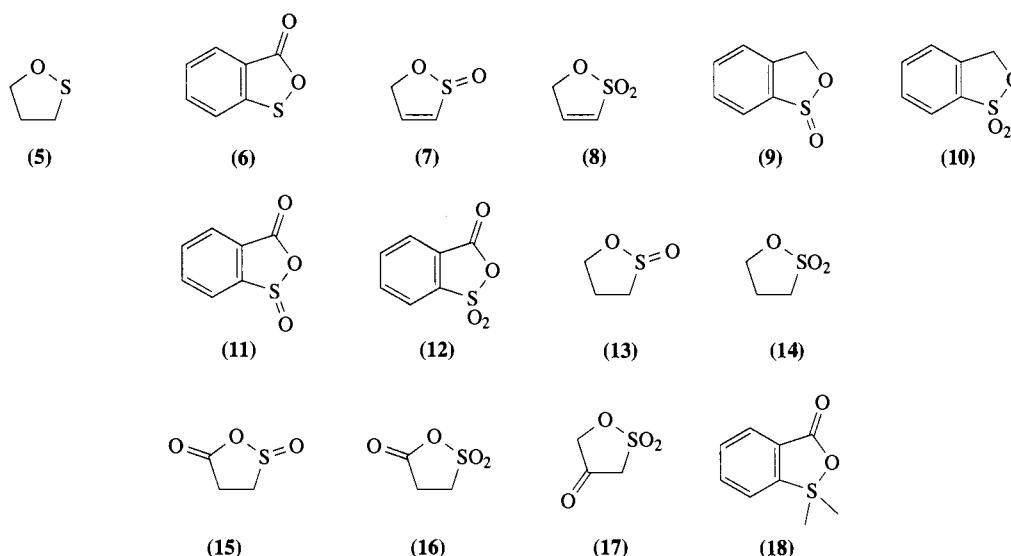
3.09.1 INTRODUCTION

As described in Chapter 4.30 of the first edition of *Comprehensive Heterocyclic Chemistry* (CHEC-I) <84CHEC-I(6)749>, the majority of work on 1,2-dioxole systems has been on derivatives of

the fully saturated 1,2-dioxolane (1) and, as cyclic peroxides, these have been the subject of two major reviews <88HOU(E13)424, 95MI 309-01>. A derivative of 1,2-dioxole (2) has been characterized spectroscopically for the first time. New results on the chemistry of 1,2-dioxolane-3-ones (3) and -3,5-diones (4) have also appeared.



Further properties of the parent 1,2-oxathiolane (5) have been described and representative 2,1-benzoxathiol-3-ones (6) have been prepared. The majority of work has, however, been on *S*-oxidized derivatives including 5*H*-1,2-oxathiole 2-oxides (7) and 2,2-dioxides (8), and their benzo derivatives (9) and (10), as well as the corresponding 2,1-benzoxathiol-3-one 1-oxides (11) and 1,1-dioxides (12). New material on the saturated analogues, 1,2-oxathiolane 2-oxides (13) and 2,2-dioxides (14), as well as the 1,2-oxathiolan-5-one 2-oxide (15) and 2,2-dioxide (16) and 1,2-oxathiolan-4-one 2,2-dioxide (17) systems is also included. Finally there have been a few reports on sulfuranes of the λ^4 -*S*-2,1-benzoxathiol-3-one structure (18).



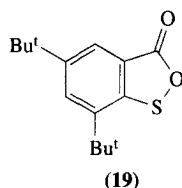
3.09.2 THEORETICAL METHODS

There has been little work in this area, but MNDO calculations on 1,2-oxathiolane (5) indicate a planar structure and have been used to assign the observed photoelectron spectrum <83CB2374>.

3.09.3 EXPERIMENTAL STRUCTURAL METHODS

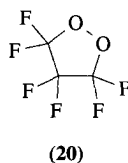
3.09.3.1 X-ray Diffraction

The x-ray structure of (19) has been determined and shows the heterocyclic ring to have the following dimensions: S—O, 1.682 Å; O—CO, 1.374 Å; CO—C, 1.469 Å; C—C, 1.374 Å; and C—S, 1.748 Å; C—S—O, 93.1°; S—O—CO, 114.1°; O—CO—C, 109.3°; CO—C—C, 114.3°; and C—C—S, 109.1° <82CB3842>.



3.09.3.2 Electron Diffraction

Electron diffraction has been used to obtain the following dimensions for the heterocyclic ring of the perfluorinated 1,2-dioxolane (**20**): O—O, 1.443 Å; C—O, 1.377 Å; and C—C, 1.531 Å; C—C—C, 98.1°; C—C—O, 107.3°; and C—O—O, 102.9° <92JST(274)163>.



3.09.3.3 NMR Spectroscopy

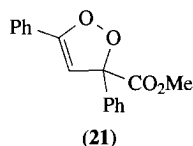
3.09.3.3.1 Proton NMR

The spectroscopic data for some simple systems which were not included in the first edition, namely the *cis* and *trans* isomers of 3,5-dimethyl-1,2-dioxolane together with the *S*-oxidized 1,2-oxathiolane systems (**13**) and (**14**) and some simple derivatives are shown in Table 1.

Table 1 Proton NMR data for some 1,2-dioxolane and 1,2-oxathiolane 2-oxide and 2,2-dioxide derivatives.

Compound	δ_{H}			Ref.
	3- <i>H</i>	4- <i>H</i>	5- <i>H</i>	
<i>cis</i> -3,5-Dimethyl-1,2-dioxolane	4.25	1.71, 2.77	4.25	78JCS(P1)522
<i>trans</i> -3,5-Dimethyl-1,2-dioxolane	4.30	2.19	4.30	78JCS(P1)522
1,2-Oxathiolane 2-oxide (13)	1.35	1.35	3.45	71JOC322
<i>cis/trans</i> -3-Methyl-1,2-oxathiolane 2-oxide		1.7–1.35	4.2–4.9	76CJC3012
<i>cis/trans</i> -4-Methyl-1,2-oxathiolane 2-oxide		2.2–3.4	4.7–5.2	76CJC3012
1,2-Oxathiolane 2,2-dioxide (14)	3.1	2.5	4.82	64JA4641
5-Methyl-1,2-oxathiolane 2,2-dioxide	3.3	2.5	4.8	64JA4641
5,5-Dimethyl-1,2-oxathiolane 2,2-dioxide	3.4	2.5		64JA4641

The first 1,2-dioxole (**21**), generated by photooxidation of a furan as described in Section 3.09.5.2, is only stable below -60°C but showed a characteristic ^1H NMR signal at δ 5.62 due to the 4-*H* <91JCS(P1)1479>.



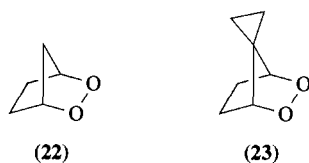
3.09.3.3.2 Carbon-13 NMR

The *cis* and *trans* isomers of 3,5-dimethyl-1,2-dioxolane are clearly distinguishable by ^{13}C NMR showing the following signals: *cis* δ 19.25 (Me), 49.34 (C-4) and 77.30 (C-3,5); *trans* δ 18.40 (Me),

48.61 (C-4) and 77.04 (C-3,5) $\langle 78JCS(P1)522 \rangle$. The 1,2-dioxole (**21**) showed the following characteristic ^{13}C NMR signals due to the ring carbons: δ 94.5 (C-3), 93.0 (C-4), and 154.7 (C-5), indicating the expected high degree of polarization in the C-4—C-5 bond $\langle 91JCS(P1)1479 \rangle$.

3.09.3.3 Oxygen-17 NMR

This powerful technique has only been applied in relatively few cases. The chemical shifts obtained, δ_{O} (with respect to H_2^{17}O) of +280 for (**1**) and +303 and +310 for the bridged analogues (**22**) and (**23**), respectively, are in the expected range for peroxides $\langle 85JOC4484 \rangle$.



3.09.3.4 UV-Visible, Infrared, and Photoelectron Spectroscopy

Few UV-visible spectra of compounds of this type have been reported, but 1,2-oxathiolane (**5**) has a weak absorption at 317 nm (ϵ 53) $\langle 81CC741 \rangle$.

There has been no systematic study of the IR spectra of compounds in this class. The principal absorptions of 1,2-dioxolane (**1**) occur at 1150 cm^{-1} , 1110 cm^{-1} , 987 cm^{-1} , 925 cm^{-1} , and 780 cm^{-1} $\langle 79JA4290 \rangle$. A prominent absorption assigned to $\text{S}=\text{O}$ occurs in the spectrum of (**13**) at 1105 cm^{-1} $\langle 71JOC322 \rangle$, and in its 3-, 4- and 5-methyl derivatives at 1100 cm^{-1} , 1120 cm^{-1} , and 1100 cm^{-1} , respectively $\langle 76CJC3012 \rangle$.

Photoelectron spectroscopy of 1,2-dioxolane (**1**) has given values for its first and second ionization energies of 9.86 eV and 11.13 eV, respectively $\langle 79JA1533 \rangle$. For the bridged analogues (**22**) and (**23**), values of 8.99 eV and 11.23 eV, and 8.87 eV and 11.15 eV, respectively, have been reported $\langle 84MI309-01 \rangle$. For 1,2-oxathiolane (**5**) the first, second and third ionization energies are 8.51 eV ($n_s\pi$), 10.89 eV ($n_o\pi$), and 11.8 eV, respectively, with the assignment supported by MNDO methods $\langle 83CB2374 \rangle$.

3.09.3.5 Mass Spectroscopy

Although there has been little attempt to rationalize fragmentation patterns, mass spectra of 1,2-dioxolane (**1**) $\langle 79JA4290 \rangle$, 3,5-dimethyl-1,2-dioxolane $\langle 78JCS(P1)522 \rangle$, 1,2-oxathiolane (**5**) $\langle 81CC742 \rangle$, and 1,2-oxathiolane 2-oxide (**13**) $\langle 71JOC322 \rangle$ have been reported. The mass spectral fragmentation of 1,2-oxathiolan-5-one 2,2-dioxide (**16**) has been analyzed in detail $\langle 68BCJ1388 \rangle$.

3.09.3.6 Dipole Moments

Dipole moments of 1,2-oxathiolane 2-oxide (**13**) and the 2,2-dioxide (**14**) have been measured as 3.88 D and 5.16 D, respectively, in benzene at 25°C $\langle 72CJC548 \rangle$.

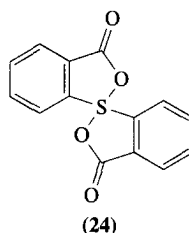
3.09.4 THERMODYNAMIC ASPECTS

There has been no systematic attempt to study the pattern of melting and boiling points for compounds of this type. Some data for simple 1,2-oxathiolane derivatives with oxidized sulfur, which were not included in the first edition, are presented in Table 2.

Table 2 Physical properties of selected 1,2-oxathiolane 2-oxide and 2,2-dioxide derivatives.

Compound	mp (°C)	bp (°C/Torr)	Ref.
1,2-Oxathiolane 2-oxide (13)		48–49/0.2	71JOC322
1,2-Oxathiolane 2,2-dioxide (14)	31	155–157/14	49LA(562)34
3-Methyl-1,2-oxathiolane 2,2-dioxide	–14	150/12	54LA(586)151
4-Methyl-1,2-oxathiolane 2,2-dioxide	29	137–138/0.5	58CB2130
3,3-Dimethyl-1,2-oxathiolane 2,2-dioxide		158–161/0.5	58CB2130
4,4-Dimethyl-1,2-oxathiolane 2,2-dioxide	51.5–52		56JOC388
5,5-Dimethyl-1,2-oxathiolane 2,2-dioxide	70–71		59JA2002
4,5,5-Trimethyl-1,2-oxathiolane 2,2-dioxide	61–63		59JA2002
3,4,5,5-Tetramethyl-1,2-oxathiolane 2,2-dioxide	76–77		59JA2002
4,4,5,5-Tetramethyl-1,2-oxathiolane 2,2-dioxide	145–146		59JA2002
1,2-Oxathiolan-5-one 2,2-dioxide (16)	76–77		40JA925
4-Methyl-1,2-oxathiolan-5-one 2,2-dioxide		135–145/3–5	40JA2393

There has been no systematic study of chromatographic properties, but the enantiomers of the spiro sulfurane (**24**) have been separated using liquid chromatography on a commercially available chiral stationary phase <93TA2329>.



3.09.5 REACTIVITY OF 1,2-DIOXOLES AND 1,2-OXATHIOLES

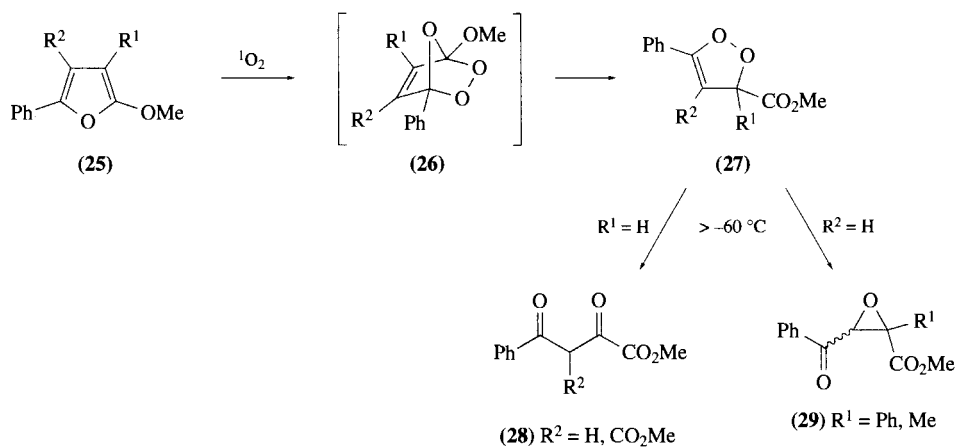
3.09.5.1 Introduction

With a single exception, that of the unstable 1,2-dioxoles (**27**), work in this area has involved 1,2-oxathiole 2-oxides and 2,2-dioxides or their benzo analogues and the reactions involve either thermal extrusion of SO or SO₂ or nucleophilic attack at the cyclic sulfinate or sulfonate functions.

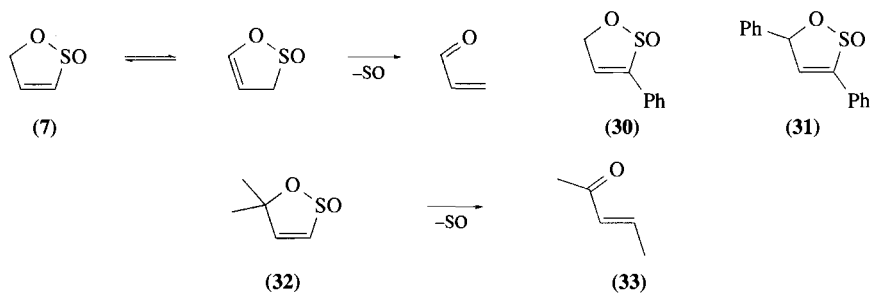
3.09.5.2 Unimolecular Reactions

The first 1,2-dioxoles (**27**) are formed as intermediates in the photosensitized oxygenation of furans (**25**), by rearrangement of the initial [4 + 2] cycloadducts (**26**). As described in Section 3.09.3, these have been detected spectroscopically, but rearrange thermally at temperatures above –60°C. For R¹ = H, the products are the α,γ -dioxoesters (**28**), while for R² = H and R¹ ≠ H, the epoxides (**29**) are the main products (Scheme 1) <91JCS(P1)1479>.

The 1,2-oxathiole 2-oxides (**7**) which may be formed by thermal or photochemical ring expansion of thiete 1,1-dioxides (see Section 3.09.8.1), undergo ready thermal extrusion of the unusual fragment SO to afford α,β -unsaturated carbonyl compounds. The reaction is likely to proceed by initial tautomerization from the 5*H* to the 3*H* form which can then undergo a simple electrocyclic process. Where there is a hydrogen at the 5-position, as in the case of (**7**) itself <70CJC3704>, (**30**) <72TL4781> or (**31**) <77JOC3506>, this is straightforward and the products are acrolein, cinnamaldehyde and chalcone, respectively. For (**32**) a 1,3-methyl migration occurs to give pentenone (**33**) (Scheme 2) <69CC32, 70CJC3704>.

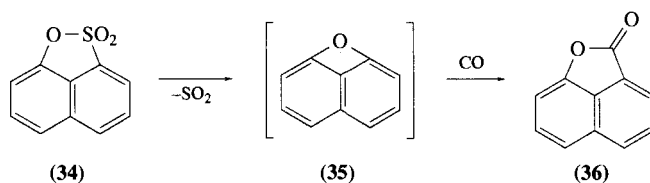


Scheme 1

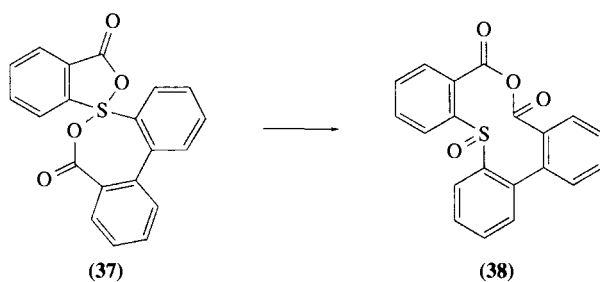


Scheme 2

Flash vacuum pyrolysis of the naphthalene-1,8-sultone (34) at 650°C results in extrusion of SO_2 to give a reactive intermediate which may be formulated as (35). This abstracts hydrogen to give 1-naphthol, whose yield is increased in the presence of methanol, and may be trapped by CO to give (36) (Scheme 3) <71TL4093>. Pyrolysis of (12) results in extrusion of SO_2 and CO_2 to generate benzyne <66CC275, 67AJC139>. The spiro sulfurane (37) undergoes an unusual thermal rearrangement to afford the sulfoxide-anhydride (38) (Equation (1)) <94JST(317)279>.



Scheme 3



(1)

3.09.5.3 Nucleophilic Attack at Carbon

Nucleophilic ring opening of the cyclic sulfinic-carboxylic anhydride (**11**) is found to occur exclusively by attack at C=O <86KFZ843, 88IZV1633>.

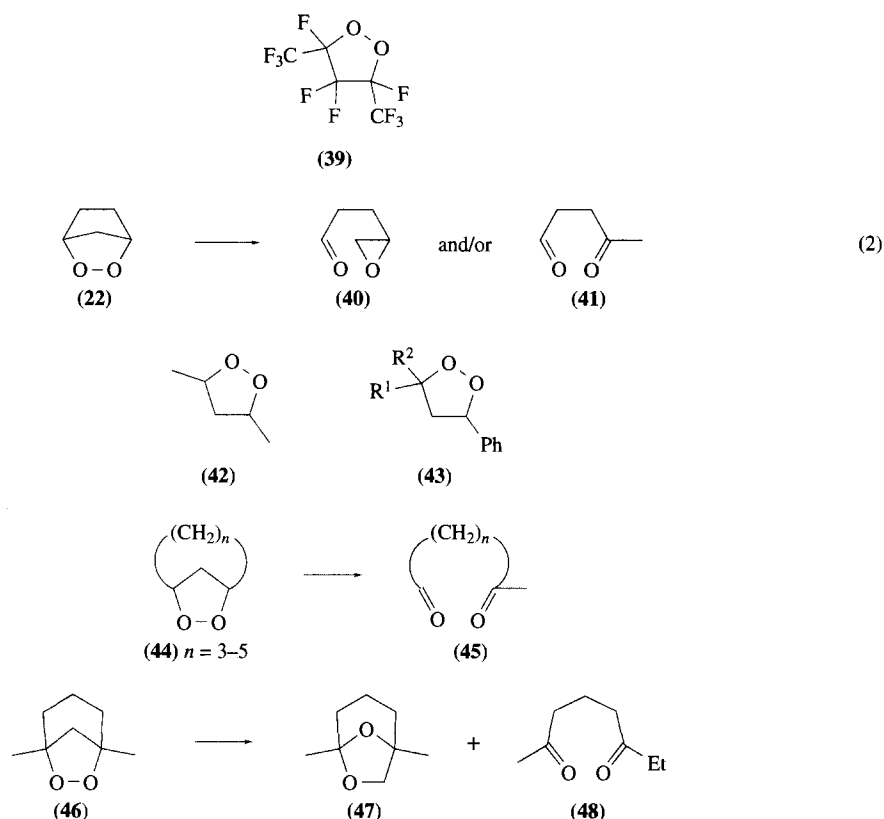
3.09.6 REACTIVITY OF 1,2-DIOXOLANES AND 1,2-OXATHIOLANES

3.09.6.1 Introduction

There has been continued interest in the thermolysis of 1,2-dioxolanes but most studies in this area have involved reactions of *S*-oxidized 1,2-oxathiolane systems.

3.09.6.2 Unimolecular Reactions

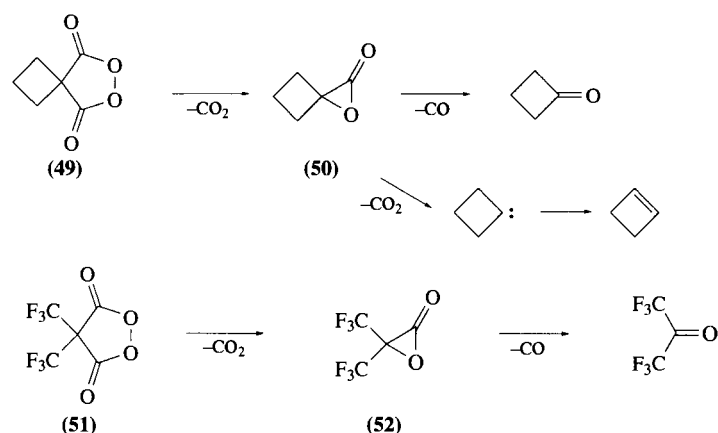
In an early study, the perfluorinated dioxolane (**39**) was found to decompose in the gas phase to give two molecules of CF₃COF and, presumably, difluorocarbene, although the fate of the latter was unclear <65JOC1429>. Solution thermolysis of the bicyclic dioxolane (**22**) gives the epoxy aldehyde (**40**) in nonpolar solvents, but the keto aldehyde (**41**) in more polar solvents, thus suggesting a polar transition state for the process (Equation (2)) <78JA660>. Flash vacuum pyrolysis of (**22**) at 450°C and 10⁻³ Torr gives only (**40**) and monocyclic dioxolanes such as (**42**) <81CC547>, and (**43**) <83JA6279> similarly give mixtures of epoxides and carbonyl compounds. In contrast to (**22**), the analogues (**44**) with a longer bridge give only the ω -keto aldehydes (**45**) upon FVP at 450°C, while (**46**) gives mainly the 1,3-dioxolane (**47**) together with diketone (**48**) (Scheme 4) <82CC1034>.



Scheme 4

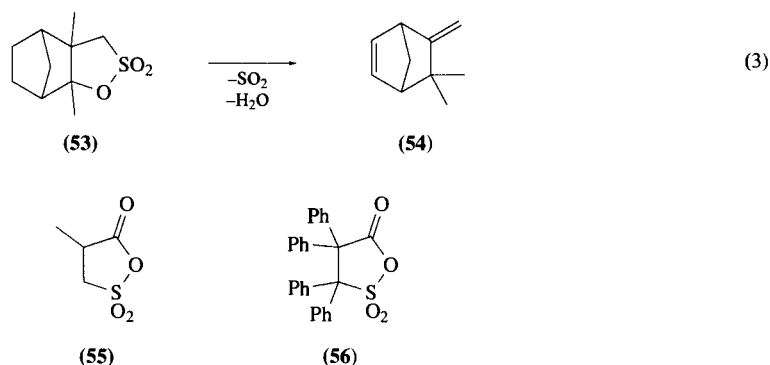
The spiro 1,2-dioxolane-3,5-dione (**49**) decomposes upon FVP by loss of CO₂ and CO to give cyclobutanone as the main product, together with a small amount of cyclobutene. The latter was rationalized by invoking the intermediacy of the α -lactone (**50**) which mainly loses CO but also to a lesser extent CO₂ giving cyclobutylidene which goes on to cyclobutene (Scheme 5) <73JOC3422>.

The analogous sequence is observed for (51), where low-temperature photolysis or thermolysis generates the α -lactone (52) which gives hexafluoroacetone on warming above room temperature <73JOC2269>.



Scheme 5

Gas-phase thermolysis of 1,2-oxathiolane 2-oxide (13) between 500°C and 1130°C leads to loss of oxygen to form 1,2-oxathiolane (5) <81JCS(P2)1166>, and pyrolysis of (5) itself in a static system at 130–180°C cleanly gives acrolein by loss of H_2S <84CB1393>. Heating the tricyclic camphene sultone (53) with zinc oxide results in loss of SO_2 and water to afford (54) (Equation (3)) <51CB666>. The thermal behavior of 1,2-oxathiolan-5-one 2,2-dioxide derivatives depends on the substitution pattern. The parent compound (16) loses SO_2 slowly on heating at 180°C to give acrylic acid <66TL2419>, and the 4-methyl derivative (55) similarly affords methacrylic acid <68BCJ1388>. On the other hand, the 4,4-dimethyl compound gives complex decomposition products, while the tetraphenyl compound (56) loses both SO_2 and CO_2 either on heating at 240°C or on photolysis, to give respectively tetraphenylethylene or its photocyclization product 9,10-diphenylphenanthrene <79JA5431>.



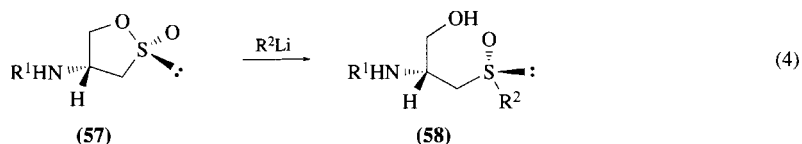
3.09.6.3 Nucleophilic Attack at Carbon

Nucleophiles such as alcohols attack at the carbonyl group in the cyclic sulfinic–carboxylic anhydride (15) to give β -acylsulfinic acids <86KFZ843, 88IZV1633>. Alcoholysis of 1,2-oxathiolane 2,2-dioxide (14) proceeds by attack at the 5-carbon to give γ -alkoxysulfonic acids <54LA(586)151>. In the case of the cyclic sulfonic–carboxylic anhydrides (16), the result depends on the nucleophile used, but methanol attacks at the carbonyl group to give the 2-methoxycarbonylsulfonic acids <40JA2393>.

3.09.6.4 Nucleophilic Attack at Sulfur

In contrast to the last result mentioned in Section 3.09.6.3, ammonia and aniline attack at the sulfonyl group of (16) to give 3-sulfonamidocarboxylic acids, isolated as their ammonium salts

<40JA2393>. The nucleophilic attack on cystine-derived chiral 4-amino-1,2-oxathiolane 2-oxides (**57**) by alkylolithiums takes place at the sulfur atom with inversion of configuration to afford (**58**) (Equation (4)) <81JOC5408>.



3.09.6.5 Reaction with Radicals

Hydrogen atom abstraction from 1,2-oxathiolane 2,2-dioxide (**14**) using, for example, $\text{OH}\cdot$ has been examined and is found to give a 2 : 1 ratio of the 4- and 5-radicals, both of whose ESR spectra have been recorded <75JCS(P2)1245>.

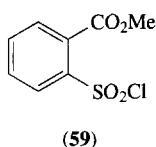
3.09.7 RING SYNTHESIS

3.09.7.1 One-bond Formation Between Heteroatoms

Oxidative addition of elemental fluorine to appropriate 1,3-dicarbonyl compounds provides a convenient synthesis of perfluorinated 1,2-dioxolanes. In this way (**20**) may be formed from difluoromalonyl fluoride, $\text{F}_2\text{C}(\text{COF})_2$ <92JST(274)163>, and (**39**) is similarly prepared from either hexafluoroacetylacetone or the copper(II) or nickel(II) chelate of trifluoroacetylacetone with concomitant replacement of all remaining hydrogen atoms by fluorine <65JOC1429>.

Chlorination of 1,3-thiolalcohols using either Cl_2 or SO_2Cl_2 affords substituted derivatives of 1,2-oxathiolane 2-oxide (**13**) by way of an intermediate 3-hydroxysulfinyl chloride <89TL2763>, and (**57**) is prepared similarly by treatment of *N*-alkylcystinol with NCS or NBS <81JOC5408>. In an early report, treatment of cysteinol hydrochloride with bromine water was found to give the 4-amino-1,2-oxathiolane 2,2-dioxide, although in poor yield <56JCS4066>.

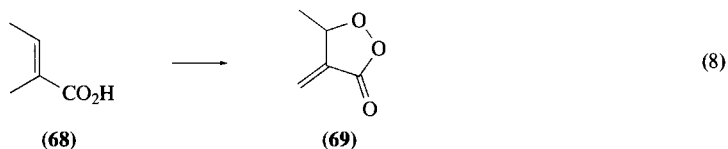
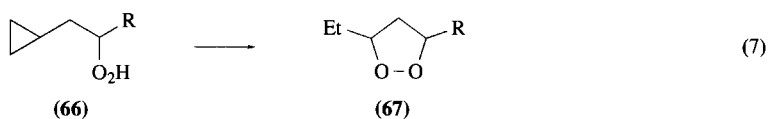
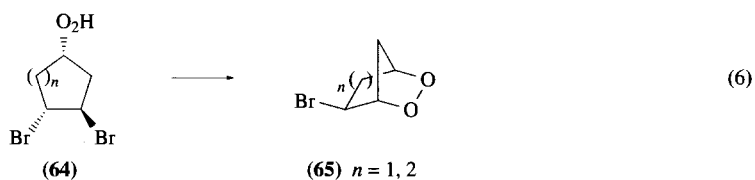
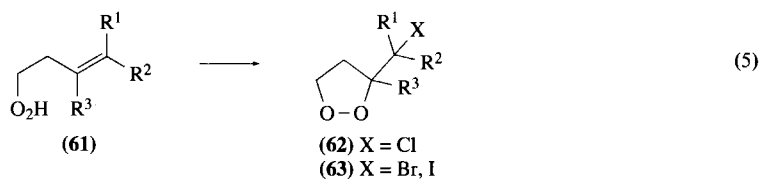
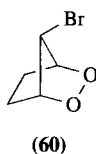
As cyclic sulfonic-carboxylic anhydrides, the 1,2-oxathiolan-5-one 2,2-dioxides (**16**) are conveniently prepared by dehydrative cyclization of the corresponding diacids, typically using thionyl chloride <40JA925>. The latter can be obtained by photochemical sulfonation of propionic acids with SO_2Cl_2 <40JA2393>. The benzo derivative (**12**) is formed in 91% yield by reaction of (**59**) with ZnCl_2 at 200°C <83USP4408058>.



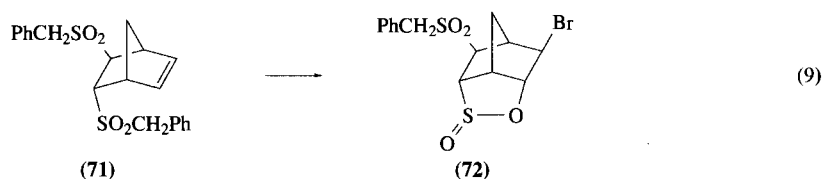
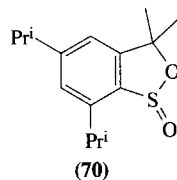
3.09.7.2 One-bond Formation Adjacent to a Heteroatom

A considerable number of new studies have appeared on the formation of 1,2-dioxolanes either by *endo* cyclization of allylic hydroperoxides <92T3835> or by *exo* cyclization of homoallylic hydroperoxides, upon treatment with a variety of electrophilic reagents. Examples of the former process include oxymercuration of lipid-derived allylic hydroperoxides <84JCS(P1)2207> and treatment of 3-hydroperoxycyclopentene with Br_2 followed by a silver salt to give (**60**) <81JCS(P1)3272>. Cyclization of homoallylic hydroperoxides (**61**) can be achieved either with Bu^tOCl to give (**62**) <90TL7077> or, in a radical process, with NBS, NIS, Br_2 , or I_2 to afford (**63**) (Equation (5)) <89CC173>. Treatment of 3-bromocycloalkylhydroperoxides (**64**) with silver salts affords the bicyclic 1,2-dioxolanes (**65**) (Equation (6)) <81JCS(P1)3272>. Cycloperoxymercuration has also been applied to cyclopropylethylhydroperoxides (**66**) to give (**67**) (Equation (7)) <91TL6953>. Treatment of tiglic acid

(68) with singlet oxygen followed by acidification affords the 4-methylene-1,2-dioxolan-3-one (69) (Equation (8)) <85AG(E)1070>.

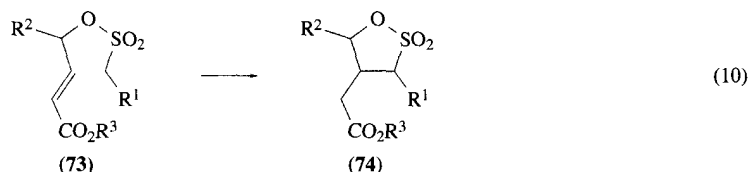


Heating 3-phenoxypropanesulfonic acids at 140–180°C results in cyclization with elimination of phenol to afford (14) and 3-substituted derivatives <84GEP3225887>. The 2,1-benzoxathiole 1-oxide (70) is obtained as a by-product in Friedel–Crafts reactions using 2,4,6-triisopropylbenzenesulfonyl chloride <90SC2999>, and treatment of (71) with Br₂ gives a mixture of (72) and the corresponding *S,S*-dioxide (Equation (9)) <91G533>.



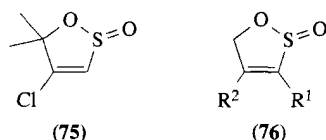
3.09.7.3 One-bond Formation Remote from Heteroatoms

A single example of this unusual approach is provided by treatment of the 4-sulfonyloxycrotonates (**73**) with LDA and either CuCN or AgCN which results in diastereoselective conjugate addition of the anion to give (**74**) (Equation (10)) <94SL185>.



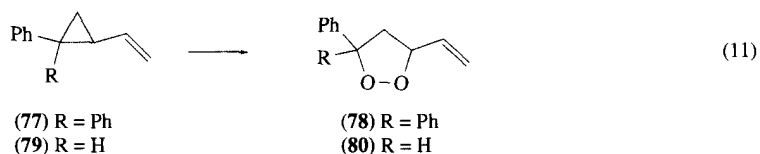
3.09.7.4 Two-bond Formation from [4 + 1] Atom Fragments

There have been few reports of this approach to these compounds. The reaction of the alkynic alcohol $\text{HC}\equiv\text{C}-\text{C}(\text{Me})_2\text{OH}$ with thionyl chloride and pyridine to afford (**75**) probably proceeds by addition of SOCl_2 across the triple bond followed by cyclization of the resulting hydroxysulfinyl chloride <86AKZ124>. In a related process, reaction of $\text{R}^1\text{C}\equiv\text{CCH}_2\text{OH}$ with a Grignard reagent, R^2MgX and SO_2 gives (**76**) <82H(19)2247>.

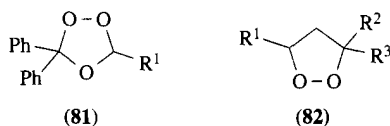


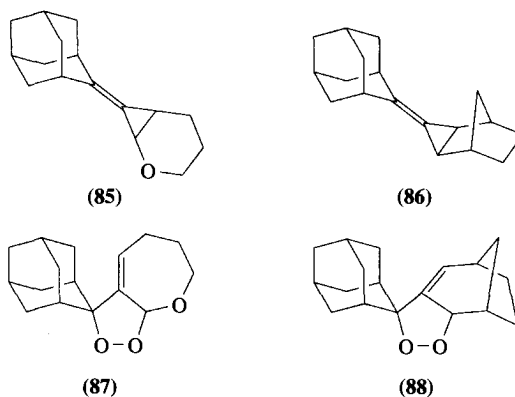
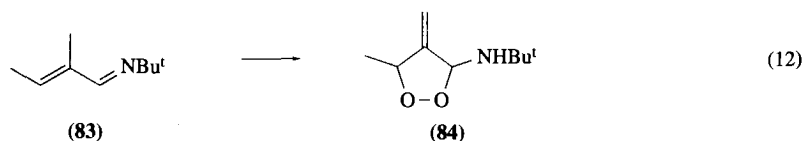
3.09.7.5 Two-bond Formation from [3 + 2] Atom Fragments

Photooxygenation of di- and tetra-arylcyclopropanes provides direct access to the corresponding 1,2-dioxolanes <84MI 309-02, 90JOC4079, 91TL7695> although the reaction is nonstereospecific. Photooxygenation of (**77**) likewise gives (**78**) <86JOC2817>, and the addition can also be radical-mediated, as in the conversion of (**79**) into (**80**) by treatment with O_2 in the presence of PhSeSePh and AIBN (Equation (11)) <86JA1328>. Cyclopropanes have also been converted to the corresponding 1,2-dioxolanes in a multistep sequence involving initial *t*-butylperoxymercuration <86JOC2110>.

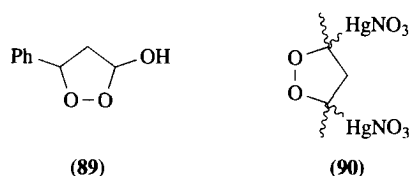


In the presence of BF_3 , the secondary ozonides (**81**) decompose with loss of benzophenone to give coordinated carbonyl oxides which can be trapped by 1,3-dipolar cycloaddition with an added alkene, $\text{R}^2\text{R}^3\text{C}=\text{CH}_2$, to give dioxolanes (**82**) <82CC397, 83JA6279>. Carbonyl oxides are also formed in the ozonolysis of enol ethers and they can be trapped to form 1,2-dioxolanes either by cycloaddition to the starting enol ether <85JOC3365>, or intramolecularly by a suitably placed double bond <92SL214>. α,β -Unsaturated imines such as (**83**) react directly with singlet oxygen to give the 3-amino-1,2-dioxolanes (**84**) (Equation (12)) <89H(28)445>. The same reagent results in conversion of polycyclic alkylidenecyclopropanes such as (**85**) and (**86**) into (**87**) and (**88**), respectively <87TL217>.

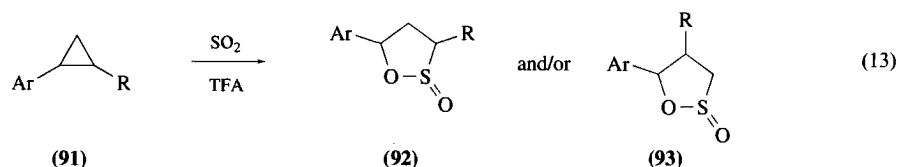




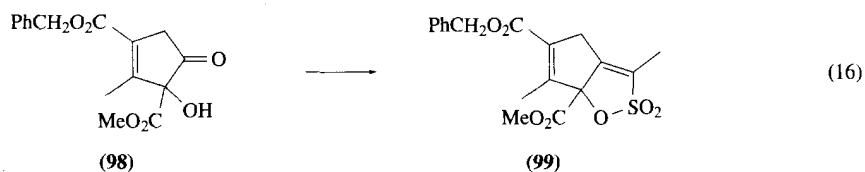
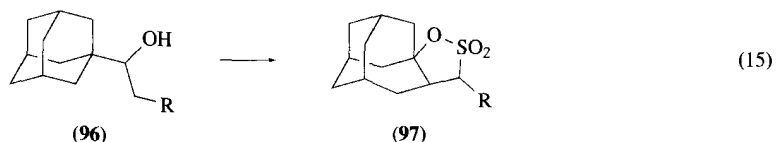
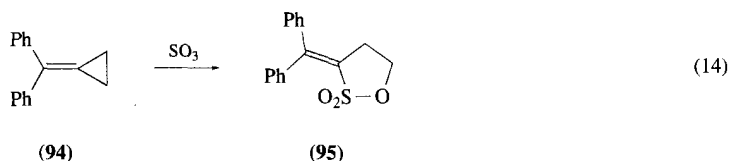
Cinnamaldehyde is converted by H_2O_2 under basic conditions into the 3-hydroxy-1,2-dioxolane (89) <86ZOR669>. Full details of the peroxymercuration of 1,4-pentadiene to give 3,5-dimethyl-1,2-dioxolane have been presented <78JCS(P1)522>. Note that an erroneous structure for the intermediate in this reaction was presented in the first edition <84CHEC-I(6)749> and the correct structure is (90). The 1,2-dioxolane-3,5-dione (51) was prepared in 20% yield by reaction of bis(trifluoromethyl)malonyl fluoride with H_2O_2 <73JOC2269>.



The direct reaction of substituted cyclopropanes (91) with SO_2 in TFA to give 1,2-oxathiolane 2-oxides (92) and/or (93) (Equation (13)) has been the subject of intensive investigations by Russian workers and the regio- and stereoselectivity of the reaction has been explored in detail for various substitution patterns in the starting cyclopropanes <85ZOR671, 86URP1209694, 88ZOR1937, 90ZOR281, 90ZOR553, 92MI 309-01, 93MI 309-01>.



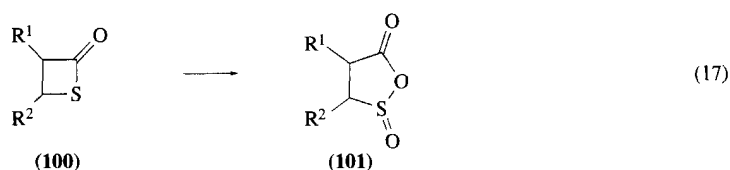
Treatment of the methylenecyclopropane (94) with SO_3 affords (95) directly (Equation (14)) <89JOC1680>. The adamantyl alcohols (96) undergo skeletal rearrangement followed by trapping with SO_3 upon treatment with H_2SO_4 and TFAA or Ac_2O to give homoadamantane-fused sultones (97) (Equation (15)) <88ZOR738>. In an unusual reaction, treatment of α -hydroxyketone (98) with EtSO_2Cl and Et_3N gives (99) (Equation (16)) <90CPB234>.



3.09.8 RING SYNTHESIS BY TRANSFORMATION OF OTHER HETEROCYCLIC RINGS

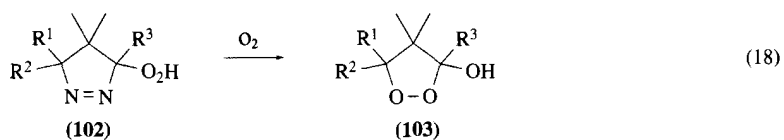
3.09.8.1 Four-membered Rings

Gas-phase thermolysis of thietane *S*-oxide at 500–1130°C and 10^{-4} Torr provides one method for generation of 1,2-oxathiolane (**5**) <81JCS(P2)1166>. As described in the first edition, thermal ring expansion of thiete 1,1-dioxide provides the most convenient access to 1,2-oxathiole 2-oxide (**7**) and this reaction has also been used to obtain the 3-phenyl- <72TL4781>, 3,5-diphenyl- <77JOC3506>, and 5,5-dimethyl derivatives <69CC32>, (**30**), (**31**), and (**32**), respectively, which as mentioned in Section 3.09.5.2 undergo loss of SO upon further pyrolysis. The benzo-fused derivative (**9**) is similarly obtained from benzothiete 1,1-dioxide <76JOC3044> and this method has been applied to formation of the 2,3- <69JOC1310> and 1,8-naphtho-fused derivatives <67LA(703)96>. Oxidative ring expansion occurs upon treatment of thietan-2-ones (**100**) with chlorine or SO_2Cl_2 and acetic anhydride to give (**101**) as a major product (Equation (17)) <92IZV2153>.



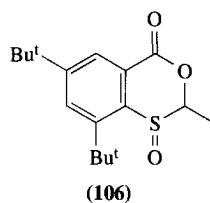
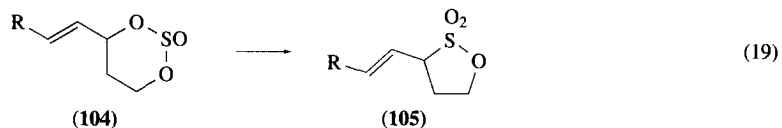
3.09.8.2 Five-membered Rings

As described in Section 3.09.5.2, the first 1,2-dioxoles (**27**) were obtained starting from reaction of furans (**25**) with singlet oxygen. The formation of 1,2-dioxolanes (**82**) starting from 1,2,4-trioxolanes (**81**) was also included in Section 3.09.7.5. The 3-hydroperoxypyrazolines (**102**) react readily with oxygen with loss of N_2 to give the 3-hydroxy-1,2-dioxolanes (**103**) (Equation (18)) <92JOC393>.



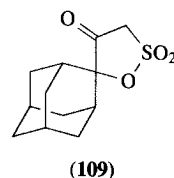
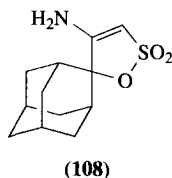
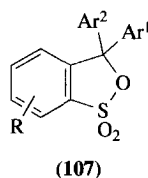
3.09.8.3 Six-membered Rings

The cyclic sulfites (**104**) undergo ring contraction upon treatment with $\text{BF}_3 \cdot \text{Et}_2\text{O}$ to give the 1,2-oxathiolane 2,2-dioxides (**105**) (Equation (19)) <93TL3667>. Access to the 2,1-benzoxathiol-3-one (**19**) was also gained by thermal elimination of acetaldehyde from the six-membered ring precursor (**106**) <82CB3842, 83CB1708>.



3.09.9 APPLICATIONS

There have been remarkably few new applications of compounds in this class, but aromatic sultones of general structure (**107**) related to phenol red have been patented for use as heat-sensitive recording materials <93JAP0509187>, and the spiro adamantane sultones (**108**) and (**109**) have been evaluated as antiviral agents, although they proved to have disappointing activity <92BMC647>.



3.10

1,3-Dioxoles and 1,3-Oxathioles

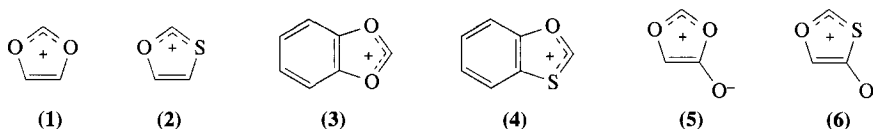
R. ALAN AITKEN and LAWRENCE HILL
University of St. Andrews, UK

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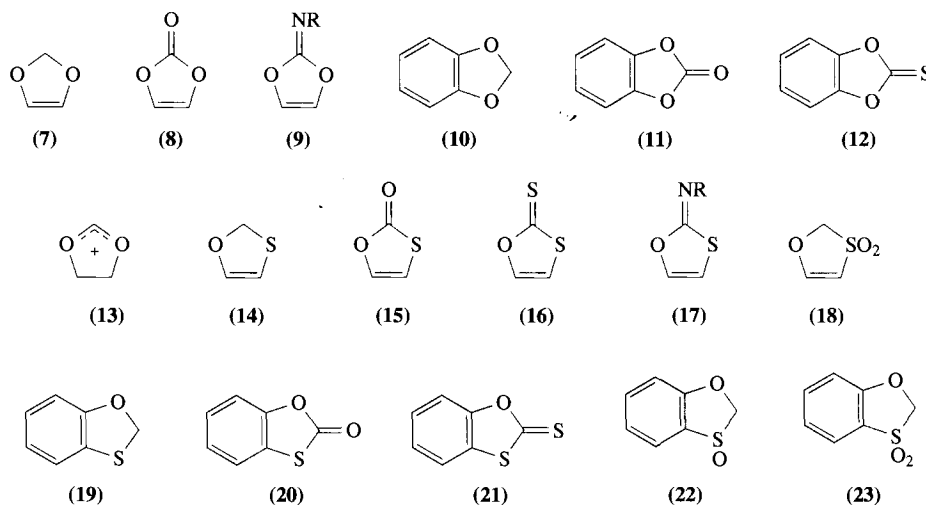
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3.10.1 INTRODUCTION

Since the publication of the first edition of *Comprehensive Heterocyclic Chemistry* (CHEC-I), there has been relatively little new work on the fully conjugated systems, the 1,3-dioxolium salts (**1**), 1,3-oxathiolium salts (**2**), and their benzo analogues (**3**) and (**4**), but comprehensive reviews of these compounds have appeared [93HOU(E8a)1, 93HOU(E8a)10]. A few reports on the mesoionic systems (**5**) and (**6**) have also appeared.



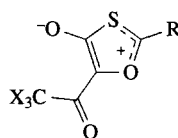
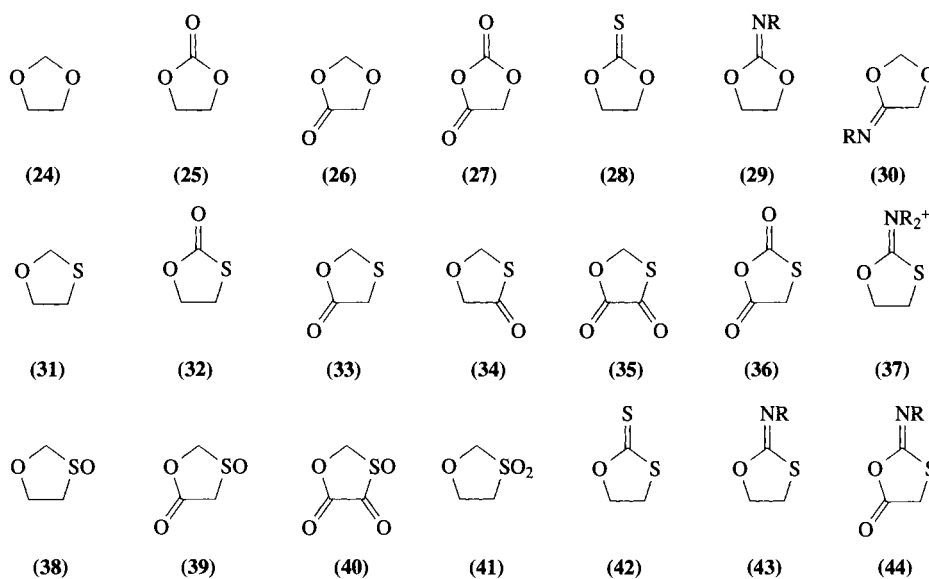
A much larger volume of work is concerned with the 1,3-dioxoles (**7**) and 1,3-oxathioles (**14**) and material on these and the related systems (**8**)–(**13**) and (**15**)–(**23**) is included here.



As in CHEC-I [84CHEC-I(6)749], the majority of studies have involved the fully saturated systems 1,3-dioxolane (**24**) and 1,3-oxathiolane (**31**) and results on these and the derivatives (**25**)–(**30**) and (**32**)–(**44**) are covered in this chapter. Major reviews have appeared covering 1,3-dioxolanes [91HOU(E14a/1)1] and 1,3-oxathiolanes [83RCR350, 91HOU(E14a/1)794].

3.10.2 THEORETICAL METHODS

There have been few applications of theoretical methods in this area, but attempts have been made to rationalize the structure and reactivity toward cycloaddition of the mesoionic compounds (**45**) using MNDO and FMO (frontier molecular orbital) methods [86CB2308, 86CB2317].

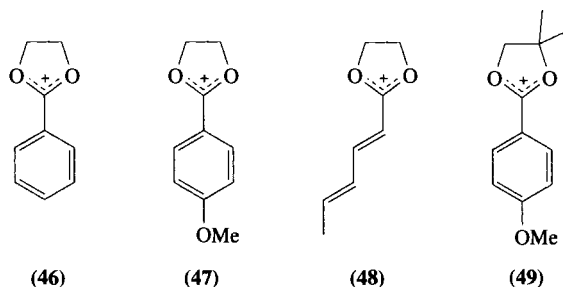


(45) R = SMe, NMe₂
X = Cl, F

3.10.3 EXPERIMENTAL STRUCTURAL METHODS

3.10.3.1 X-ray Diffraction

A systematic study of the structure of the series of 1,3-dioxolan-2-ylum cations (46)–(49) as their hexafluoroantimonate salts has given the molecular dimensions listed in Table 1 and shows the structures to be essentially planar at C-2 <93CJC836>. The dimensions obtained from the x-ray structure of the 2-imino-1,3-oxathiole (50) are also presented in Table 1 <93JCS(P1)351>. New x-ray studies include the spiro benzodioxole compound (51) <93ACS999> and the bis-dioxolane (52), where the diffraction study was used to establish the relative configuration as being that shown <90BCJ2450>.

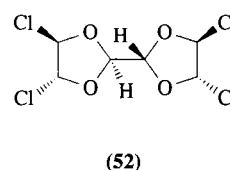
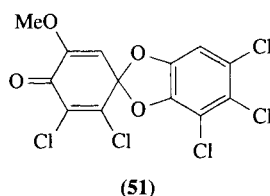
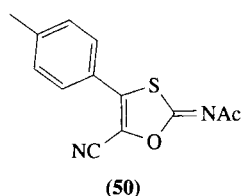


3.10.3.2 Electron Diffraction

There has been very little work in this area but an early electron diffraction study gave bond lengths for 1,3-dioxolane (24) in the gas phase of 1.54 Å (C—C) and 1.42 Å (C—O) <50AX46>.

Table 1 X-ray structural data for compounds (46)–(50).

Compound	Bond lengths (Å)					Internal angle (°) at				
	O—C-2	C-2—X	X—C-4	C-4—C-5	C-5—O	O-1	C-2	X-3	C-4	C-5
(46)	1.281	1.282	1.472	1.505	1.480	108.1	103.4	103.1	108.6	116.8
(47)	1.292	1.294	1.475	1.504	1.468	109.2	103.2	103.5	108.7	115.3
(48)	1.288	1.290	1.469	1.515	1.472	108.7	103.2	103.0	109.0	115.9
(49)	1.30	1.29	1.51	1.58	1.46	112	101	102	109	115
(50)	1.361	1.743	1.763	1.318	1.394	112.0	111.3	90.3	110.1	116.2



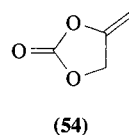
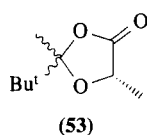
3.10.3.3 NMR Spectroscopy

3.10.3.3.1 Proton NMR

The ^1H NMR spectra of 1,3-dioxolane and 2-substituted derivatives were discussed in CHEC-I <84CHEC-I(6)749> but some further chemical shift data for the ring protons of simple derivatives including dioxolanones and dioxolanethiones are listed in Table 2. Data for a wide range of 1,3-dioxolan-4-ones have been published <70BSF332>, and the relative configuration of the diastereomers of (53) formed from pinacolone and lactic acid has been determined using ^1H NMR <93BSF133>. The simple methylenedioxolanone (54) gives signals at δ 5.04 (5-H) and 4.91 and 4.47 (=CH) <83JOC3346>.

Table 2 ^1H NMR data for ring protons of 1,3-dioxolane derivatives.

Compound	δ_{H}			Ref.
	2-H	4-H	5-H	
4,4-Dimethyl-1,3-dioxolane	4.90		3.51	71JCS(B)1302
cis-2,2,4,5-Tetramethyl-1,3-dioxolane		4.15	4.15	62JA747
trans-2,2,4,5-Tetramethyl-1,3-dioxolane		3.38	3.38	62JA747
cis-4,5-Dimethyl-1,3-dioxolan-2-one		5.84	5.84	62JA747
trans-4,5-Dimethyl-1,3-dioxolan-2-one		5.66	5.66	62JA747
2-Imino-1,3-dioxolane (29; R = H)		4.40	4.40	74JOC3442
1,3-Dioxolan-4-one (26)	5.48		4.18	70BSF332
1,3-Dioxolane-2-thione (28)		4.78	4.78	69JOC3011
4-Methyl-1,3-dioxolane-2-thione		4.15–5.1		70JOC2347
cis-4,5-Dimethyl-1,3-dioxolane-2-thione		5.0–5.25		70JOC2347
trans-4,5-Dimethyl-1,3-dioxolane-2-thione		4.65		70JOC2347
1,4,6,9-Tetraoxaspiro[4.4]nonane		4.05	4.05	70JOC2347



Data for 1,3-oxathiolane and 2-substituted derivatives were included in CHEC-I <84CHEC-I(6)749> but this is extended to other substitution patterns as well as to oxathiolanones, oxathiolanethiones and oxathiolane 3,3-dioxides in Table 3.

Table 3 Proton NMR data for ring protons of 1,3-oxathiolane derivatives.

Compound	δ_{H} 2-H	4-H	5-H	Ref.
5-Methyl-1,3-oxathiolane	4.72/4.89	2.5/3.0	3.96	72T3943
2,2-Bis(methylthio)-1,3-oxathiolane		3.10	4.26	78S286
<i>cis</i> -4,5-Dimethyl-1,3-oxathiolane	4.68/4.92	3.36	3.91	77JCS(P2)343
<i>trans</i> -4,5-Dimethyl-1,3-oxathiolane	4.86	3.00	3.46	77JCS(P2)343
<i>cis</i> -2,4-Dimethyl-1,3-oxathiolane	5.18	3.60	3.82	74JCS(P2)466
<i>trans</i> -2,4-Dimethyl-1,3-oxathiolane	5.29	3.00	3.46	74JCS(P2)466
<i>cis</i> -2,5-Dimethyl-1,3-oxathiolane	5.11	2.62/2.95	3.94	72T3943
<i>trans</i> -2,5-Dimethyl-1,3-oxathiolane	5.28	2.52/3.08	4.43	72T3943
1,3-Oxathiolan-2-one (32)		3.59	4.53	69JOC3011
1,3-Oxathiolan-5-one (33)	5.21	3.52		76ACS(A)457
1,3-Oxathiolane-2-thione (42)		3.73	4.98	69JOC3011
<i>cis</i> -4,5-Dimethyl-1,3-oxathiolane-2-thione		4.04	5.21	78S286
<i>trans</i> -4,5-Dimethyl-1,3-oxathiolane-2-thione		3.86	4.80	78S286
2-Phenylimino-1,3-oxathiolane (43; R = Ph)		3.31	4.40	74JOM(72)103
1,3-Oxathiolane 3,3-dioxide (41)	4.34	3.15	4.37	66RTC323
1,3-Benzoxathiole 3,3-dioxide (23)	5.22			66RTC323

3.10.3.3.2 Carbon-13 NMR

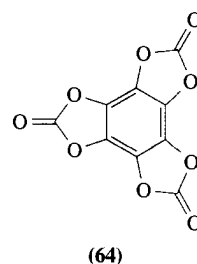
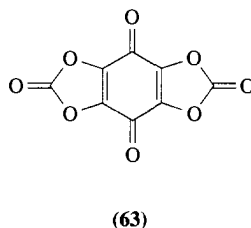
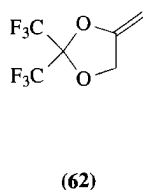
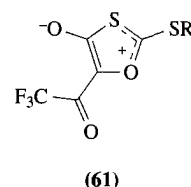
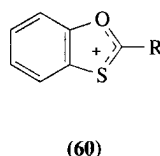
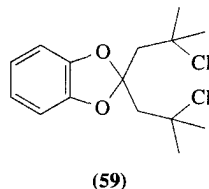
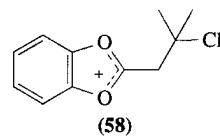
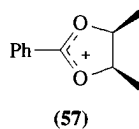
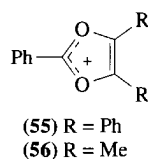
A compilation of new ^{13}C NMR data is presented in Table 4. The high frequency of the C-2 signals in 1,3-dioxolium salts such as (55), (56) and (58) is notable when compared with reference systems such as (59). The slightly higher C-2 frequency in (57) as compared with (56), together with the different methyl positions in the two, provides evidence for delocalization in (56). For the benzoxathiolium salts (60), C-2 comes at even higher frequency and data for a further range of 2-substituted derivatives have been reported <86S1074>. The mesoionic compounds (61) show the expected high frequencies for C-2 and C-4, together with a low value for C-5, reflecting the charge distribution in these systems. Data for the methylenedioxolane (62), the methylenedioxolanone (54) and the unusual carbon oxides (63) and (64) are also presented. Carbon-13 NMR data for a range of substituted 1,3-oxathiolanes and 1,3-oxathiolane 3,3-dioxides has also been reported <80JOC3634>.

Table 4 ^{13}C NMR data for ring carbons of 1,3-dioxole and 1,3-oxathiole derivatives.

Compound	δ_{C} C-2	C-4	C-5	Others	Ref.
(55)	174.7	146.6	146.6		87JOC375
(56)	175.4	147.9	147.9	9.1 (Me)	87JOC375
(57)	181.9	90.6	90.6	14.4 (Me)	87JOC375
(58)	182.2	144.9	144.9		88CB339
(59)	118.0	146.6	146.6		88CB339
(60; R = Me)	211.7	126.0	160.0	21.8 (Me)	88JOC2245
(60; R = Bu ^t)	223.7	125.4	160.4		86S1074
(60; R = Pr ⁿ)	215.7	125.6	160.0		86S1074
(60; R = Ph)	202.8	125.2	159.1		86S1074
(61; R = Me)	215.5	154.6	110.3		85CB774
(61; R = Pr ⁱ)	213.2	154.4	110.0		85CB774
(62)	101.5	153.2	69.1	83.9 (=CH)	93JOC972
(54)	152.8	149.1	67.8	87.1 (=CH)	83JOC3346
(63)	153.7	133.4	133.4	169.3 (CO)	84T4897
(64)	154.8	124.7	124.7		84T4897

3.10.3.3.3 Oxygen-17 NMR

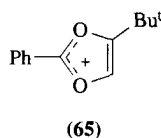
This technique has only been applied to 1,3-dioxolane (24) and a few simple derivatives. The chemical shift for the parent compound has been given variously as δ_{O} (with respect to H_2^{17}O) +34 <79BCJ3391>, +35.8 <86MRC1034>, and +34.8 <79TL3649>. The presence of a methyl substituent



increases this value and leads to signals for 2-methyl-1,3-dioxolane at +56.0, for 2,2-dimethyl-1,3-dioxolane at +64.2, and for 4-methyl-1,3-dioxolane at +36.9 (O-1) and +61.9 (O-3) <79TL3649>.

3.10.3.4 UV/Visible Spectroscopy

There have only been isolated studies in this area but the data reported include absorptions at 412–413 nm ($\log \epsilon$ 3.5–3.7) for the mesoionic compounds (61) <85CB774>, a strong absorption at 300 nm for the dioxolium salt (65) <90JA8873>, absorptions at 304 nm ($\log \epsilon$ 1.4) and 235 nm ($\log \epsilon$ 4.1) for the thione (28) <69JOC3011>, and weak but characteristic absorptions at 263–270 nm for a variety of simple 1,3-dioxolanes <57M78>.



3.10.3.5 Infrared and Raman Spectroscopy

IR and Raman spectra were recorded and assigned for 1,3-dioxolane (24) and a range of mono-, di- and trimethylated derivatives at an early date <59JCS807>. IR data for 1,3-dioxolan-2-one (25) in solid, liquid, solution and vapor phases and its Raman spectrum have also been reported <56TFS1178, 68JSP(27)285>, as have both IR and Raman spectra for 1,3-dioxol-2-one (8) <70JST(5)67>. Other simple 1,3-dioxolane systems for which IR data are available include 1,3-dioxolan-4-one (26) and a wide range of substituted derivatives <70BSF332>, 2-imino-1,3-dioxolane (29; R = H) which has absorptions at 3300 cm^{-1} and 1100 cm^{-1} <74JOC3442>, and (54) which has absorptions at 1838 cm^{-1} and 1698 cm^{-1} <83JOC3346>.

The simple 1,3-oxathiolane systems for which IR data are available include 2-methyl-1,3-oxathiolane <59CJC1104>, 1,3-oxathiolan-5-one (33) with a CO absorption at 1771 cm^{-1} <76ACS(A)457>, and 1,3-oxathiolan-2-one (32), its isomer (28) and the thione (42) whose spectra have been compared <69JOC3011>. The 1,3-oxathiolane 3,3-dioxides have a characteristic pair of absorptions due to the SO_2 group which occur at 1320 cm^{-1} and 1130 cm^{-1} for (41) and at 1300 cm^{-1} and 1140 cm^{-1} for the benzo derivative (23) <66RTC323>.

3.10.3.6 Photoelectron Spectroscopy

The first ionization energy of 1,3-dioxolane-2-thione (**28**) has been reported as 8.88 eV and further ionization energies have also been determined $\langle 75\text{ZN(B)862} \rangle$.

3.10.3.7 Dipole Moments

Dipole moments determined for simple methylated 1,3-dioxolanes in benzene solution include: 2-methyl-, 1.21 D; 2,2-dimethyl-, 1.12 D; 2,4-dimethyl-, 1.32 D; 2,4,4,5,5-pentamethyl-, 1.29 D $\langle 37\text{JA1590} \rangle$; and 4,4-dimethyl-, 1.56 D $\langle 71\text{JCS(B)1302} \rangle$. The dipole moment of 1,3-dioxolan-2-one (**25**), again in benzene solution, has been reported to be 4.60 D $\langle 53\text{TFS228} \rangle$ or 4.87 D $\langle 58\text{JCS1936} \rangle$, and in the latter study the effect of substituents was examined giving the following values: 4-methyl-, 4.94 D; 4-chloro-, 3.99 D; 4,5-dichloro-, 3.44 D; and 4-chloromethyl-, 4.68 D.

3.10.4 THERMODYNAMIC ASPECTS

3.10.4.1 Melting Points and Boiling Points

There has been no systematic study of melting and boiling points for these compounds, but a compilation of data for simple 1,3-dioxolane and 1,3-oxathiolane derivatives is presented in Tables 5 and 6, respectively.

Table 5 Melting and boiling points of simple 1,3-dioxolane derivatives.

Compound	<i>m.p.</i> (°C)	<i>b.p.</i> (°C/Torr)	Ref.
(<i>R</i>)-4-Methyl-1,3-dioxolane		84.2/atm.	50JA5491
<i>cis</i> -2,4-Dimethyl-1,3-dioxolane		90.1/atm.	50JA5490
<i>trans</i> -2,4-Dimethyl-1,3-dioxolane		93.0/atm.	50JA5490
4,4-Dimethyl-1,3-dioxolane		92/atm.	71JCS(B)1302
(<i>R,R</i>)-4,5-Dimethyl-1,3-dioxolane		95.5–96/atm.	50JA5497
(<i>R,R</i>)-4,5-Dimethyl-1,3-dioxolan-2-one	21–21.5	104.8/atm.	50JA5497
(<i>R,R</i>)-2,4,5-Trimethyl-1,3-dioxolane		102.5–103/atm.	50JA5497
1,3-Dioxolan-4-one (26)		157–160/atm.	40GEP737623
5-Methyl-1,3-dioxolan-4-one		152–153/atm.	35CB609
2,5-Dimethyl-1,3-dioxolan-4-one		154–155/atm.	35CB609
5,5-Dimethyl-1,3-dioxolan-4-one		150/atm.	35CB609
2,5,5-Trimethyl-1,3-dioxolan-4-one		151–152/atm.	35CB609
<i>cis</i> -4,5-Dimethyl-1,3-dioxolan-2-one		116–117/5	62JA747
4-Methylene-1,3-dioxolan-2-one (54)	28–29.5		83JOC3346
1,3-Dioxolane-2-thione (28)	54.5–55.5		69JOC3011
1,3-Dioxolane-2-thione (28)		99/0.3	70JOC2347
4-Methyl-1,3-dioxolane-2-thione		78/0.1	70JOC2347
4,5-Dimethyl-1,3-dioxolane-2-thione (<i>cis/trans</i>)		115/3	70JOC2347
2-Imino-1,3-dioxolane (29 ; R = H)	38–45		74JOC3442
1,3-Dioxolane-2,4-dione (27)	18	49/0.1	51JCS1357
1,4,6,9-Tetraoxaspiro[4.4]nonane	143–143.5		70JOC2347

Table 6 Melting and boiling points of simple 1,3-oxathiolane derivatives.

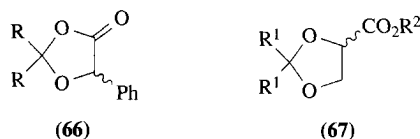
Compound	<i>m.p.</i> (°C)	<i>b.p.</i> (°C/Torr)	Ref.
2-Methyl-1,3-oxathiolane		130.5/atm.	59CJC1104
4-Methyl-1,3-oxathiolane		70–74/64	74JCS(P2)466
5-Methyl-1,3-oxathiolane		62–64/64	72T3943
2,4-Dimethyl-1,3-oxathiolane (<i>cis</i> and <i>trans</i>)		68–70/64	74JCS(P2)466
2,5-Dimethyl-1,3-oxathiolane (<i>cis</i> and <i>trans</i>)		40–42/35	72T3943
1,3-Oxathiolan-2-one (32)	–20	105/14	41RTC453
1,3-Oxathiolan-5-one (33)		84/12	76ACS(A)457
1,3-Oxathiolane-2-thione (42)		125–130/2	64ZOB2996
1,3-Oxathiolane-2,5-dione (36)	68–70		51JCS1357
1,3-Oxathiolane 3-oxide (38)		123–125/11	73IJS397
1,3-Oxathiolane 3,3-dioxide (41)	87–88		66RTC323
1,3-Benzoxathiole 3,3-dioxide (23)	139–141		66RTC323

3.10.4.2 Other Physical and Thermodynamic Properties

The surface tension of 1,3-dioxolane (**24**) has been reported to be 34.05 g s^{-2} at 20°C <50IZV291>, and other properties of this compound include a latent heat of evaporation of 35.6 kJ mol^{-1} and a standard enthalpy of combustion of $-1700 \text{ kJ mol}^{-1}$ <59JCS580> and a heat capacity C_p ranging from $0.685 \text{ J g}^{-1} \text{ K}^{-1}$ at 80 K to $1.026 \text{ J g}^{-1} \text{ K}^{-1}$ at 160 K in the solid state, and from $1.476 \text{ J g}^{-1} \text{ K}^{-1}$ at the melting point of 175.93 K to $1.593 \text{ J g}^{-1} \text{ K}^{-1}$ at 300 K <69MI 310-01>. Properties reported for 1,3-dioxolan-2-one (**25**) include a dielectric constant ranging from 90.8 at 36°C to 77.3 at 70°C <58JPC127>, a latent heat of fusion of $12.63 \text{ kJ mol}^{-1}$ <69JPC1968> and a standard enthalpy of combustion of $-1170 \text{ kJ mol}^{-1}$ <61JPC694>.

3.10.4.3 Chromatographic Behavior

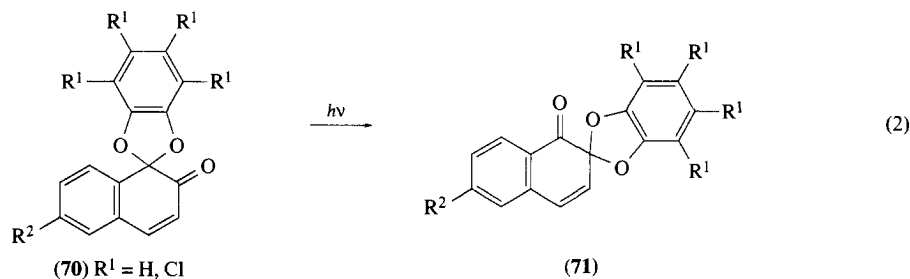
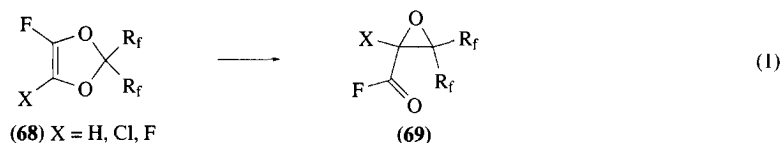
There has been some recent interest in the separation of enantiomers of 1,3-dioxolane systems by chromatography on chiral stationary phases and examples include separation of the dioxolan-4-ones (**66**) on a chiral HPLC column <89LA103> and of the dioxolane esters (**67**) by chiral GC <93MI 310-01>.



3.10.5 REACTIVITY OF CONJUGATED RINGS, 1,3-DIOXOLES AND 1,3-OXATHIOLES

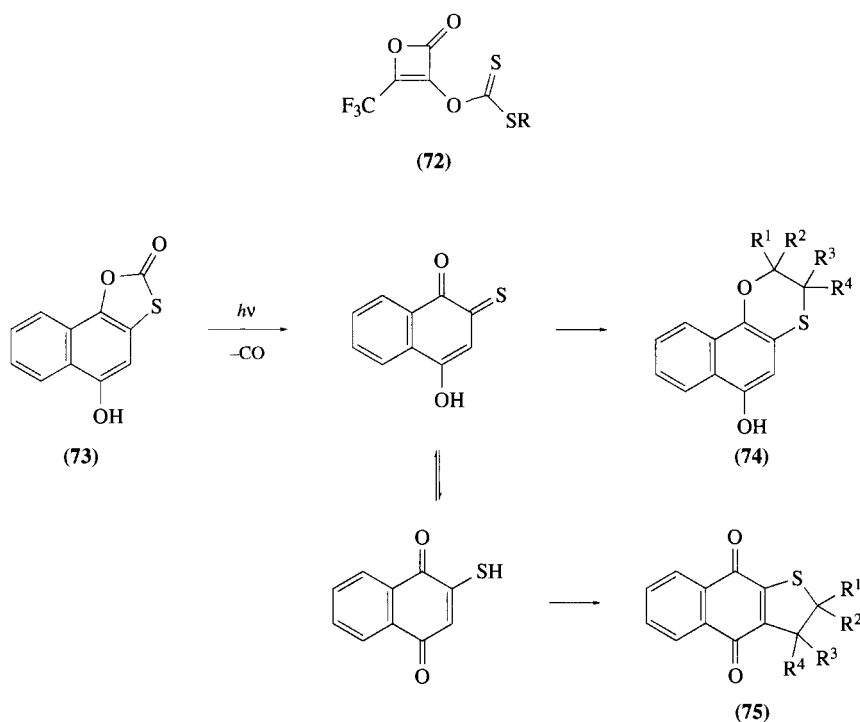
3.10.5.1 Unimolecular Reactions

A variety of fluorinated 1,3-dioxoles (**68**) undergo thermal rearrangement to the epoxides (**69**) (Equation (1)) <90JA9671>. The spiro benzodioxoles (**70**) undergo a novel photochemical isomerization to give (**71**), a process which for some groups R^1 and R^2 can be reversible (Equation (2)) <84TL2253>. When the mesoionic compounds (**61**) are heated under vacuum they decompose with extrusion of CO_2 and COS, presumably via the intermediate (**72**) to give $\text{F}_3\text{C}-\text{C}\equiv\text{C}-\text{SR}$, although this product was not isolated <85CB774>. Photochemical loss of CO from the naphthooxathiolone (**73**) gives an intermediate with the two tautomeric forms shown in Scheme 1, both of which can be trapped by cycloaddition to an added alkene to give (**74**) and (**75**) <93CC807>. Thermolysis of the oxathiole dioxide (**76**) results both in simple fragmentation to give benzil, diphenylacetylene and SO_2 and, by a more unusual mechanism involving (**77**), formation of the furanone (**78**) (Scheme 2) <74JOC2722>.

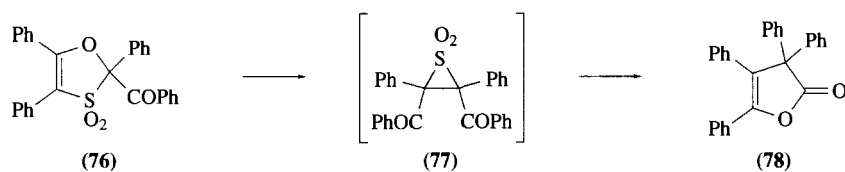


3.10.5.2 Electrophilic Attack at Carbon

As mentioned in CHEC-I, electrophilic substitution on the heterocyclic ring of dioxoles or oxathioles is essentially unknown. Reaction of 1,3-benzoxathioles bearing bulky substituents at



Scheme 1

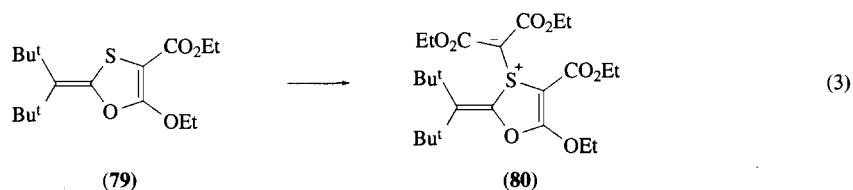


Scheme 2

C-2 with $\text{Ac}_2\text{O}/\text{MgBr}_2$ leads to some acetylation at position 5 on the benzene ring but this is accompanied by acylation at oxygen and cleavage of the O—C-2 bond to give (2-acyloxyphenylthio)alkyl bromides <84JHC573>.

3.10.5.3 Electrophilic Attack at Sulfur

A rare example of this type of reaction is the formation of (80) in the rhodium catalyzed reaction of di-*t*-butylthioetene with diethyl diazomalonate, which first affords the oxathiole (79) (Equation (3)). This may then undergo electrophilic attack by the carbenoid to give (80) for which an x-ray structure was determined <89TL1249>.

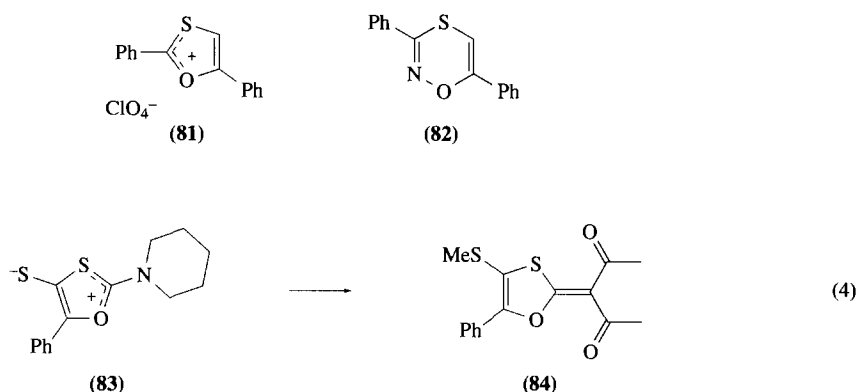


3.10.5.4 Electrophilic Attack at Ring CH

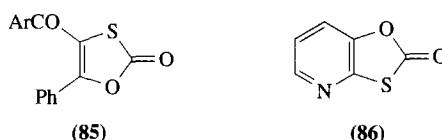
The reaction of 4,7-di-*t*-butyl-1,3-benzodioxole with trityl cation results in hydride abstraction from the 2-position to give the dioxolium cation which can be conveniently trapped by alcohols to give the 2-alkoxy derivatives <84IZV1632>.

3.10.5.5 Nucleophilic Attack at Carbon

The dioxolium salt derived from 2,2-dichloro-1,3-benzodioxole and BCl_3 reacts with isobutylene by nucleophilic attack at C-2 to afford (59) after a second attack on the cation (58) <88CB339>. The 1,3-benzoxathiolium salts are able to carry out electrophilic substitution on a variety of electron-rich arenes and heteroarenes <87S311>, including pyrroles <88JOC2245>, to give the 2-arylbenzoxathioles. Monocyclic 1,3-oxathiolium salts such as (81) react with NaN_3 by attack at C-2, followed by loss of nitrogen and rearrangement to give the corresponding 1,4,2-oxathiazines (82) and the same products can also be obtained by treatment of (81) with NH_3/I_2 . Treatment of (81) with sulfenamides, RSNH_2 , results in a complex reaction to afford 5-(alkylthio)thiazoles and di(5-thiazolyl)sulfides <92BCJ668>. Reaction of the mesoionic compound (83) with the anion of acetylacetone followed by MeI gives the 2-alkylideneoxathiole (84) (Equation (4)) <85CC1154>.



The regioselectivity of nucleophilic ring opening by nitrogen species has been examined in several cases. With 1,3-benzoxathiole reaction with metal dialkylamides in HMPA may result in cleavage of either the $\text{C}(2)\text{—S}$ or the $\text{C}(2)\text{—O}$ bond depending on whether the metal used is sodium or lithium <83JHC1413>. In the 1,3-oxathiol-2-ones (85), secondary amines react with cleavage of the CO—O bond to give the *S*-dibenzoylmethylthiolocarbamates, while anilines cause cleavage of the =C—O bond and loss of CO_2 to give *N*-aryl- β -thio- β -benzoylenamines <93JHC501>. Reaction of primary and secondary amines with the pyridooxathiolone (86) has similarly been investigated <91JOC891>.



Efficient processes for the conversion of 2,2-dichloro-1,3-benzodioxole to the 2,2-difluoro analogue have been the subject of industrial interest and generally involve treatment with a metal fluoride and a catalyst in sulfolane <84GEP3315147, 87GEP3642256, 91EUP423009>. The 2,2-difluoro compound can also be prepared from the thione (12) by reaction with NIS and $\text{Bu}^n_4\text{N}^+ \text{H}_2\text{F}_3^-$ <94SL251>.

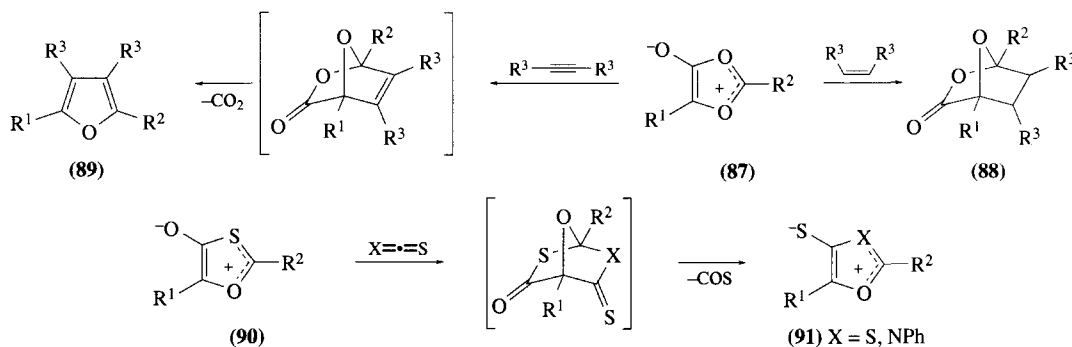
3.10.5.6 Radical and Electrochemical Reactions

Photolysis of 1,3-benzodioxole (10) in the presence of pyridine results in homolytic substitution by the benzodioxol-2-yl radical at the 2- and 4-positions <90MI 310-01> and a similar reaction in hex-1-ene gives mainly 2-hexylbenzodioxole <90MI 310-02>. The 2-benzodioxolyl radical can also be generated by treatment with ferrous sulfate and *t*-butylhydroperoxide and brings about homolytic substitution at the 2- and 4-positions of pyridine and at the 5-position of 2-methylquinoline <86DOK(290)1130>. A range of 2-substituted-1,3-benzodioxoles undergo photochemical dimerization through the 2-position in the presence of di-*t*-butylperoxide <89MI 310-01>.

Electrochemical methoxylation has been achieved by anodic oxidation of substituted 1,3-benzodioxoles in NaOMe/MeOH saturated with CO_2 , leading to the 2-methoxy derivatives <85S31>.

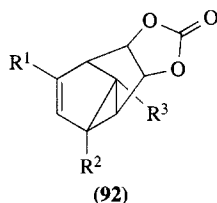
3.10.5.7 Cycloaddition Reactions

The mesoionic 1,3-dioxolium-4-olates (**87**) undergo ready cycloaddition with a variety of alkene dipolarophiles to give bicyclic adducts (**88**) which can be isolated in some cases $\langle 85CC1319 \rangle$, but with alkyne dipolarophiles the initial cycloadducts lose CO_2 to afford substituted furans (**89**) $\langle 85CC190 \rangle$ (Scheme 3). The analogous 1,3-oxathiolium-4-olates (**90**) behave in the same way, giving isolable bicyclic adducts with alkenes, but furans by loss of COS from the initial adducts with alkynes $\langle 82AG(E)773, 86CB2317 \rangle$. Addition of (**90**) to CS_2 or PhNCS proceeds by formation of bicyclic adducts as shown in Scheme 3 which lose COS to give new mesoionic systems, the 1,3-oxathiolium- and oxazolium-4-thiolates (**91**) $\langle 85CC1154 \rangle$.



Scheme 3

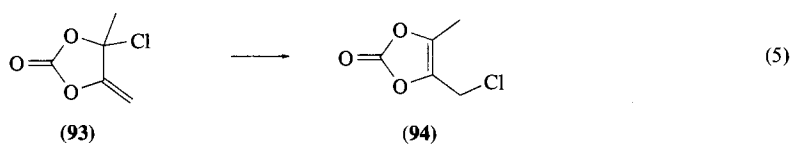
Diels–Alder cycloaddition of 1,3-dioxole (**7**) with 3-tosyl-2-pyranone has been used in natural product synthesis $\langle 90T4573 \rangle$, and 1,3-dioxol-2-one (**8**) undergoes an unusual *meta* cycloaddition upon photolysis in benzonitrile or anisole to give mixtures of regio- and stereoisomers of the tetracyclic adducts (**92**) where the CN or OMe group can be at any of the three positions shown $\langle 85TL1577 \rangle$.

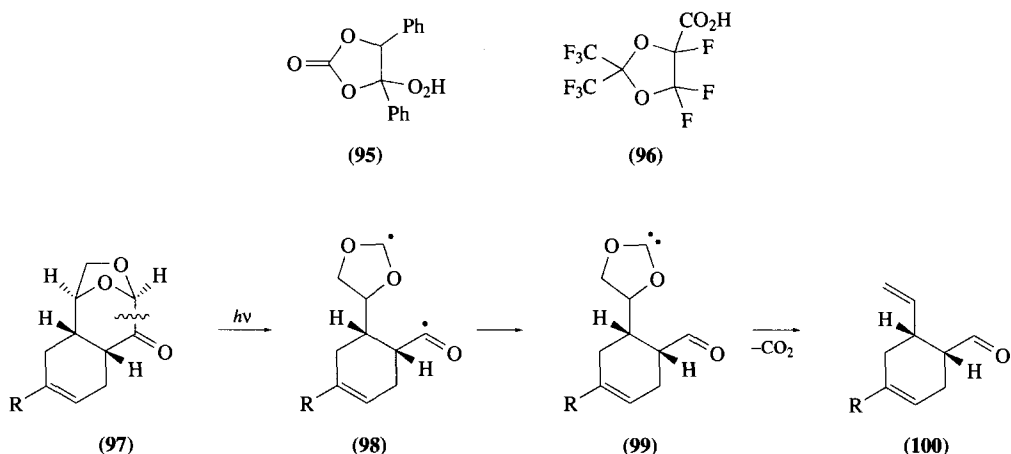


3.10.6 REACTIVITY OF 1,3-DIOXOLANES AND 1,3-OXATHIOLANES

3.10.6.1 Unimolecular Reactions

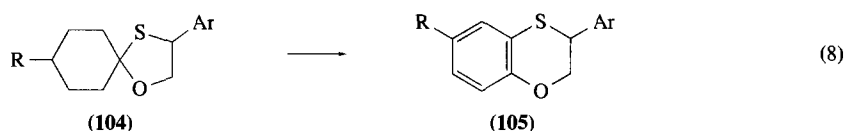
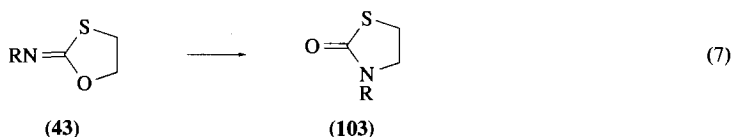
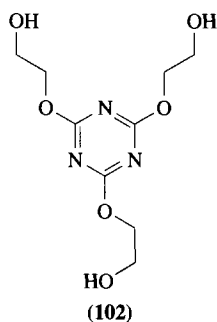
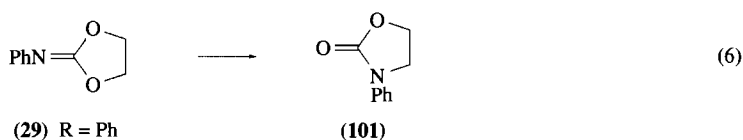
A variety of 4-methylene-1,3-dioxolanes undergo acid or base catalyzed rearrangement to the 4-methyl-1,3-dioxoles $\langle 83S208 \rangle$, and (**93**), formed by chlorination of 4,5-dimethyl-1,3-dioxol-2-one with SO_2Cl_2 , similarly isomerizes to (**94**) on heating at 90°C (Equation (5)) $\langle 85MIP8500037 \rangle$. Thermolysis of the hydroperoxydioxolanone (**95**) results in complete fragmentation to give benzoic acid, benzaldehyde and CO_2 $\langle 83MI\ 310-01 \rangle$. Thermal decomposition of the perfluorinated dioxolanecarboxylic acid (**96**) has been analyzed in detail $\langle 93MI\ 310-02 \rangle$. Photochemical decarboxylation of laevoglucosenone (**97**) proceeds by an unusual mechanism involving initial homolysis to give the diradical (**98**) which then undergoes hydrogen atom abstraction to give (**99**) which spontaneously loses CO_2 to give the product (**100**) (Scheme 4) $\langle 94CC2155 \rangle$.





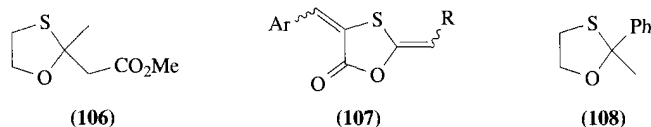
Scheme 4

Pyrolytic extrusion of CO_2 from both 1,3-oxathiolan-2-ones (**32**) and -5-ones (**33**) to afford thiiranes was described in CHEC-I. The related 1,3-oxathiolane-2-thione (**42**) undergoes analogous loss of COS to afford thiirane $\langle 64\text{ZOB}2996 \rangle$, while substituted derivatives of the isomeric 1,3-oxathiolan-4-one (**34**) are converted, by heating at $150\text{--}250^\circ\text{C}$ in the presence of $(\text{Me}_2\text{N})_3\text{P}$, into the corresponding alkenes $\langle 70\text{CC}1225 \rangle$. The 2-phenyliminodioxolane (**29**; $\text{R} = \text{Ph}$) undergoes isomerization to the oxazolidinone (**101**) upon heating at 200°C with LiCl (Equation (6)) $\langle 61\text{CB}3287 \rangle$, while the parent compound (**29**; $\text{R} = \text{H}$) undergoes spontaneous isomerization and trimerization to give the 1,3,5-triazine (**102**) with time $\langle 74\text{JOC}3442 \rangle$. The 2-imino-1,3-oxathiolanes (**43**) rearrange to the isomeric thiazolidinones (**103**) at 80°C for $\text{R} = \text{alkyl}$ but not for $\text{R} = \text{Ph}$, and there is competitive breakdown to RNCO and thiirane (Equation (7)) $\langle 77\text{BCJ}3271 \rangle$. The spirooxathiolanes (**104**) undergo oxidative rearrangement to give (**105**) upon treatment with NBS followed by Bu^nLi (Equation (8)) $\langle 94\text{JCS}(\text{P}1)1241 \rangle$.



3.10.6.2 Electrophilic Attack at Sulfur

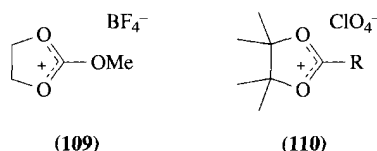
Oxidation of 1,3-oxathiolanes to the corresponding 3-oxides is readily achieved, as illustrated by the conversion of **(106)** to its 3-oxide in 99% yield using peroxyacetic acid $\langle 86\text{JOC}2789 \rangle$. The 1,3-oxathiolan-5-ones **(107)** are similarly oxidized to their 3-oxides using MCPBA $\langle 85\text{CPB}2256 \rangle$. Asymmetric 3-oxidation of oxathiolanes such as **(108)** using $\text{Bu}^t\text{OOH}/\text{Ti}(\text{OPr})_4/\text{diethyl tartrate}$ has been examined and, although the diastereoselectivity was reasonable, the *ee* was only 3% $\langle 86\text{TL}6257 \rangle$.



3.10.6.3 Nucleophilic Attack at Carbon

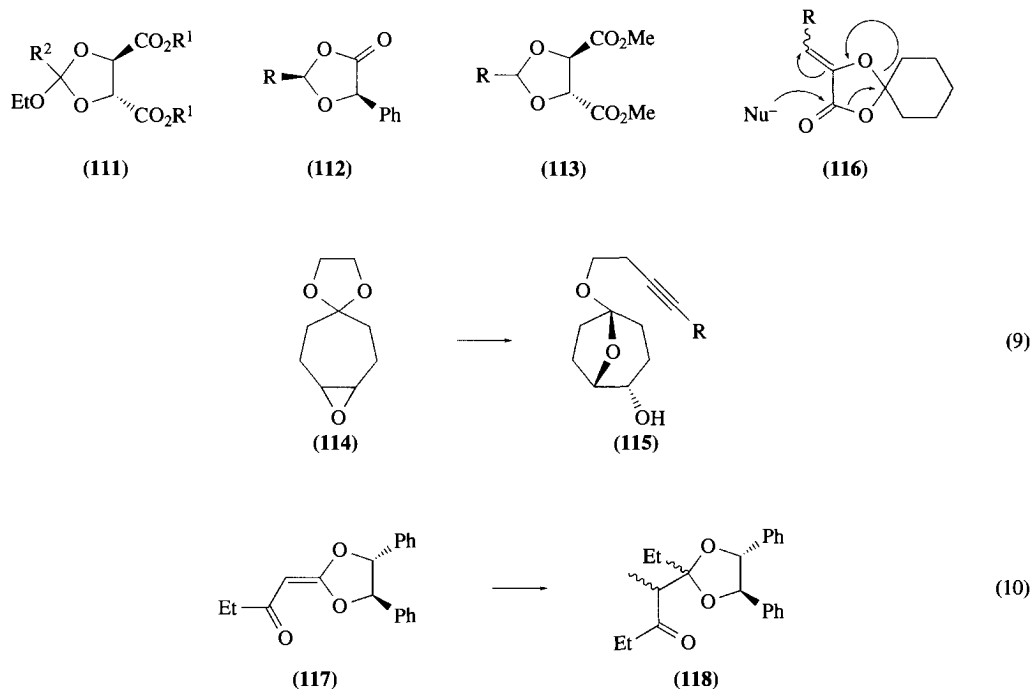
New catalysts for the efficient hydrolysis of 2,2-disubstituted-1,3-dioxolanes to carbonyl compounds include *ddq* in aqueous MeCN $\langle 92\text{CC}979 \rangle$ and TeCl_4 $\langle 92\text{PS}(67)261 \rangle$. The latter catalyst is also applicable to 1,3-oxathiolanes and these may also be cleaved by $\text{Bu}^t\text{S}-\text{NO}$ $\langle 93\text{PS}(74)249 \rangle$, or by transacetalization with *p*-nitrobenzaldehyde catalyzed by TMSOTf $\langle 94\text{CC}1937 \rangle$. Studies on the hydrolysis of 2-methoxy-1,3-dioxolanes $\langle 88\text{JA}2909 \rangle$ and spiro bis-dioxolanes $\langle 89\text{BCJ}945 \rangle$ have also appeared. Reduction of 2-substituted 1,3-oxathiolanes with Bu^t_2AlH proceeds by attack of H^- at C-2 with C(2)—O bond cleavage to afford 2-hydroxyethyl alkyl sulfides $\langle 87\text{KGS}563 \rangle$, while treatment of 2-phenyl-1,3-dioxolane with LAH/ ZrCl_4 gives benzyl 2-hydroxyethyl ether when the reaction is performed in Et_2O , but toluene and benzyl alcohol in benzene solution $\langle 91\text{OPP}427 \rangle$.

There have been few studies on the reaction of stable cations of this class with nucleophiles, but 2-methoxy-1,3-dioxolan-2-ylum fluoroborate **(109)** reacts with NaOMe at C-2, but with NaHCO_3 or LiCl at C-4 to give ring-opened 2-hydroxyethyl or 2-chloroethyl methyl carbonates, respectively $\langle 85\text{MI} 310-01 \rangle$. Reaction of salts **(110)** with acetylenic Grignard reagents takes place at C-2 $\langle 83\text{MI} 310-02 \rangle$, and the reaction of salts of type **(37)** with nucleophiles has also been examined $\langle 90\text{MI} 310-03 \rangle$.

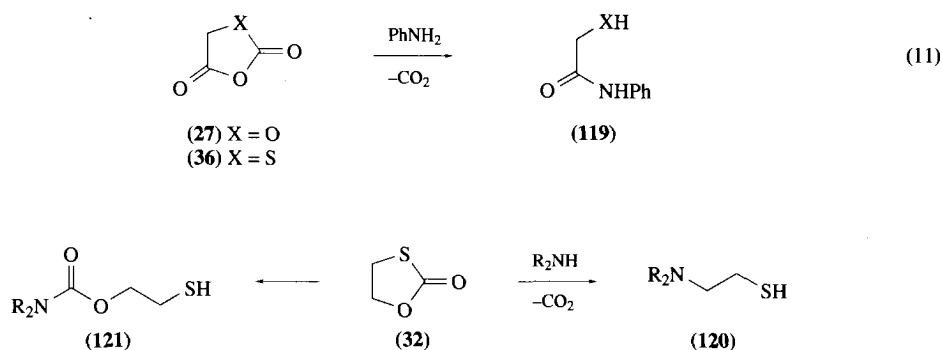


There has been considerable work on C—C bond formation by attack on suitable dioxolane systems by carbanions or their equivalents, and use of chiral dioxolanes to achieve asymmetric synthesis has been of particular interest. Achiral 2-alkyl-2-methoxy-1,3-dioxolanes react with the silyl dienol ether derived from crotonaldehyde to give 4-(2-dioxolanyl)crotonaldehydes $\langle 84\text{S}227 \rangle$, while the corresponding reaction of tartrate-derived 2-ethoxy-1,3-dioxolanes **(111)** with silyl enol ethers results in acylation in up to 80% *de* $\langle 90\text{CC}759 \rangle$. Nucleophilic attack of cuprate reagents at C-2 of both the mandelic acid-derived chiral dioxolan-4-ones **(112)** $\langle 92\text{TL}5201 \rangle$ and the tartrate-derived dioxolanes **(113)** $\langle 91\text{TL}5453 \rangle$ allows asymmetric synthesis of secondary alcohols. In special circumstances nucleophiles can attack at C-4 of 1,3-dioxolanes, as in the case of **(114)** which reacts with an alkynylaluminum compound mainly by direct opening of the epoxide, but also by attack at C-4 of the dioxolane to give **(115)** (Equation (9)) $\langle 84\text{TL}1761 \rangle$. Nucleophilic attack occurs at the carbonyl group in the spiro dioxolanones **(116)** in the manner shown to afford cyclohexanone and the enolate of an α -oxo acid derivative $\langle 84\text{JCS}(P1)1531 \rangle$. Simple derivatives of 1,3-dioxolane-2-thione **(28)** can be converted into the 2,2-difluorodioxolanes using NIS/ $\text{Bu}^n_4\text{N}^+\text{H}_2\text{F}_3^-$ $\langle 94\text{SL}251 \rangle$. Addition of alkylolithiums to 2-acylmethylene-1,3-dioxolanes occurs in the usual conjugate addition sense at the 2-position to give enolates which may be trapped either by protonation or alkylation $\langle 91\text{T}975 \rangle$,

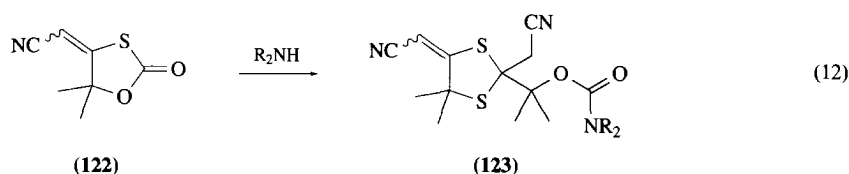
and the reaction can be applied to chiral dioxolanes such as **(117)**, which with EtLi followed by MeI gives **(118)** (Equation (10)) <91TL465>.

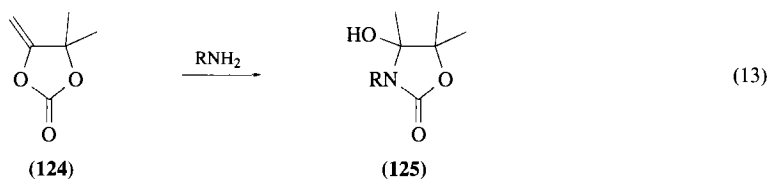


Reaction of 1,3-dioxolane-2,4-dione (**27**) and its oxathiolane analogue (**36**) with aniline proceeds with loss of CO₂ to give the α -hydroxy and α -mercaptoacetanilides (**119**) respectively (Equation (11)), and (**27**) also undergoes Friedel–Crafts reaction with benzene to give α -hydroxyacetophenone <51JCS1357>. Secondary amines, R₂NH, react with (**32**) in toluene with loss of CO₂ to give thioethylamines (**120**) <61JOC5109>, but when the same reaction is performed in dioxane, the thioethylcarbamates (**121**) are produced <61JOC5111> (Scheme 5). With the substituted analogue (**122**) the reaction takes an unexpected course and the 1,3-dithiolanes (**123**) are formed (Equation (12)) <89KGS855, 92KGS335>. The 4-methylenedioxolanone (**124**) reacts with a variety of nitrogen nucleophiles including amino acids to give (**125**) (Equation (13)) <93SL423>.

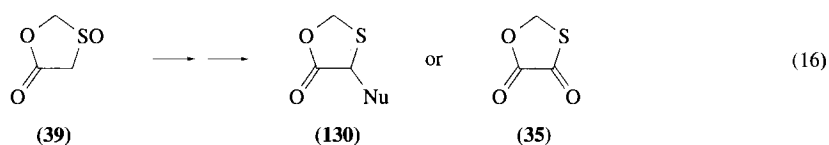
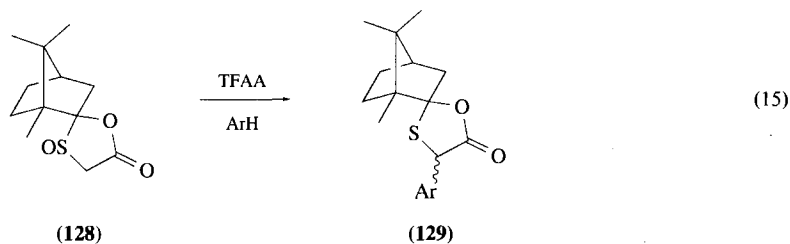
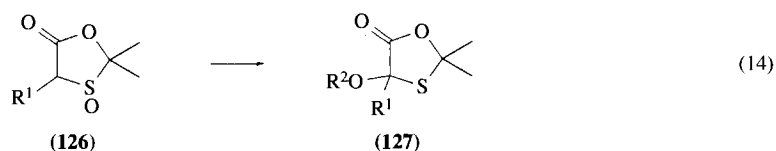


Scheme 5



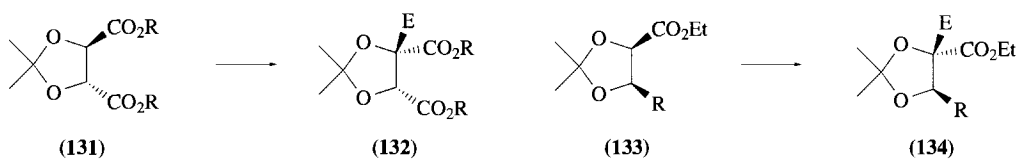


Pummerer reaction of the 1,3-oxathiolan-5-one 3-oxide (**126**; $\text{R}^1 = \text{H}$) provides access to the 4-trifluoroacetoxy compound (**127**; $\text{R}^2 = \text{CF}_3\text{CO}$) in moderate yield, but with a 4-substituent as in (**126**; $\text{R}^1 = \text{Me}$) hydrolysis of the intermediate affords the 4-hydroxy compound (**127**; $\text{R}^2 = \text{OH}$) in low yield (Equation (14)) <85CJC3313>. Reaction of the chiral oxathiolanone oxide (**128**) with TFAA and an arene gives some asymmetric induction in the formation of (**129**) (Equation (15)) <90TA143>. With the unsubstituted compound (**39**), Pummerer reaction allows the introduction of a variety of nucleophiles at the 4-position to give (**130**) and oxidation of the intermediate with pyridine *N*-oxide affords access to the little known 4,5-dione (**35**) (Equation (16)) <93JHC663>.

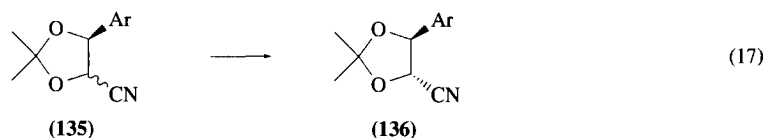


3.10.6.4 Nucleophilic Attack at Ring CH

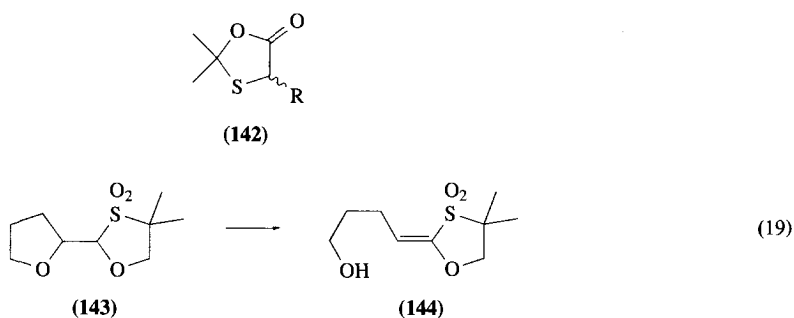
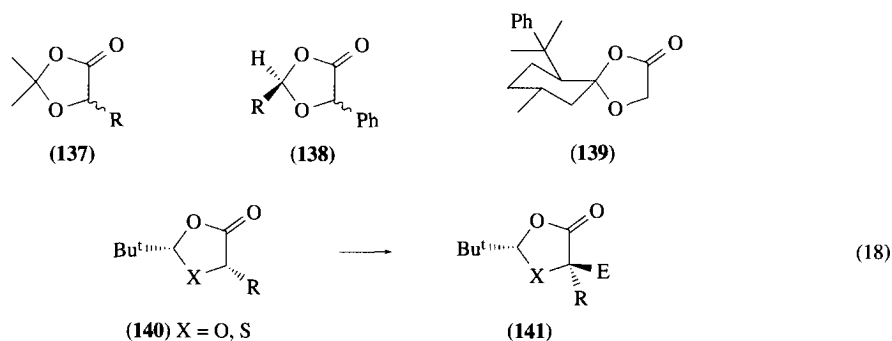
A number of important synthetic methods involving deprotonation of dioxolane and dioxolanone systems followed by stereoselective reaction with an electrophile have been developed. Thus, the tartrate-derived chiral dioxolanes (**131**) can be deprotonated and alkylated to afford mainly (**132**) <81AG(E)1030>, while the related *cis* compounds (**133**) similarly give (**134**) with a selectivity of up to 95% <82AG(E)449, 83CB3413> (Scheme 6). Deprotonation and reprotonation of the chiral cyanodioxolanes (**135**) results in “deracemization” to give the *trans* products (**136**) (Equation (17)) <89TL5157>.



Scheme 6



Asymmetric protonation of the enolates or silyl enol ethers derived from 1,3-dioxolan-4-ones (137) similarly allows either enantiomer to be obtained with high selectivity and proton sources used include Rebek's polycyclic imides <90AG(E)1420> and polymer-supported mandelic acid <94TL2891>. Stereocontrol of protonation can also be intramolecular, either from a simple 2-substituent as in (138) <94CB1495>, or from a chiral substituent as in (139), which undergoes alkylation at the 5-position with very high *de* <86JOC3746>. Condensation of chiral α -hydroxy- or α -thioacids with pivalaldehyde gives the dioxolanones or oxathiolanones (140) and the stereochemical information is retained at C-2 when the enolate is formed by deprotonation adjacent to CO. Subsequent alkylation gives products (141) with apparent retention of configuration (Equation (18)) <84T1313>. The 1,3-oxathiolan-5-ones (142) may be deprotonated and alkylated with reactive electrophiles at C-4 for R = Me, but not for R = H <84JOC1036>, and the stereoselective protonation of enolates derived from (142; R = Ph) has also been reported <93AG(E)398, 94CB1981>. Deprotonation of 1,3-oxathiolane 3-oxide (38) with KOBu^t gives the unstable 4-anion which fragments to formaldehyde and potassium vinylsulfenate <73JCS397>. Attempts to use the oxathiolane dioxide (143) as a synthetic equivalent of the tetrahydrofuryl acyl anion are frustrated by ring opening of the 2-anion generated with BuⁿLi to give (144) (Equation (19)) <84CC1028>.

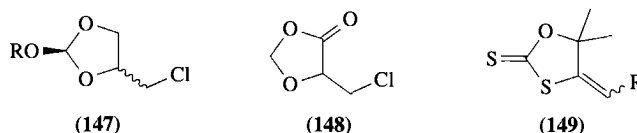


3.10.6.5 Radical and Carbene Reactions, Oxidation and Reduction

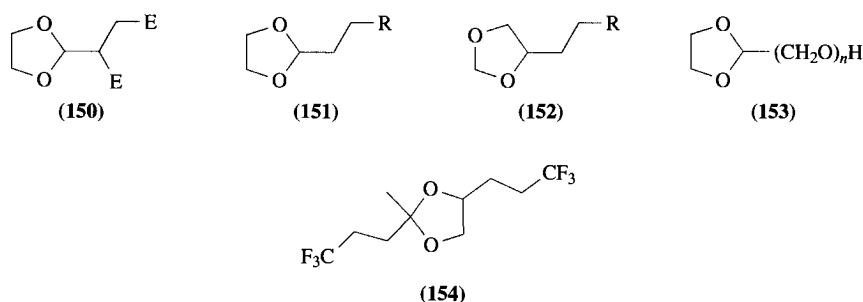
Rate constants have been determined for hydrogen atom abstraction from 1,3-dioxolane (24) and its 2-methyl, 2-isopropyl and 2,2-dimethyl derivatives <86MI 310-01>. The generation and reactivity of the chiral dioxolan-4-one radicals (145) <93T7871> and the dioxolane radical (146) <93T4589> have been reported.



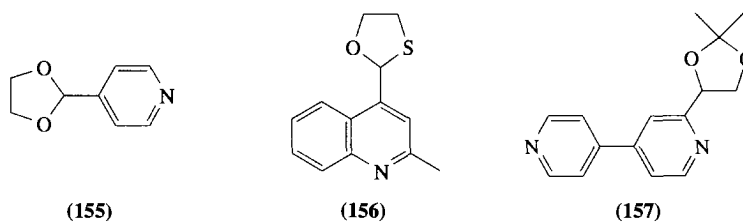
A variety of radical reactions have been used for functionalization of dioxolanes. These include conversion of 1,3-dioxolane (**24**) <86URP1227631> and 2-substituted derivatives <82URP950729> into the corresponding 2-hydroperoxy compounds with O_2 in the presence of the cobalt salt of a fatty acid, photolysis of 2-alkoxydioxolanes (**147**) with Bu^tOOH which results in dimerization through the 2-position as well as loss of the alkyl group to give the dioxolan-2-one <92MI 310-01>, and radical chlorination of (**148**) with Cl_2 and benzoyl peroxide which gives monochlorination at C-2 <86KGS187>. The 1,3-oxathiolane-2-thione (**149**) reacts with Bu^t_3SnH to give the desulfurized 1,3-oxathiolane <83TL339>.



Homolytic addition of 1,3-dioxolanes and 1,3-oxathiolanes to double bonds has been examined in detail under a variety of conditions and reported examples include the addition of dioxolane (**24**) itself to electron-deficient alkenes, $ECH=CHE$, to give (**150**) <83BCJ1428, 83DOK(272)122>, and to electron-rich alkenes such as hex-1-ene and vinyl acetate which gives both (**151**) and (**152**) <84ZOR1096>. A similar reaction with formaldehyde gives the polyethers (**153**) where $n = 1-5$ <86USP4628108>. 2-Methyl-1,3-dioxolane behaves similarly, adding to dimethyl fumarate through the 2-position, to hex-1-ene through either the 2- or 4-positions <85MI 310-02>, and to 3,3,3-trifluoropropene through both positions to give (**154**) <92IZV2768>. Addition of 2-ethoxy-1,3-dioxolane to dec-1-ene also occurs through either the 2- or 4-position <85IZV2051>. The corresponding homolytic addition of 1,3-oxathiolane (**31**) and the 2-methyl derivative to both electron-deficient and electron-rich alkenes generally occurs through the 2-position but is accompanied by more side reactions than in the dioxolane case <82ZOB2328, 83ZOR2215, 84ZOB1152, 86KGS259>.

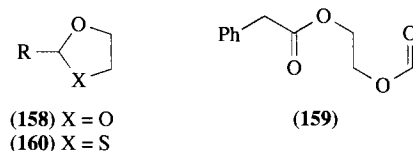


Treatment of 1,3-dioxolane (**24**) with ferrous sulfate and a peroxide in the presence of pyridine gives predominantly the 4-(2-dioxolanyl)pyridine (**155**) together with smaller amounts of the products from reaction at the 4-position of dioxolane and at the 2-position of pyridine <85ZOR193>. A similar reaction with 2-methylquinoline results in addition of the dioxolane at the 4-position of the quinoline, but joined through either the 2- or 4-position <84KGS25>, while reaction of 1,3-oxathiolane with 2-methylquinoline gives only (**156**) <83ZOR1785>. In a similar way radical addition of 2,2-dimethyl-1,3-dioxolane to 4,4'-bipyridyl gives mainly (**157**), together with some of the 2,2'-disubstituted product <85ZOR1141>.

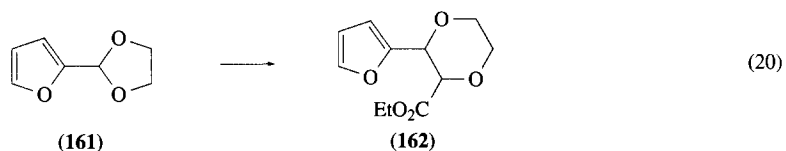


A number of radical methods resulting in ring cleavage have also been described. Reaction of 2-substituted 1,3-dioxolanes (**158**) with cumene or *t*-butyl hydroperoxides gives the 2-hydroxyethyl esters, $RCO_2CH_2CH_2OH$, and ethyl esters, RCO_2Et <85DOK(285)1131, 85MI 310-03> while with N_2O_4 , only the former are produced <87DOK(293)120>. Cobalt catalyzed oxidation of 2-benzyl-1,3-dioxolane

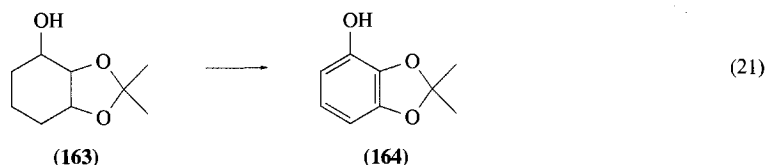
in DME gives both **(159)** and phenylacetic acid <93CJC84>. Peroxide oxidation of 2-ethoxy-1,3-oxathiolane gives mainly diethyl thiocarbonate, EtSCO_2Et , together with ethylene sulfite and other minor products <81ZOR1539, 85KGS919>. Reductive cleavage of 2-substituted 1,3-oxathiolanes **(160)** using $(\text{TMS})_3\text{SiH}$ occurs at the $\text{C}(2)\text{—S}$ bond to afford $\text{RCH}_2\text{OCH}_2\text{CH}_2\text{S—Si}(\text{TMS})_3$ and 1,3-oxathiolan-5-ones behave similarly <91TL2853>.



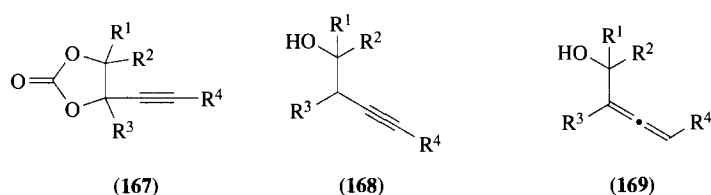
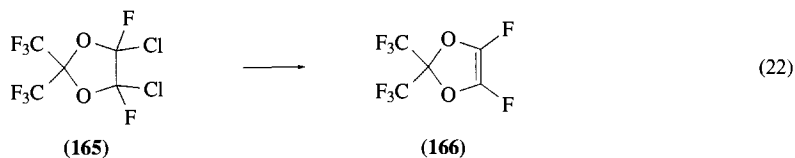
Reaction of 1,3-dioxolanes with carbenes generally proceeds by insertion into the $\text{C}(2)\text{—H}$ bond and this has been examined for phase-transfer generated $\text{Cl}_2\text{C:}$ and $\text{Br}_2\text{C:}$ <89DOK(308)135, 92ZOR1301> and for various arylchlorocarbenes, ArClC: <90DOK(310)889, 90ZOR138>. Ethoxycarbonylcarbene behaves differently and reacts with **(161)**, for example, by insertion into $\text{C}(2)\text{—O}$ to give **(162)** (Equation (20)) <92ZOR2320>.



A kinetic study on the oxidation of simple 1,3-dioxolanes with O_2 has been reported <94JPR155> and oxidation of some OH-containing 1,3-dioxolanes using LTA has been examined <93JSC269>. An efficient process for catalytic dehydrogenation of **(163)** to give the benzodioxole **(164)** has been described (Equation (21)) <81JAP81164178>.



Reductive dehalogenation of appropriate dioxolanes such as **(165)** to give **(166)** can be achieved using either magnesium with a catalytic amount of I_2 and a mercury promoter <83USP4393227>, or LAH/TiCl_4 <89GEP3842986> (Equation (22)), and convenient reductive dehalogenation of 4,5-dihalo-1,3-dioxolan-2-ones to give the 1,3-dioxol-2-ones using H_2 and a palladium catalyst has been described <90JAP02111767>. Transfer hydrogenolysis of the alkynyldioxolanones **(167)** using formic acid in the presence of a palladium catalyst takes a different course depending on which phosphine ligand is used. With Bu^3P the homopropargylic alcohol **(168)** is formed, while with $\text{Ph}_2\text{PCH}_2\text{CH}_2\text{PPh}_2$ the product is the isomeric allene **(169)** <94SL457>.

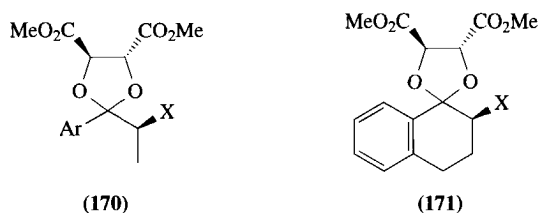


3.10.7 REACTIVITY OF SUBSTITUENTS ATTACHED TO RING CARBON ATOMS

Since the publication of CHEC-I there has been a good deal of work in this area, mostly involving 1,3-dioxolanes and dioxolanones and often with the objective of achieving asymmetric synthesis using the chirality of the dioxolane to direct the reaction at the substituent.

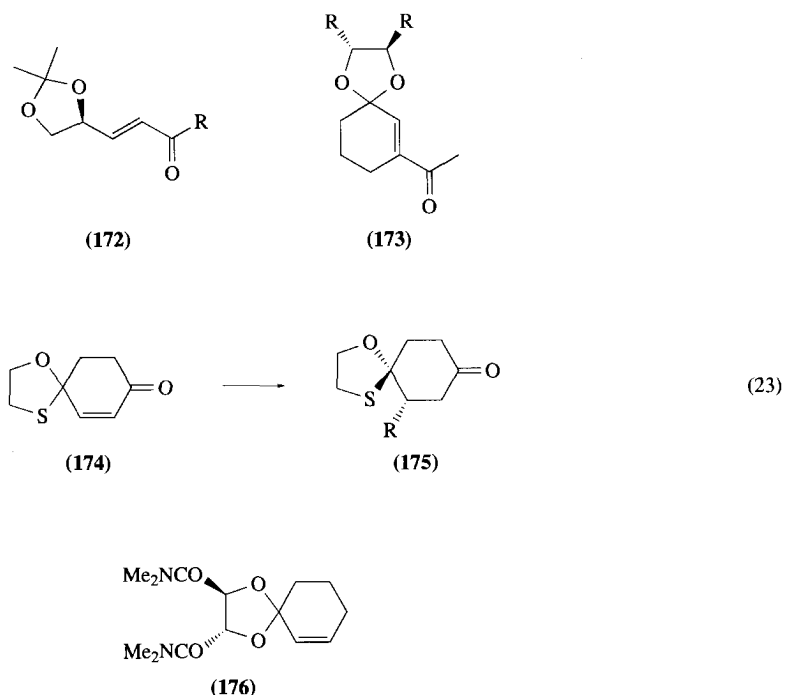
3.10.7.1 Halogenation of Alkyl Substituents

Efficient procedures have been reported for the α -bromination of 4-alkyl-1,3-dioxol-2-ones under radical conditions using either Br_2 <83JAP58152879> or NBS <83JAP58150585>. Bromination of the propiophenone ketal (**170**; $\text{X} = \text{H}$) is efficiently controlled by the dioxolane auxiliary to give (**170**; $\text{X} = \text{Br}$) in 80–88% *de* <86AG(E)259>, and the tetralone derivative similarly gives (**171**; $\text{X} = \text{Cl}$, Br) with good selectivity <90JOC5400, 92JOC2765>.



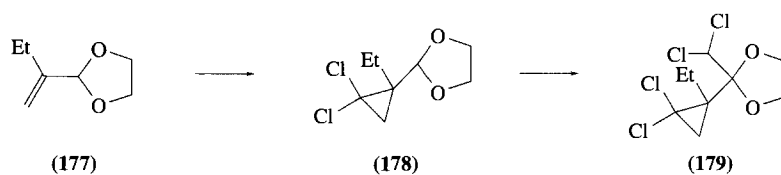
3.10.7.2 Nucleophilic Addition to Alkene Substituents

The chiral dioxolanyl enones (**172**), readily obtained from glyceraldehyde acetonide, undergo stereoselective conjugate addition of lithium enolates <94TL143> and vinylolithiums <92SL741> and also hydrosilylation with Ph_2SiH_2 <91TL3683>. The spiro dioxolanes (**173**) similarly undergo conjugate addition of cuprates with moderate stereocontrol <90TL623> and copper catalyzed addition of Grignard reagents to the spiro oxathiolane (**174**) gives 94% *de* in favor of the isomer (**175**) (Equation (23)) <92TL3145>. The chiral cyclohexenone ketal (**176**) reacts with Me_3Al followed by Ac_2O to give 3-methylcyclohexanone in 77% *ee* <84TL5911>.

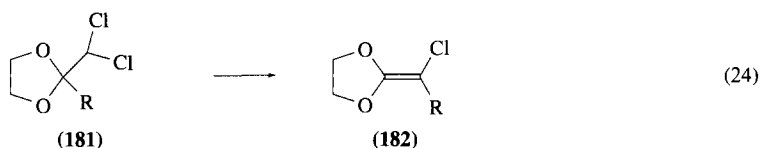
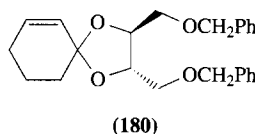


3.10.7.3 Cyclopropanation of Alkene Substituents and Other Carbene Reactions

A variety of 2-substituted 4-methylene-1,3-dioxolanes react readily with either Cl_2C : <83KGS1607, 92ZOR2156> or $\text{EtO}_2\text{C}-\text{CH}:$ <92ZOR2320> by addition to give the corresponding cyclopropanes. Reaction of (177) with Cl_2C : also proceeds by initial cyclopropanation to give (178), but this is followed by insertion to afford (179) (Scheme 7) <93MI 310-03>. Asymmetric cyclopropanation of the double bond in both (172) <93TL2695> and the cyclohexenone ketal (180) <85JA8256> has been achieved. Base-induced α -elimination occurs on treating (181) with KO^tBu to give the dioxolanylchlorocarbene which undergoes a 1,2-migration of R to afford the α -chloroalkylidene compounds (182) (Equation (24)) <92ZOB1436>.

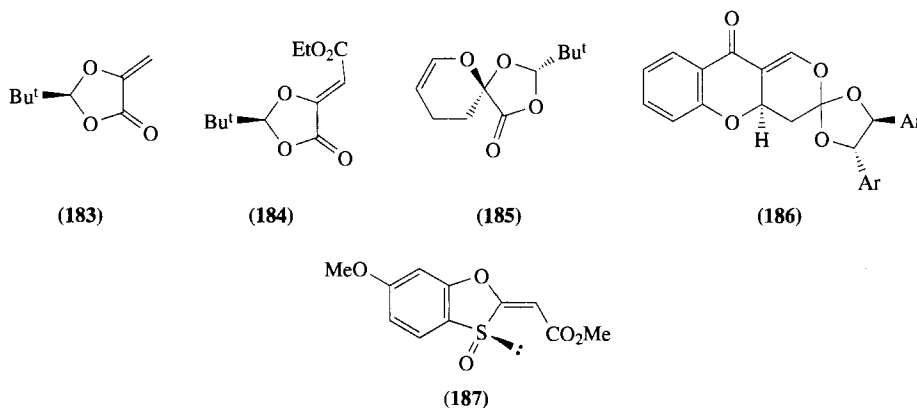


Scheme 7



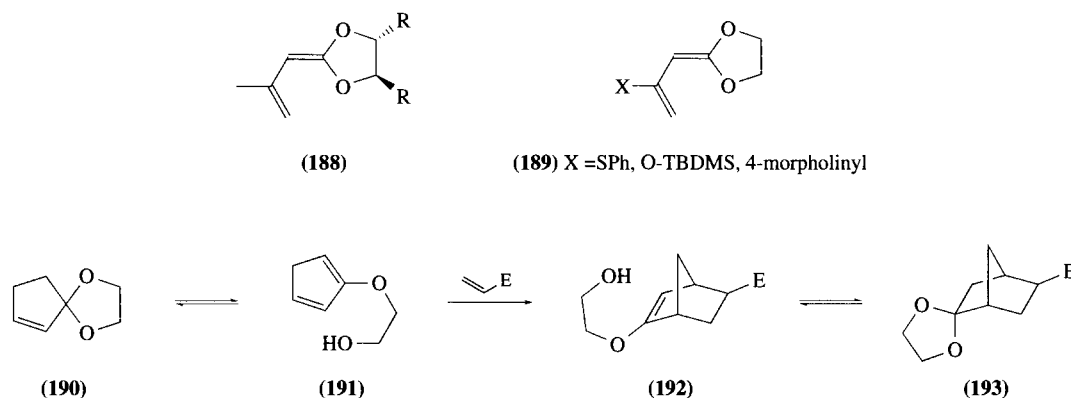
3.10.7.4 Cycloaddition with Dienes

A variety of 2-substituted 5-methylene-1,3-dioxolan-4-ones such as (183) <89CB327, 92JOC3380> and (184) <90S599> are readily prepared in enantiomerically pure form and the stereoselectivity of cycloaddition of cyclopentadiene and other dienes to the double bond has been examined. An enone can also act as the diene component and (183), for example, reacts with acrolein to give (185) <90SL145>. Chiral 4,5-diaryl-2-methylenedioxolanes react with 3-formylbenzopyranone in a similar way to give (186) <91CC1707>. Diels-Alder cycloaddition to the double bond of the chiral benzoxathiole 3-oxide (187) has also been examined <93TL8201>.



3.10.7.5 Cycloaddition with Dienophiles

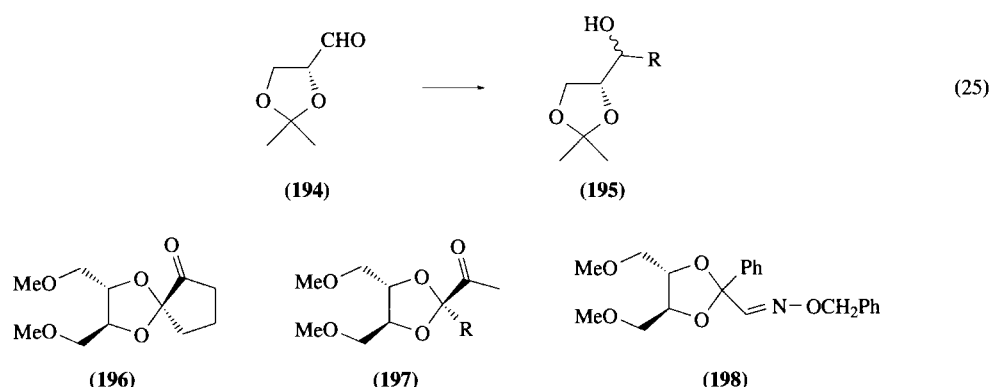
The chiral propenylmethylenedioxolanes (**188**) undergo highly stereoselective Diels–Alder reactions with a variety of dienophiles $\langle 89JA4515, 91T4519 \rangle$, and the hetero-substituted dienes (**189**) react similarly $\langle 93TL4587 \rangle$. The cyclopentenone ketal (**190**) can act as a Diels–Alder diene in an unusual way by tautomerization to the ring-opened form (**191**) which then undergoes cycloaddition to give (**192**) followed by ring closure back to the dioxolane (**193**) (Scheme 8) $\langle 91CC37, 93JOC5200, 93MI 310-04 \rangle$.



Scheme 8

3.10.7.6 Nucleophilic Addition to Carbonyl and Imine Substituents

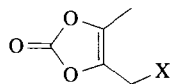
Addition of organometallic reagents to the formyl group of (**194**) occurs with good stereoselectivity to give (**195**) (Equation (25)) and the reagents used include organotitanium and zinc reagents $\langle 83TL2843 \rangle$, vinyl cuprates $\langle 93T10597 \rangle$, diallylzinc $\langle 84AG(E)704 \rangle$, and crotylboranes $\langle 86JA294 \rangle$. The same products (**195**) can also be obtained by hydride reduction of the corresponding 4-acyldioxolanes $\langle 89BCJ2121 \rangle$. Stereocontrolled addition of Grignard reagents to a 2-acyl substituent in systems such as (**196**) $\langle 86TL81 \rangle$ and (**197**) $\langle 86TL2117 \rangle$ has also been reported. Organocerium reagents add to the imine function of (**198**) with good diastereoselectivity $\langle 89CPB602 \rangle$.



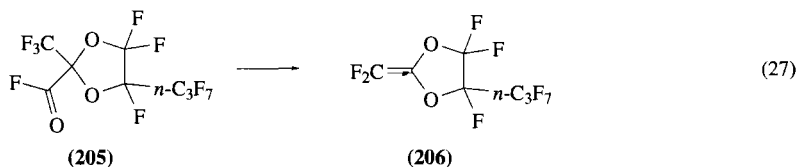
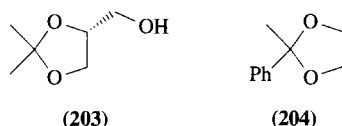
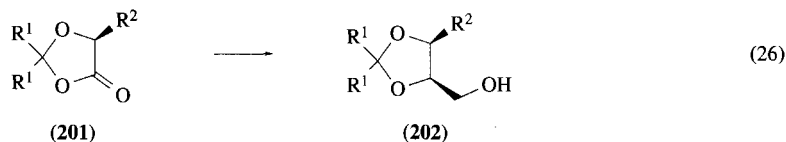
3.10.7.7 Miscellaneous Reactions

The dioxolan-2-ylum salt (**109**) reacts with NaHCO_3 or LiCl to afford 1,3-dioxolan-2-one (**25**) $\langle 85MI 310-01 \rangle$. Transformation of the bromomethyldioxolone (**199**) to the hydroxymethyl compound (**200**) without disrupting the ring may be achieved by treatment with potassium formate followed by methanol $\langle 84JAP59212488 \rangle$. Stereoselective conversion of the dioxolanones (**201**) into the hydroxymethyl compounds (**202**) has been reported by methylenation using the Tebbe reagent

followed by hydroboration (Equation (26)) <94TL2537>. Metal catalyzed oxidation of (**203**) to the corresponding acid under mild conditions which avoid racemization has been described <94EUP611762>, and kinetic resolution of racemic (**203**) has been carried out by lipase catalyzed esterification with succinic anhydride <89CPB1653>. Nitration of 2-phenyl-1,3-dioxolanes occurs readily on the aromatic ring with little cleavage of the heterocycle when the reaction is carried out using NO_2 in the presence of ozone and MgO <94JCS(P1)1367>. The dioxolane ring in the acetophenone ketal (**204**) directs *ortho* lithiation of the aromatic ring using Bu^nLi <84SC373>. An unusual reaction occurs upon thermolysis of (**205**) in the presence of KOH in ethanol: carbonyl fluoride is lost to afford (**206**) (Equation (27)) <93JAP05213929>.



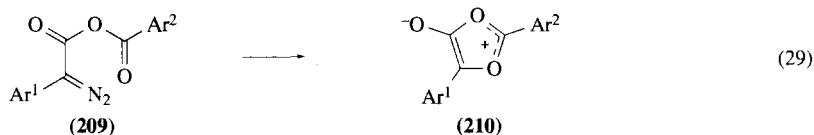
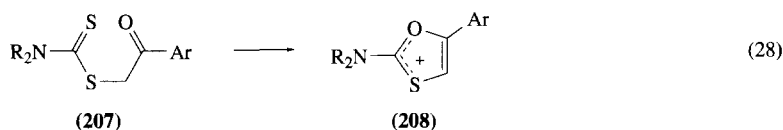
(199) $\text{X} = \text{Br}$
(200) $\text{X} = \text{OH}$



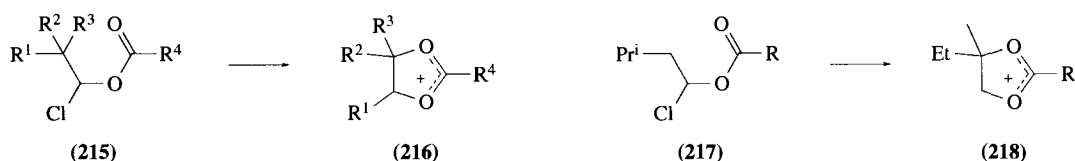
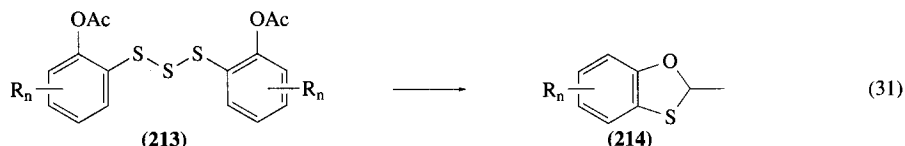
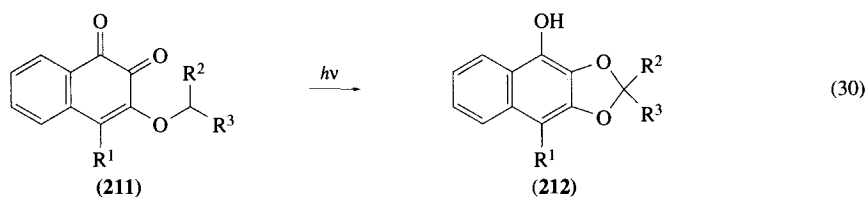
3.10.8 RING SYNTHESIS

3.10.8.1 One-bond Formation Adjacent to a Heteroatom

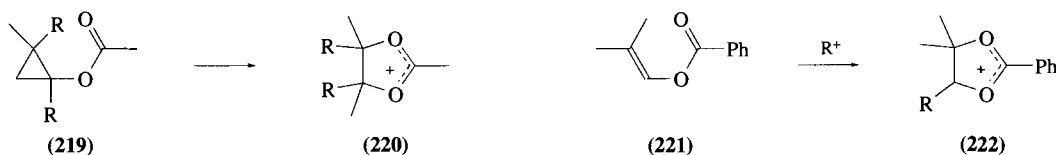
The main methods available to prepare 1,3-oxathiolium salts and their mesoionic 4- and 5-olates are of this type and were covered in CHEC-I <84CHEC-I(6)749> but two important new methods have been described. The 2-amino-1,3-oxathiolium salts (**208**) can be obtained by desulfurization of the phenacyldithiocarbamates (**207**) with a silver, mercury, or copper salt (Equation (28)) <92JAP04364178>. The 1,3-dioxolium-4-olates (**210**) have been generated from the α -diazo anhydrides (**209**) by palladium-catalyzed decomposition to give the carbene which then undergoes electrocyclization (Equation (29)) <85CC190>.



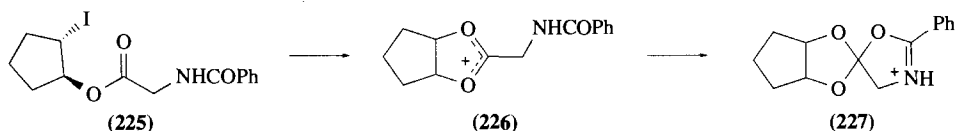
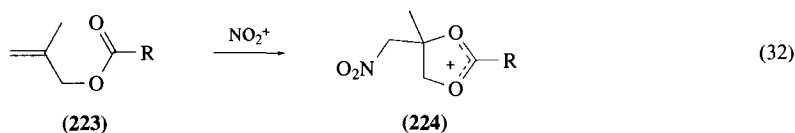
Photoinduced intramolecular cyclization of (211) gives the naphthodioxole (212) (Equation (30)) <87CL727> and the benzoxathioles (214) can be prepared by treating trisulfides (213) with zinc in acetic acid (Equation (31)) <85EUP157603>. New cationic cyclization methods have been used to generate a variety of 1,3-dioxolan-2-ylum salts. Treatment of the chloroesters (215) and (217) with SbCl_5 results in cyclization with rearrangement of the carbon skeleton to give the hexachloroantimonate salts of (216) <83ZOR2154> and (218) <81ZOR2233>, respectively (Scheme 9). The cyclopropyl acetates (219) react similarly with HClO_4 in Ac_2O to give the perchlorates of (220), and the vinyl esters (221) react with benzoyl or *t*-butyl hexachloroantimonate to give (222) (Scheme 10) <81ZOR2234, 85ZOR2067>. Cyclization of the allyl esters (223) occurs with $\text{NO}_2^+ \text{BF}_4^-$ to give the tetrafluoroborates of (224) (Equation (32)) <82TL3281> and the iodoalkyl hippuric acid ester (225) reacts with either AgBF_4 or AgClO_4 to give the spiro iminium salts (227) by way of the dioxolanylium salts (226) (Scheme 11) <84T3399>.



Scheme 9



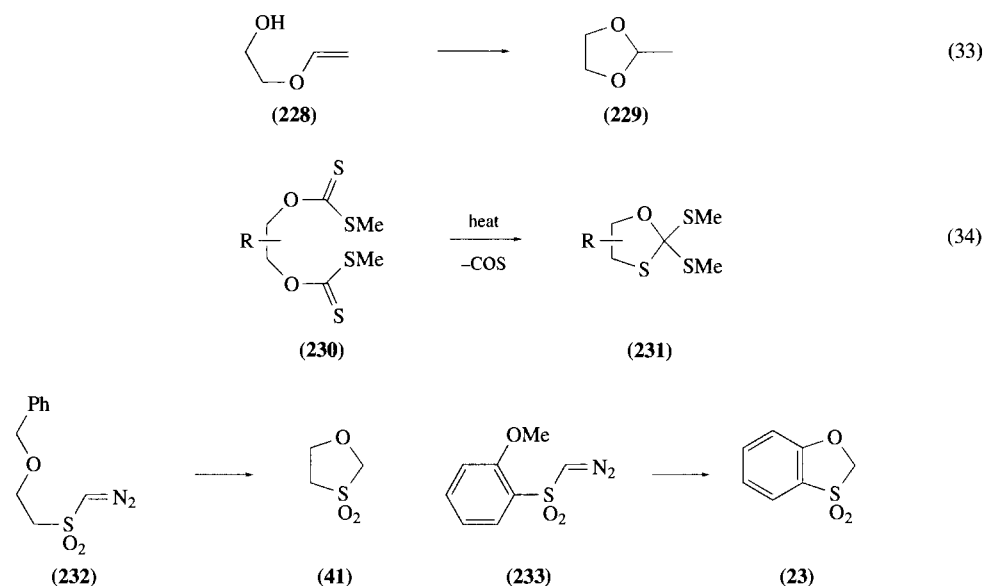
Scheme 10



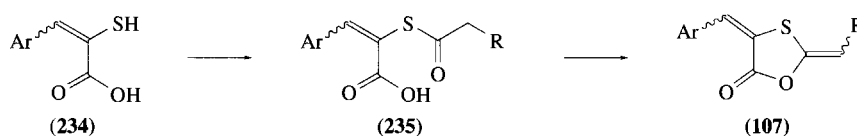
Scheme 11

A simple preparation of 2-methyl-1,3-dioxolane (229) involves heating the vinyl ether (228) with KOH to give the product in 66% yield (Equation (33)) <84IZV1670, 86ZOR1583>. Thermolysis of the bis(dithiocarbonates) (230) results in loss of COS to afford the 1,3-oxathiolanes (231) in up to 90%

yield (Equation (34)) <78S286>. The original preparation of 1,3-oxathiolane 3,3-dioxide (**41**) involved treatment of the diazosulfone (**232**) with BF_3 and (**23**) was similarly prepared from (**233**) (Scheme 12) <66RTC323>. Access to the 1,3-oxathiolan-5-ones (**107**) may be gained either by cyclization of (**235**) with SOCl_2 or directly from (**234**) by treatment with the anhydride $(\text{RCH}_2\text{CO})_2\text{O}$ (Scheme 13) <84S595, 85CPB2256>.

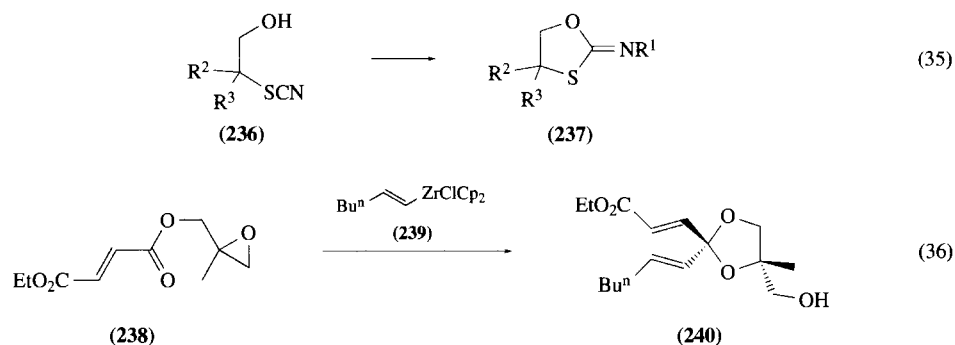


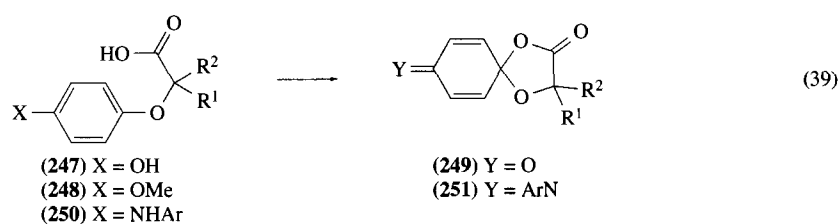
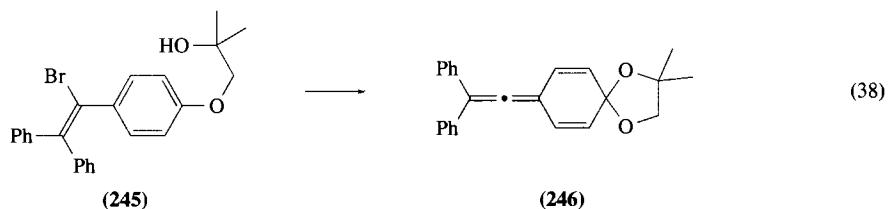
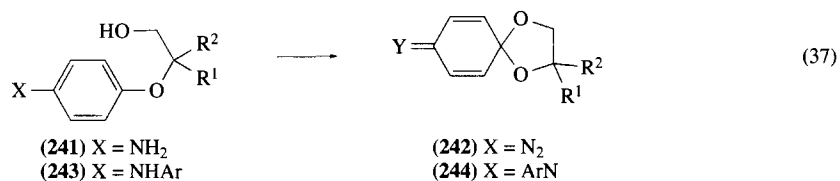
Scheme 12



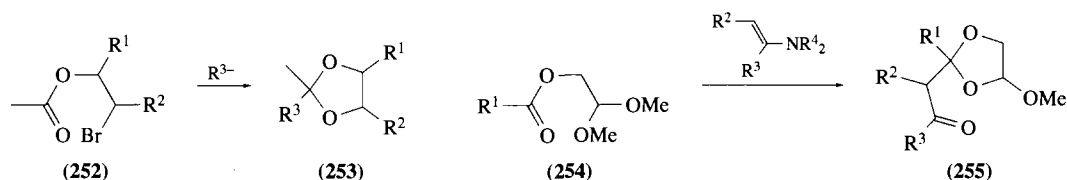
Scheme 13

A variety of cation-induced cyclization approaches to systems of this type have been introduced. Reaction of hydroxyethylthiocyanates (**236**) with a tertiary alcohol, R^1OH , in sulfuric acid gives the 2-iminooxathiolanes (**237**) (Equation (35)) <92ZOR418> and treatment of glycidyl esters such as (**238**) with cationic zirconium complexes such as (**239**) and AgClO_4 gives the dioxolane (**240**) (Equation (36)) <93JOC5880>. Cyclization onto an aromatic ring induced by a suitable group in the *para* position gives quinone-type spiro dioxolanes as exemplified by diazotization of (**241**) to give (**242**) <93JOC6146> and anodic or LTA oxidation of (**243**) to afford (**244**) <88JCR(S)241> (Equation (37)). In a similar way (**245**) cyclizes to (**246**) upon photolysis in the presence of NaOPr^i (Equation (38)) <89CC1154>. The analogous processes from suitable phenoxyacetic acids give the corresponding spiro dioxolanones and examples include the preparation of (**249**) either by reaction of (**247**) with NBS <82SC427> or by anodic oxidation of (**248**) <84TL4471>, and formation of (**251**) by anodic or LTA oxidation of (**250**) <88JCR(S)241> (Equation (39)).

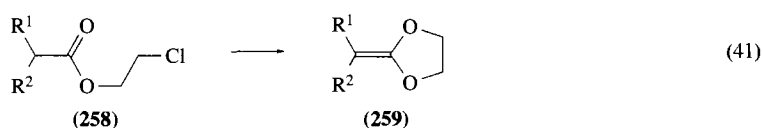
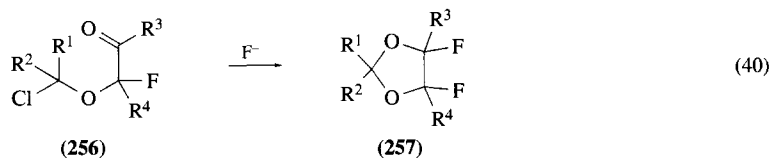




Formation of 2,2-disubstituted 1,3-dioxolanes may be achieved by nucleophilic attack on 2-haloalkyl esters and similar compounds as illustrated by the reaction of **(252)** with stabilized carbanions to give **(253)** <86JPC1285> and reaction of **(254)** with enamines to afford **(255)** <90SC2197> (Scheme 14). Attack of fluoride anion on **(256)** similarly gives **(257)** (Equation (40)) <82JFC(21)107>. Convenient access to 2-alkylidene-1,3-dioxolanes **(259)** is provided by *O*-alkylation of the enolates derived from the 2-chloroethyl esters **(258)** and examples reported include those with R¹ and/or R² = CO₂R, CN, CF₃ and COMe (Equation (41)) <85JOC1117, 88S981, 90IZV2662, 91DOK(319)619>. The esters **(258)** can in some cases be prepared by treating an acidic methylene compound with 2-chloroethyl chloroformate.



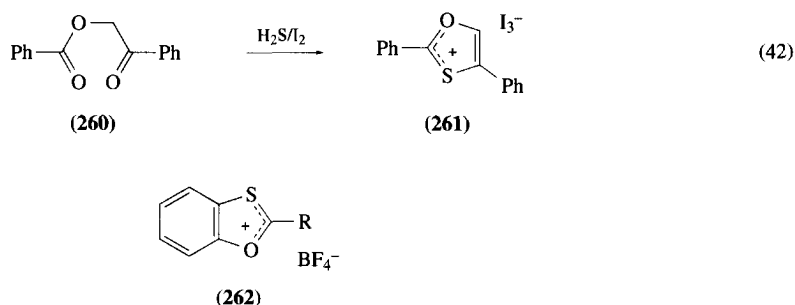
Scheme 14



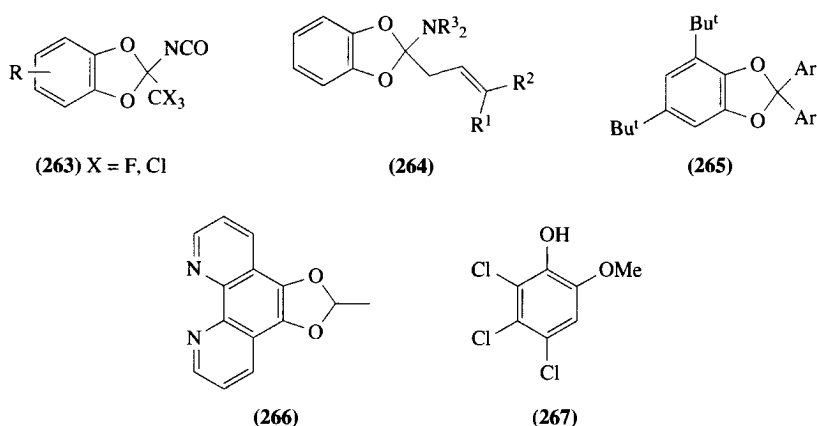
3.10.8.2 Two-bond Formation from [4 + 1] Atom Fragments

As stated in CHEC-I, almost all methods of this type involve addition of C-2 as the one-atom fragment, the first example mentioned here representing a rare exception. New routes to fully

conjugated systems include the reaction of phenacyl benzoate (**260**) with H_2S and iodine to give the oxathiolium salt (**261**) in 88% yield (Equation (42)) <86MI 310-02>, and treatment of 2-hydroxythiophenol with a wide range of carboxylic acid derivatives in the presence of HBF_4 or $\text{BF}_3 \cdot \text{Et}_2\text{O}$ to afford the benzoxathiolium salts (**262**) <86S1074>.

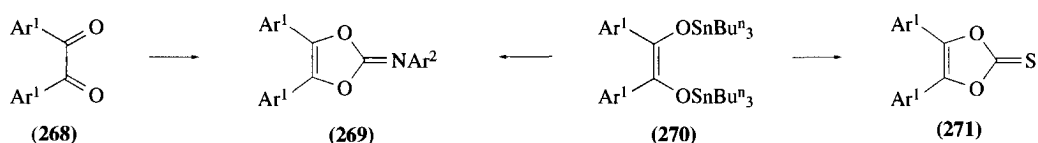


A mild and efficient method for conversion of catechols into the corresponding 1,3-benzodioxoles involves treatment with BrCH_2Cl and Cs_2CO_3 in DMF <91TL2461> and the preparation of 3,4-methylenedioxypyphenol labeled with ^{14}C at the CH_2 position has been described <93MI 310-05>. Access to 1,3-benzodioxoles with unusual substituents at the 2-position may be gained by treating the corresponding catechols with $\text{X}_3\text{C}-\text{C}(\text{Cl})_2\text{NCO}$ to afford (**263**) <89ZOR883, 92UKZ675>, and with the enynamines $\text{R}^1(\text{R}^2)\text{C}=\text{CH}-\text{C}\equiv\text{C}-\text{NR}^3_2$ to give (**264**) <83URP998464>. A range of benzodioxoles (**265**) have been prepared by reaction of the corresponding *o*-benzoquinone with $\text{Ph}_3\text{P}=\text{CAr}_2$ <92PS(66)285> and (**266**) has been obtained by base-induced condensation of the phenanthrolinequinone with nitroethane <88JAP63301883>. The spiro benzodioxole (**51**) mentioned earlier was prepared by oxidation of 4,5,6-trichloroguaiacol (**267**) with periodic acid <93ACS999> and the dioxol-2-one systems (**63**) and (**64**) were obtained by heating the corresponding aromatic polyols with phosgene <84T4897>.



The 2-imino-1,3-dioxoles (**269**) can be prepared either by electrochemical reduction of benzils (**268**) in the presence of $\text{Ar}^2\text{N}=\text{CCl}_2$ <94TL2365>, or by treatment of (**270**) with Ar^2NCS (Scheme 15). Reaction of (**270**) with CS_2 similarly gives the 1,3-dioxole-2-thiones (**271**) <83BCJ1873>.

Treatment of thiobenzils (**272**) with aromatic diazo compounds $\text{Ar}^3\text{Ar}^4\text{CN}_2$ gives the 1,3-oxathi-



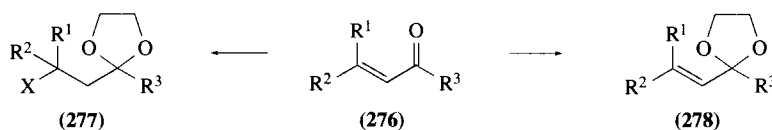
Scheme 15

oles (**273**) <79CB2744, 80JHC1655> and the α -oxothioesters (**274**) react similarly with diazomethane to afford (**275**) <90T1783> (Scheme 16).

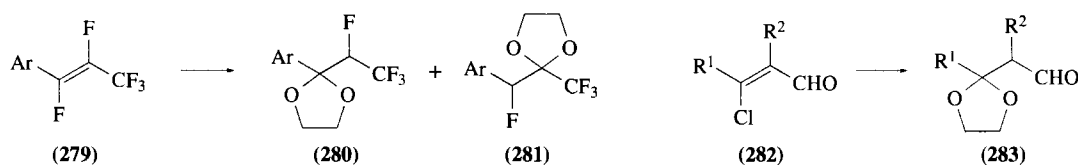


Scheme 16

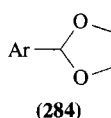
The basic method for formation of 1,3-dioxolanes, condensation of a carbonyl compound with a 1,2-diol, has been developed in several ways. An efficient process for preparation of the parent compound (**24**) in >97% purity has been described <93JAP05271217> and high pressure has been used to force ketalization of hindered or unreactive ketones with ethanediol <86JOC4964>. The previously problematic acetalization of hydroxybenzaldehydes and other carbonyl compounds proceeds efficiently in the presence of the rhodium complex of a tripodal tris(phosphine) <89TL6151, 93SL751> and the bimetallic catalyst $\text{Sn}[\text{Co}(\text{CO})_4]_4$ promotes transacetalization of aliphatic aldehydes with ethylene carbonate (**25**) <93JMOC279>. An important new method for formation of 1,3-dioxolanes involves treating a ketone with ethanediol and two equivalents of $\text{TMS}-\text{Cl}$ to give the products in 64–99% yield <83S203>. When this method is applied to α,β -unsaturated carbonyl compounds (**276**) it gives (**277**; $\text{X} = \text{Cl}$) and the use of $\text{TMS}-\text{N}_3$ <84TL3805> or $\text{TMS}-\text{Br}$ <90SC1175> similarly gives (**277**; $\text{X} = \text{N}_3, \text{Br}$) (Scheme 17). Catalytic hydrogenation of enones (**276**) in the presence of ethanediol proceeds with concomitant ketalization to give (**277**; $\text{X} = \text{H}$) <92SL867>. Acetalization of α,β -unsaturated aldehydes without affecting the double bond, to give (**278**), can be carried out in high yield by treatment with $\text{TMS}-\text{OCH}_2\text{CH}_2\text{O}-\text{TMS}$ and a catalytic amount of $\text{TMS}-\text{OTf}$ <87JOC188>. Selective ketalization of a ketone in the presence of an aldehyde can be achieved by reaction with $\text{TMS}-\text{OTf}$ and Me_2S followed by $\text{TMS}-\text{OCH}_2\text{CH}_2\text{O}-\text{TMS}$ <92TL2565>. Treatment with the sodium salt of ethanediol results in conversion of the vinyl fluorides (**279**) into a mixture of (**280**) and (**281**) <84BAP39> and of the chlorides (**282**) into the dioxolanes (**283**) <85S496> (Scheme 18). Electrolysis of substituted toluenes, ArMe , in the presence of ethanediol gives the dioxolanes (**284**) by a radical mechanism <90MI 310-04>. Oxidative cyclization of enediols (**285**) using $\text{PdCl}_2/\text{CuCl}_2/\text{O}_2$ gives the bicyclic methyl dioxolanes (**286**) (Equation (43)) <84JCS(P1)1643>. The 2-alkyldenedioxolanes (**287**) <83ZOR1762> and (**288**) <86URP1273356> are formed by treatment of the 1,2-diols with $(\text{CF}_3)_2\text{C}=\text{CF}_2$ and TCNE, respectively.

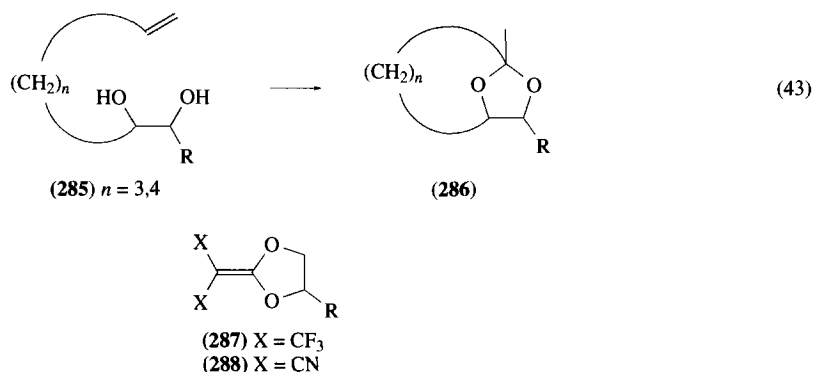


Scheme 17

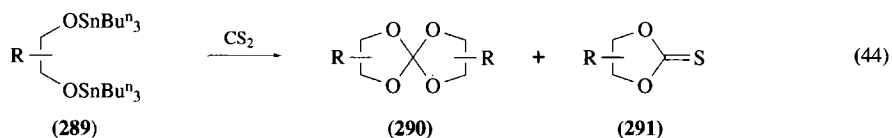


Scheme 18

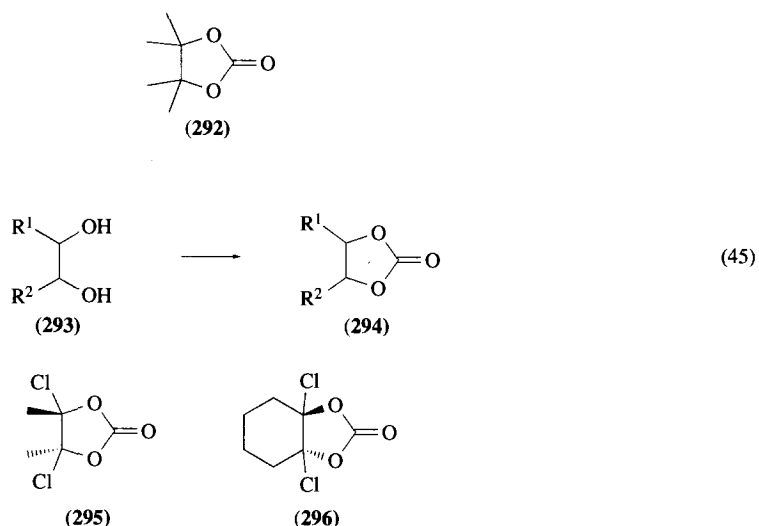




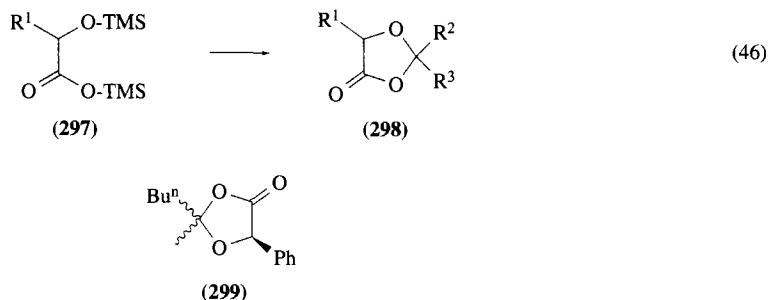
The spiro bis-dioxolane (**290**; $R = \text{H}$) can be prepared either from tetramethyl orthocarbonate, $\text{C}(\text{OMe})_4$ and ethanediol $\langle 83\text{GEP}3225818 \rangle$, or from the tin compound (**289**; $R = \text{H}$) and 1,3-dioxolane-2-thione (**28**) $\langle 74\text{JOM}(72)103 \rangle$, and reaction of (**289**) with CS_2 also affords (**290**) together with the dioxolanethiones (**291**) $\langle 70\text{JOC}2347 \rangle$ (Equation (44)).



New methods for preparation of 1,3-dioxolan-2-one (**25**) include treatment of ethanediol with either ethyl trichloroacetate $\langle 82\text{USP}4344881 \rangle$ or hexachloroacetone $\langle 82\text{USP}4353831 \rangle$ in the presence of a base, or with di-2-pyridyl carbonate $\langle 86\text{H}(24)1625 \rangle$. The tetramethyl compound (**292**) can be prepared from pinacol by treatment with $\text{Ac}_2\text{O}/\text{dmap}$ in a process which appears to involve ketene and diketene $\langle 84\text{JOC}3974 \rangle$. The 1,2-diols (**293**) react with oxalyl chloride and Et_3N in an unexpected way to give mainly (**294**) rather than the expected six-membered ring products (Equation (45)) $\langle 93\text{CPB}408 \rangle$. Treatment of 1,2-diones such as diacetyl and cyclohexane-1,2-dione with phosgene and pyridine results in addition to give (**295**) and (**296**), respectively $\langle 93\text{SC}847 \rangle$.

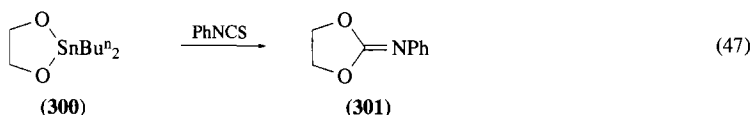


The standard method for preparation of 1,3-dioxolan-4-ones (**26**) is condensation of an α -hydroxyacid with a carbonyl compound and the reaction occurs readily in the presence of $\text{BF}_3 \cdot \text{Et}_2\text{O}$ $\langle 70\text{BSF}332 \rangle$ and for chiral α -hydroxy acids such as lactic acid to afford (**53**) $\langle 90\text{TL}2135, 93\text{BSF}133 \rangle$. An efficient new variation involves the bis(silyl) derivatives (**297**) which condense with aldehydes $\langle 87\text{JOC}1351 \rangle$, ketones or dimethylketals $\langle 87\text{JOC}1353 \rangle$ in the presence of $\text{TMS}-\text{OTf}$ or $\text{TMS}-\text{I}$ to afford (**298**) (Equation (46)). The ruthenium catalyzed reaction of (*R*)-mandelic acid with hex-1-yne to give (**299**) has been reported $\langle 93\text{JOM}(451)133 \rangle$.

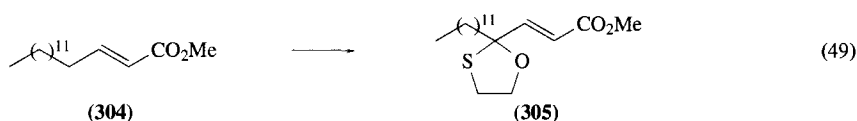
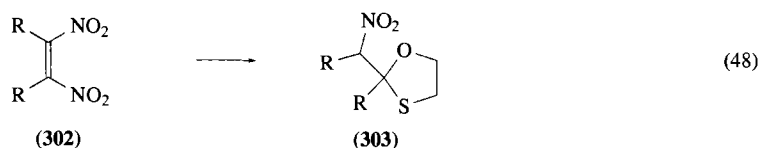


As mentioned in CHEC-I, the standard method for formation of 1,3-dioxolane-2-thione (**28**) is reaction of ethanediol with thiophosgene, but other methods include the reaction of (**289**) with CS₂ to give (**291**) as described above, and reaction of diols (**293**) with base and CS₂ followed by MeI which gives the thiones corresponding to (**294**) in addition to bis(dithiocarbonates) (**230**) <78S286>.

The 2-imino-1,3-dioxolanes such as (**301**) may be prepared either from the cyclic tin compound (**300**) and PhNCS (Equation (47)) <77BCJ3271> or from PhN=CCl₂ and the disodium salt of ethanediol <61CB3287>.

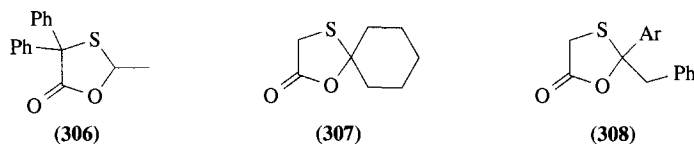


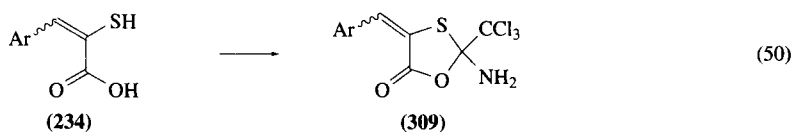
The standard method for preparation of 1,3-oxathiolanes (**31**) is condensation of a carbonyl compound with 2-thioethanol and the reaction proceeds efficiently when catalyzed by BF₃·Et₂O <68JOC2133>, SO₂ <82S831> or ZnCl₂ <88TL897>. Dimethylacetals can also be used in place of the carbonyl component <88JOC5179>. More unusual approaches include the reaction of 1,2-dinitroalkenes (**302**) with 2-thioethanol to afford (**303**) (Equation (48)) <94JOC1053>, and treatment of unsaturated fatty acid esters such as (**304**) with 2-thioethanol in acetic acid which results in functionalization of the allylic position to give (**305**) and products derived from it by thiol addition to the double bond (Equation (49)) <84MI 310-01>.



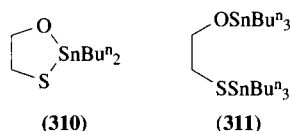
The preparation of 1,3-oxathiolan-2-one (**32**) by reaction of 2-thioethanol with phosgene was reported at an early date <41RTC453> and more recent routes to the same compound involve oxidative carbonylation of di(2-hydroxyethyl)disulfide in the presence of Se and Et₃N <74TL2899>, and reaction of 2-thioethanol with diethyl carbonate in the presence of H₂SO₄ <83URP1016286>.

In an analogous way to the 1,3-dioxolan-4-ones, the 1,3-oxathiolan-5-ones (**33**) are readily prepared by reaction of an α-thio acid with a carbonyl compound. Typical examples prepared in this way include (**306**) <20HCA447>, (**307**) <85JCS(P1)587> and (**308**) <93CCC1208>. The α-thiocinnamic acids (**234**) react with trichloroacetonitrile to furnish the benzyldeneoxathiolanones (**309**) (Equation (50)) <90MI 310-05, 91PJC1291>.



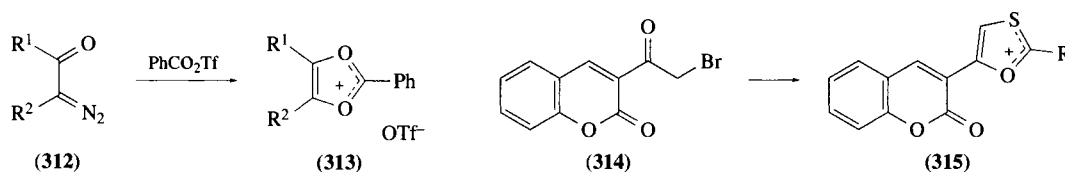


The 2-imino-1,3-oxathiolanes (**43**) may be prepared by reaction of isothiocyanates, RNCS, with either (**310**) <77BCJ3271> or (**311**) <74JOM(72)103>, and reaction of the latter with CS₂ gives 1,3-oxathiolane-2-thione (**42**).

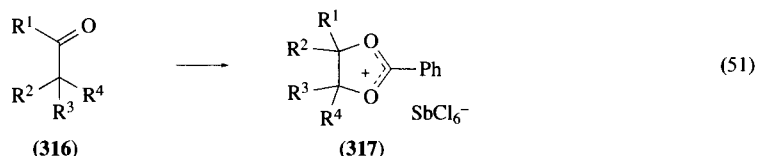


3.10.8.3 Two-bond Formation from [3 + 2] Atom Fragments

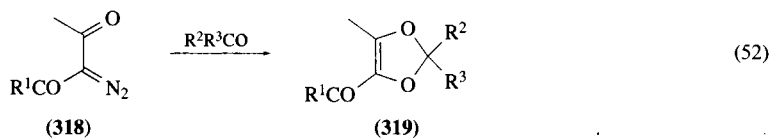
New approaches of this type to fully conjugated systems include reaction of diazo ketones (**312**) with PhCO₂Tf to give the dioxolium salts (**313**) <87JOC375> and reaction of bromoacetyl coumarin (**314**) with thioamides to afford the oxathiolium salts (**315**) <83EGP203320> (Scheme 19). The formation of 1,3-dioxolan-2-ylum salts (**317**) by treatment of ketones (**316**) with PhCO⁺ SbCl₆[−], which involves a retro-pinacol rearrangement, has been examined in detail (Equation (51)) <83ZOR458, 85URP1168560, 86DOK(287)862, 86ZOR1173>.

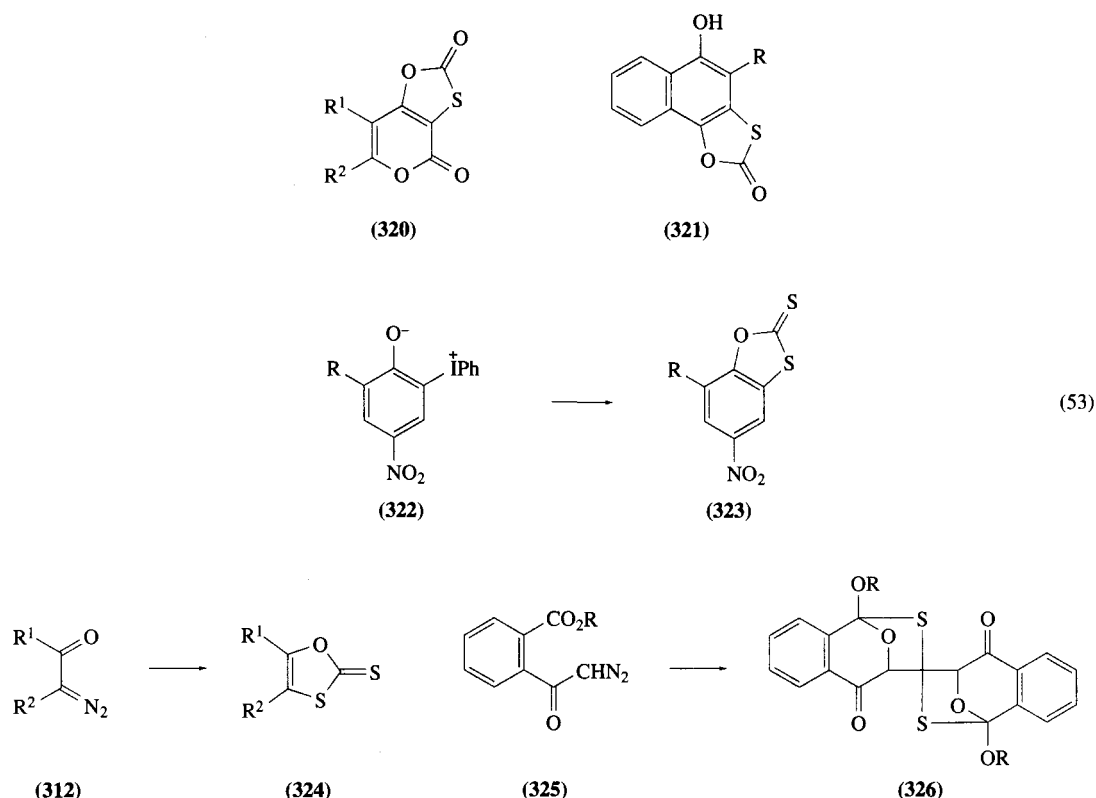


Scheme 19



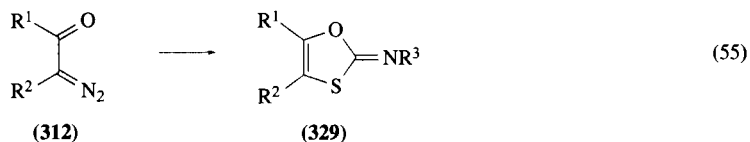
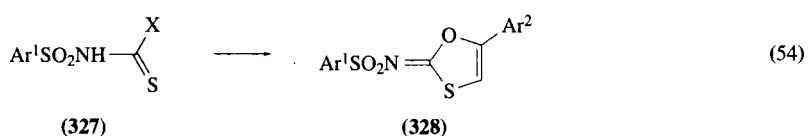
Copper-catalyzed decomposition of 2-diazo-1,3-dicarbonyl compounds (**318**) in the presence of aldehydes or ketones gives the 4-acyl-1,3-dioxoles (**319**) (Equation (52)) <81TL4181, 85JOC3445>. The 1,3-oxathiole (**79**) mentioned earlier was prepared by rhodium catalyzed decomposition of diethyl diazomalonate in the presence of di-*t*-butylthioketene <89TL1249>. The pyranone-fused oxathiolones (**320**) can be prepared from the corresponding 4-hydroxy-2-pyranones with ClCOSCl <88EGP258988> and treatment of 1,4-naphthoquinones with thiourea affords (**321**) <81JPR776>. Photochemical reaction of the zwitterionic iodonium phenoxides (**322**) in the presence of CS₂ affords the benzoxathiole-2-thiones (**323**) (Equation (53)) <85JOC1509>. Rhodium catalyzed decomposition of α-diazo ketones (**312**) in the presence of CS₂ generally gives (**324**) but where R¹ is an *o*-alkoxycarbonylphenyl group as in (**325**), the ester interacts with the carbenoid to give a carbonyl ylide which then undergoes two-fold dipolar cycloaddition with CS₂ to afford the spiro bis(oxathiolanes) (**326**) (Scheme 20) <90BCJ3096, 91BCJ771>.



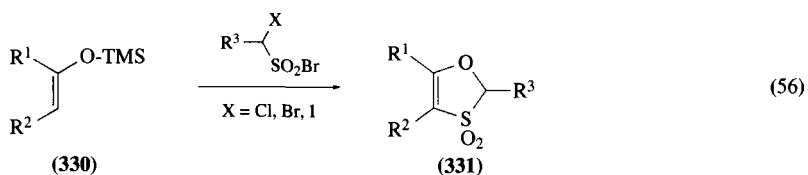


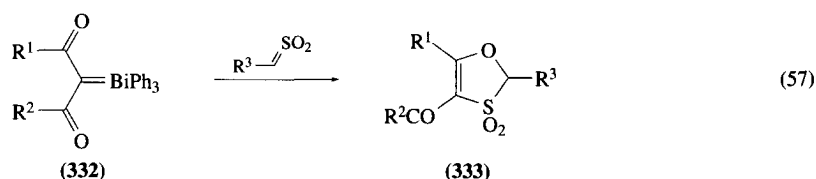
Scheme 20

The standard method for formation of 2-imino-1,3-oxathioles (**328**) is condensation of a substituted phenacyl bromide, $\text{Ar}^2\text{COCH}_2\text{Br}$, with either a dithiocarbamate (**327**; $\text{X} = \text{SR}$) [83PHA441, 84EGP215313] or a thiourea (**327**; $\text{X} = \text{NMe}_2$) [92MI 310-02] (Equation (54)). Compounds of this type can also be prepared from rhodium-catalyzed decomposition of an α -diazo ketone (**312**) in the presence of an isothiocyanate, R^3NCS to give (**329**) (Equation (55)) [92BCJ3088].

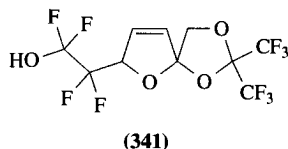
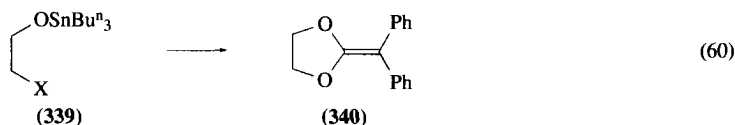
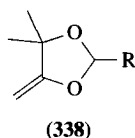
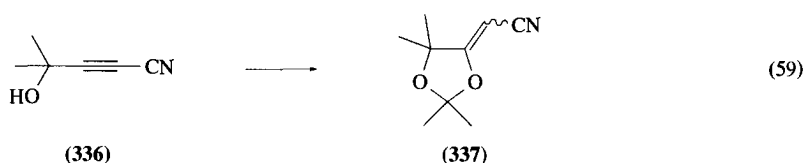
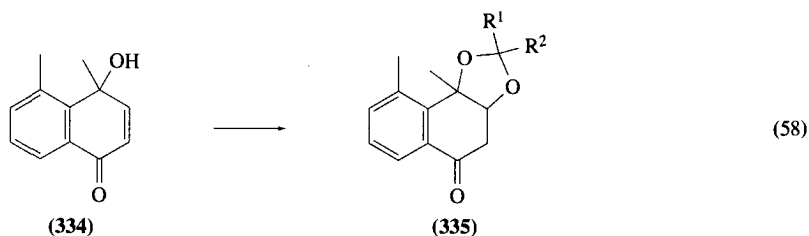


The 1,3-oxathiole 3,3-dioxides (**331**) are formed by treatment of a silyl enol ether (**330**) with an α -halosulfonyl bromide followed by dbn (Equation (56)) [84JOC3664] and the similar compounds (**333**) can be prepared by reaction of the stabilized bismuthonium ylides (**332**) with a sulfene (Equation (57)) [89CC1749].

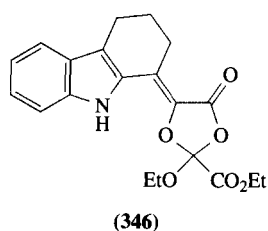
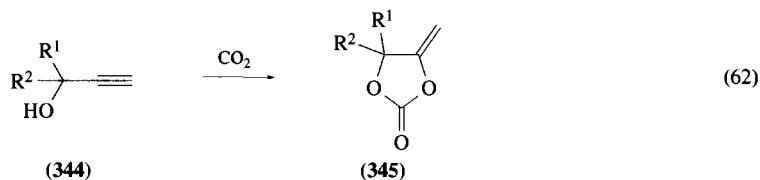
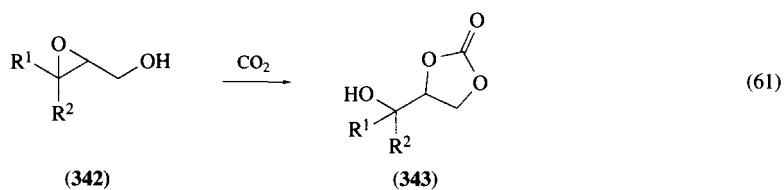




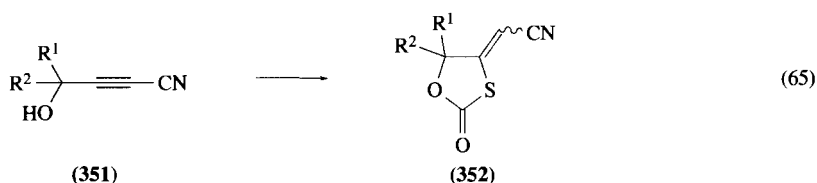
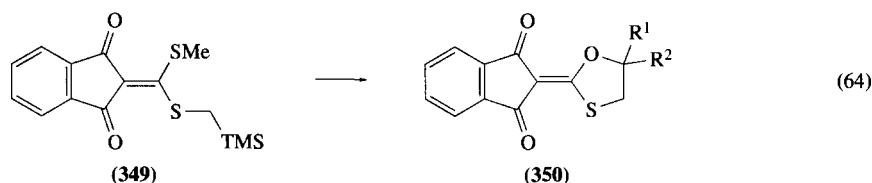
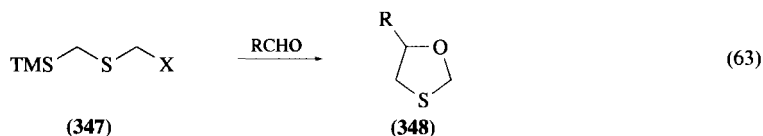
Only a few syntheses of 1,3-dioxolanes are of this type. The acid-catalyzed addition of carbonyl compounds to γ -hydroxycyclohexenones such as (334) gives the dioxolanes (335) in up to 92% yield (Equation (58)) <85S29>. Treatment of the acetylenic alcohol (336) with aqueous LiOH affords (337) whose yield is increased by adding acetone (Equation (59)) <89IZV1421>. 2,2-Dimethylcyclopropanone reacts with aldehydes to give the 4-methylene-1,3-dioxolanes (338) <70JOC2058>. Treatment of the 2-haloethoxy tin compounds (339) with diphenylketene gives (340) (Equation (60)) <86BCJ4000>. The anomalous product obtained from reaction of 2-furylmethanol with hexafluoroacetone has the spiro dioxolane structure (341) <90IZV64>. A variety of halogenated alkenes react with $\text{F}_2\text{C}(\text{OF})_2$ to give the corresponding 2,2-difluoro-1,3-dioxolanes <91EUP460948, 95JFC(71)111>.

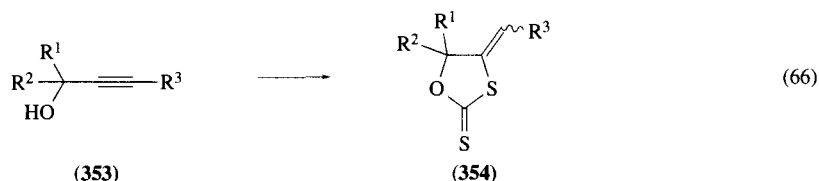


Carboxylation of the 2,3-epoxyalcohols (342) can be achieved at atmospheric pressure using Cs_2CO_3 and molecular sieves to afford (343) (Equation (61)) <88TL6389>. The carboxylation of acetylenic alcohols (344) to give methylenedioxolanones (345) proceeds well when catalyzed either by a mixture of copper and quaternary ammonium or phosphonium salts <86GEP3433403> or by a phosphine (Equation (62)) <89TL3981, 91JCS(P1)3271>. Catalysis of this reaction by a palladium salt allows subsequent alkylation at the exocyclic methylene group by allyl or aryl halides <86JOC5499, 90JMOC1>. The remarkable product (346) is obtained directly from tetrahydrocarbazole by treatment with oxalyl chloride followed by ethanol <83CB2165>.

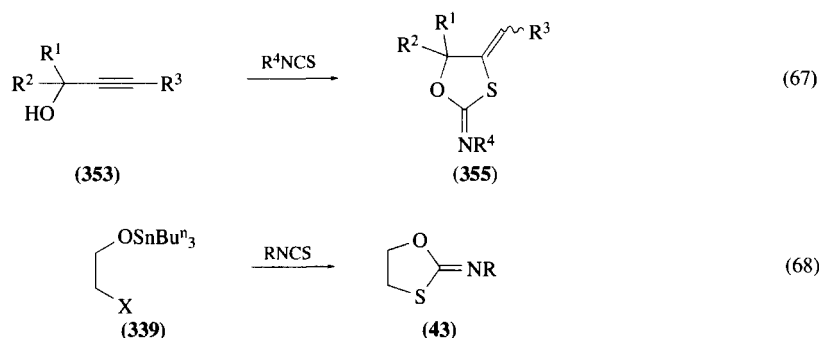


Treatment of (347; X = Cl) with CsF leads to generation of the thiocarbonyl ylide which can be trapped by addition to aldehydes to give 5-substituted 1,3-oxathiolanes (348) (Equation (63)) <87CC1442, 89EUP307000>. The analogous reaction also occurs with (347; X = OMe) although in this case treatment with sulfuric acid is necessary to complete the ring closure <92CL1073, 94JAP0680662>. A similar process is involved in the reaction of (349) with CsF and a carbonyl compound to afford (350) (Equation (64)) <94TL3555>. Reaction of the acetylenic alcohols (351) with HSCN gives the 1,3-oxathiolan-2-ones (352) (Equation (65)) <91ZOR188> and the dimethyl compound (336) reacts similarly with KSCN <88ZOR2454>, although as will be seen in Section 3.10.8.4, (351) generally gives more complex products with metal thiocyanates. In a similar process, a variety of acetylenic alcohols (353) undergo cyclization to 1,3-oxathiolane-2-thiones (354) when treated with a base followed by CS₂ (Equation (66)) <68CPB914, 68CPB1324, 69CPB2442, 83TL339, 92SC1351>. The epoxyalcohols (342) react with NaH or KH and CS₂ to give the 1,3-oxathiolane-2-thiones corresponding to (343) <91CC1421>.



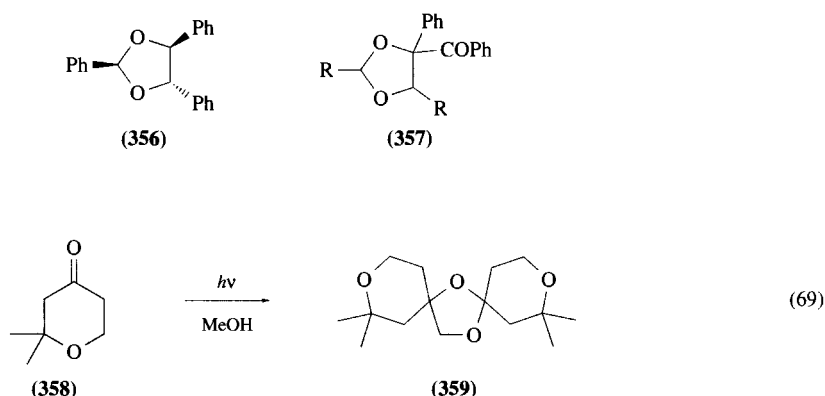


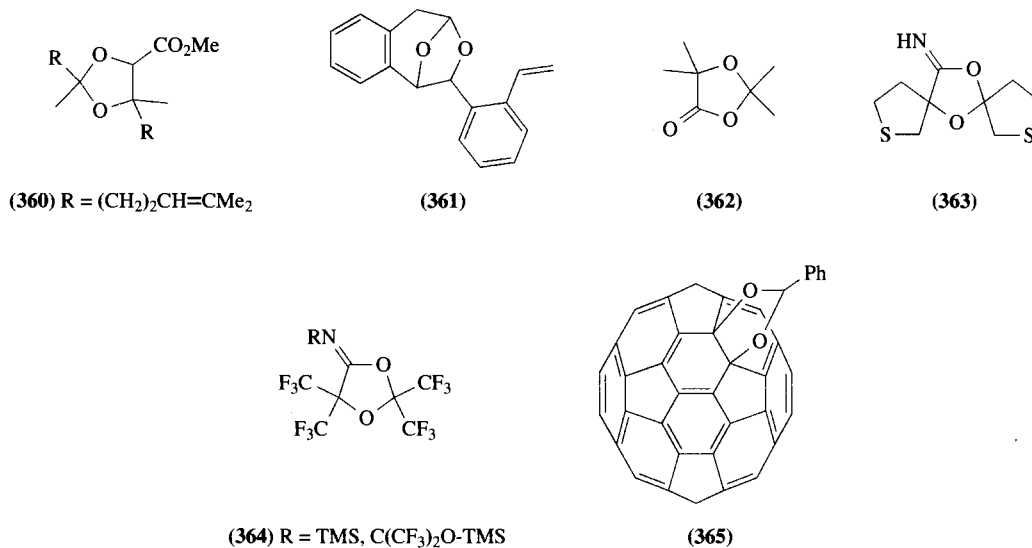
The acetylenic alcohols (353) also react with isothiocyanates to give the 2-imino-1,3-oxathiolanes (355), although in some cases the isomeric oxazolidine-2-thiones may also be formed (Equation (67)) <86CCC1119, 86IZV2491, 90MIP1039588>. Reaction of the haloethoxy tin compounds (339) with isothiocyanates similarly gives either the 2-iminooxathiolanes (43) or the oxazolidine-2-thiones depending on the conditions used (Equation (68)) <86BCJ341>.



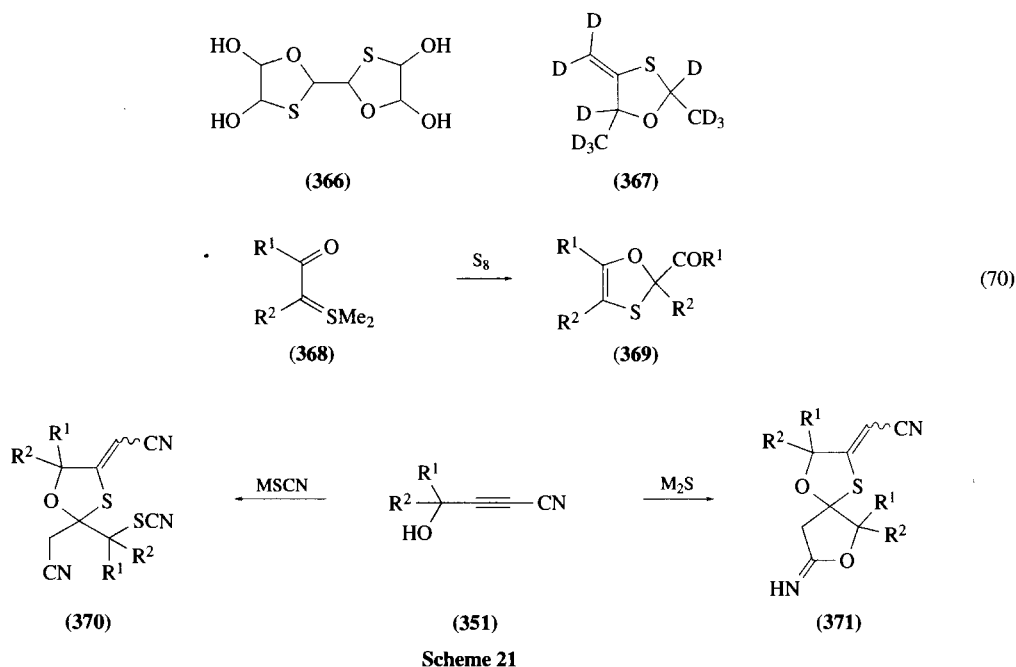
3.10.8.4 Three-bond Formation

Reactions of this type, which were not covered in CHEC-I, are relatively rare but they do provide access to some unusual 1,3-dioxolanes and oxathiolanes. Reductive coupling of benzaldehyde with NbCl_3 affords (356) in 65% yield <92T3867> while reductive coupling of benzil with an aldehyde RCHO mediated by TiCl_3 gives (357) <88SC2281>. Photolysis of the tetrahydropyranone (358) with TiCl_4 in methanol gives the spiro dioxolane (359) in which the extra carbon atom has come from the solvent (Equation (69)) <86IZV1607>. Copper bronze-catalyzed decomposition of methyl diazoacetate in the presence of the γ,δ -unsaturated ketone, RCOMe , initially gives a carbonyl ylide which then adds to a second molecule of the ketone to give (360) <88CI(L)631>. Photochemical dimerization of *o*-vinylbenzaldehyde occurs in an unusual mode to give (361) <93CC1828>. Palladium catalyzed carbonylation of isopropenyl acetate gives the 2:1 acetone/ CO adduct (362) <93CL1615>. Cyanide induced dimerization of ketones can provide access to 4-imino-1,3-dioxolanes as illustrated by the reaction of tetrahydrothiophen-3-one with NaCN to give (363) <86CI(L)361> and the reaction of hexafluoroacetone with TMS-CN to afford a mixture of iminodioxolanes (364) <86CB771, 86CZ211>. The remarkable reaction of C_{60} with benzyl alcohol and its sodium salt in air proceeds by a radical mechanism to give the phenyldioxolane (365) in which addition has occurred across a 6-6 ring-junction double bond <95CC1071>.





Reaction of aqueous glyoxal with H_2S gives a single stereoisomer of the bis(oxathiolane) (366) <92CC1035>. Heating a mixture of calcium carbide, Na_2S , D_2O and HMPA in an autoclave directly gives the deuterated methyleneoxathiolane (367) in 9% yield <82ZOR451>. Treatment of the β -oxo sulfonium ylides (368) with sulfur gives the oxathioles (369) (Equation (70)) <85TL2201>. It was mentioned earlier that the acetylenic alcohols (351) react with $HSCN$ to give 1,3-oxathiolan-2-ones (352), but with metal thiocyanates such as $NaSCN$, $KSCN$ or NH_4SCN , the reaction takes a more complex course to give (370) (Scheme 21) <89ZOR221, 91ZOR188>. In a related process, treatment of (351) with Li_2S or Na_2S gives the spiro oxathiolanes (371) <90SUL209>.

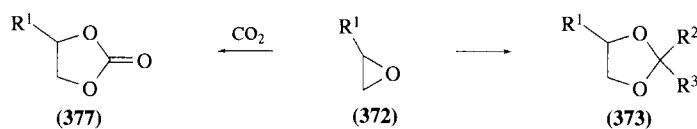


3.10.9 RING SYNTHESIS BY TRANSFORMATION OF OTHER HETEROCYCLIC RINGS

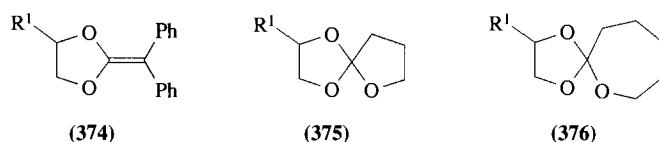
3.10.9.1 Three-membered Rings

As described in the first edition <84CHEC-I(6)749>, reaction of epoxides (372) with carbonyl compounds, R^2COR^3 , provides efficient access to 1,3-dioxolanes (373) (Scheme 22) and new catalysts for

this process include silicotungstic acid <83JAP5839680>, maleic anhydride under photolytic conditions <84ZOR421>, *N*-benzylpyridinium <90CL2019> and quaternary ammonium salts <92NKK166>, HBF_4 <91KGS33>, zeolites <91MI 310-01> and montmorillonite clay <92JMOC101>. Diphenylketene reacts with epoxides (372) to give the 2-alkylidene-1,3-dioxolanes (374) <61CB3287> and this reaction proceeds well in the presence of Bu^n_3SnI in HMPA <86BCJ4000>. The reaction also occurs with other types of carbonyl compound including γ -butyrolactone <82JAP(K)24388, 82MI 310-01, 83JAP58164592, 88URP1397449> and ε -caprolactone <88JAP63295587>, which give the spiro compounds (375) and (376), respectively, and alkyl formates which give the 2-alkoxy-1,3-dioxolanes <82EUP67361>.

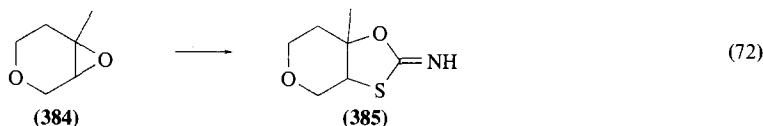
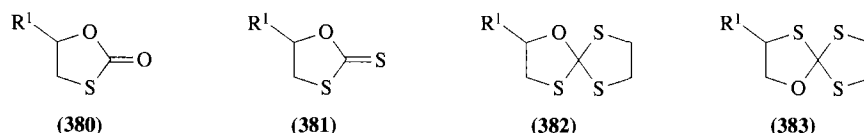
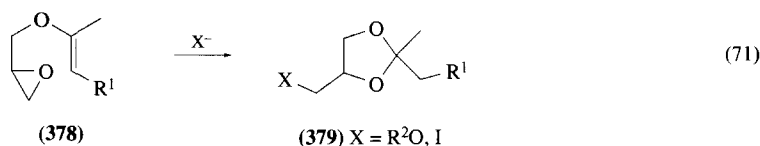


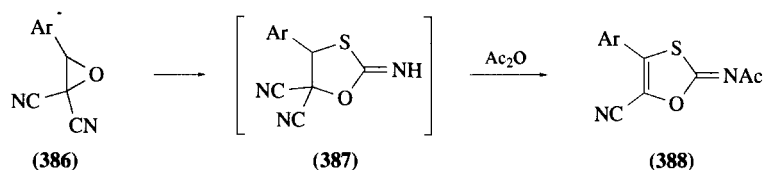
Scheme 22



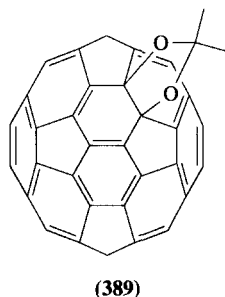
The reaction of epoxides (372) with CO_2 to afford 1,3-dioxolan-2-ones (377) (Scheme 22) was mentioned in CHEC-I but, as befits its industrial importance, there has been continued interest in the introduction of new improved catalysts for the process and these include Ph_3BiBr_2 <82JAP(K)49614>, TaCl_5 and pyridine <83EUP69494>, organoselenium compounds <83JAP58222079>, quaternary phosphonium salts <84JAP5913776>, alkali metal salts <84M205>, phosphines <84MIP8403701>, $(\text{Ph}_3\text{P})_4\text{Pd}$ <85CL199>, $\text{Bu}^n_2\text{SnBr}_2$ <86CE169>, ytterbium naphthalenide <89MI 310-02> and metal phthalocyanines <94USP5283356>. β -Butyrolactone can also be used as a CO_2 donor for the reaction <86TL3741>. Chiral epoxides have been carboxylated without racemization <86CB1090> and use of a chiral catalyst allows the reaction to proceed with kinetic resolution to give the dioxolanone and unreacted epoxide in up to 39% and 27% *ee*, respectively <94SL69>.

Nucleophilic attack on epoxides (378) by alkoxides or NaI gives the dioxolanes (379) (Equation (71)) <82S758>. Epoxides (372) react with CS_2 in the presence of Et_3N to give products including the oxathiolanones (380) and oxathiolanethiones (381) <88BCJ921> and 1,3-dithiolane-2-thione similarly gives (382) and (383) <91HCA1500>. Treatment of the epoxide (384) with KSCN gives the 2-imino-1,3-oxathiolane (385) (Equation (72)) <92KGS1039>. The initial products (387) similarly formed from (386) are unstable towards isomerization to thiazolidin-2-ones but can be trapped by added Ac_2O to give (388) (Scheme 23) <93JCS(P1)351>. Reaction of C_{60} with dimethyldioxirane gives (389) in addition to C_{60}O <92AG(E)351>.



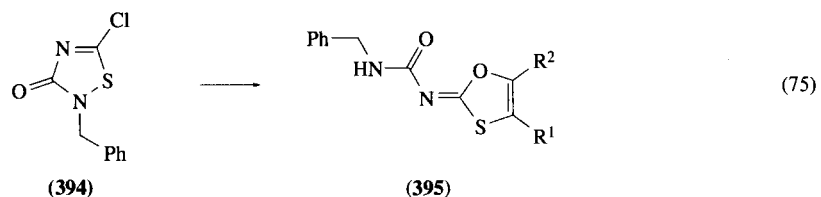
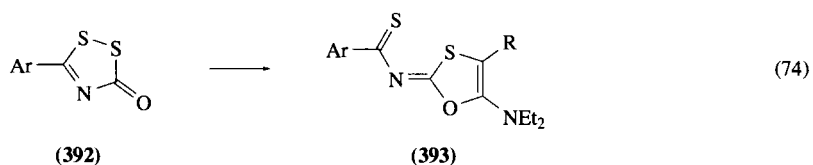
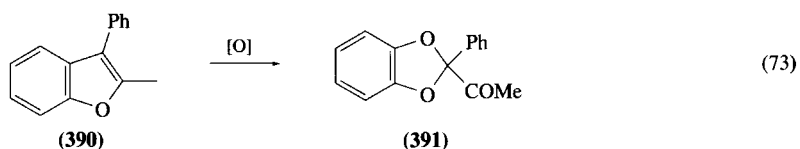


Scheme 23



3.10.9.2 Five-membered Rings

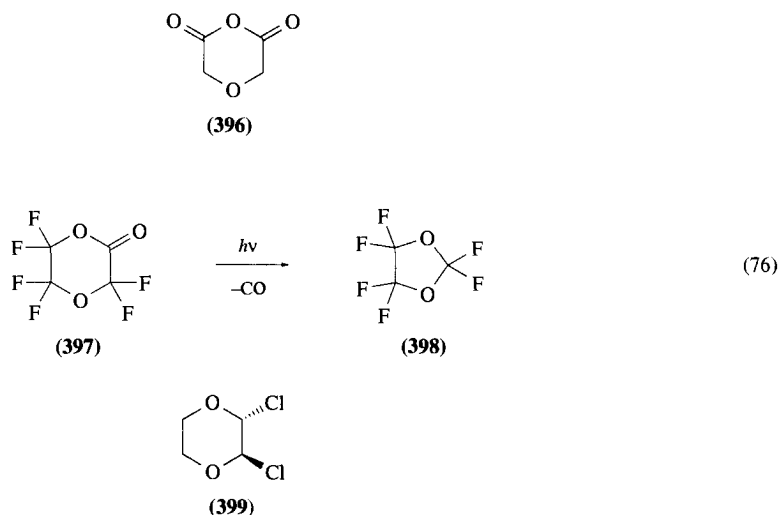
Treatment of 2-ethoxy-1,3-oxathiolane with ketones in the presence of ZnCl_2 or HgCl_2 results in transthioketalization to give 2,2-disubstituted oxathiolanes <81BCJ3237>. Transthioketalization also occurs upon treatment of dioxolane-containing polymers with 2-thioethanol to give the corresponding oxathiolane-containing polymers <94CC2063>. Reaction of 2-alkyl-1,3-dithiolanes with MeOSO_2F followed by 2-thioethanol gives the corresponding 2-alkyloxathiolanes <75TL3267>. 1,3-Dioxolan-2-one (**25**) transfers a CO unit to diols to give the corresponding 1,3-dioxolan-2-ones <81JAP81167682> and also transforms ketones into the corresponding 2,2-disubstituted 1,3-dioxolanes <82JAP57112387>. Reaction of (**377**) with diphenylketene similarly affords (**374**) <61CB3287>. Oxidation of the benzofuran (**390**) using a variety of reagents gives the benzodioxole (**391**) (Equation (73)) <94T8393>. The dithiazolone (**392**) undergoes cycloaddition to ynamines, $\text{RC}\equiv\text{CNEt}_2$, to give 2-imino-1,3-oxathioles (**393**) (Equation (74)) <85ACS(B)103>. Reaction of the thiadiazolone (**394**) with the enolates derived from $\text{R}^1\text{CH}_2\text{COR}^2$ gives 2-imino-1,3-oxathioles (**395**) (Equation (75)) <94JCS(P1)1263>.



3.10.9.3 Six-membered Rings

Examples of this relatively rare approach, which was not covered in CHEC-I, include vapor-phase pyrolysis of the dioxanedione (**396**) over alumina or manganese phosphate/carbon which

results in loss of CO to give 1,3-dioxolan-4-one (**26**) <40GEP737623> and photochemical decarbonylation of (**397**) to give (**398**) in 70% yield (Equation (76)) <69JOC3438>. The chlorinated bis(dioxolane) (**52**) described earlier is formed from (**399**) by treatment with sulfuric acid <90BCJ2450>. Radical isomerization of 1,4-oxathiane in the presence of Bu^tOOH gives 2-methyl-1,3-oxathiolane <92URP1735292>.

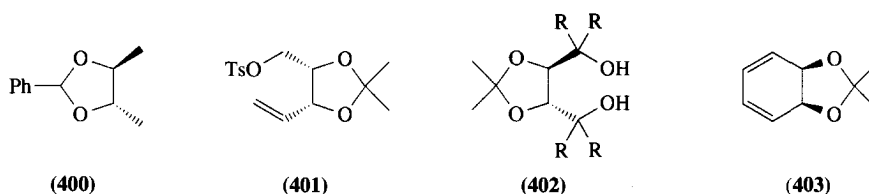


3.10.10 BEST METHODS OF SYNTHESIS

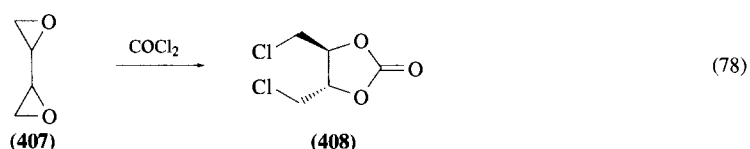
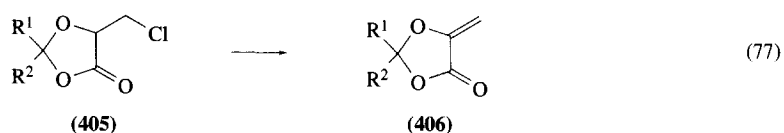
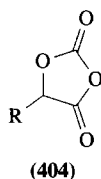
The main methods available for synthesis of the fully conjugated 1,3-dioxolium and 1,3-oxathiolium systems (**1**) and (**2**) and their benzo analogues (**3**) and (**4**) were covered in CHEC-I <84CHEC-I(6)749> and have been comprehensively reviewed <93HOU(E8a)1, 93HOU(E8a)10>. The new route to dioxolium salts (**313**) mentioned in Section 3.10.8.3 is comparable to previous methods for these compounds. The best route to the 2-substituted derivatives of (**4**), the salts (**262**), was described in Section 3.10.8.2 <86S1074>. The mesoionic 1,3-oxathiolium-4- and -5-olates were also covered in CHEC-I, and the new 1,3-dioxolium-4-olates (**210**) have only been generated from α -diazo anhydrides as described in Section 3.10.8.1.

Access to 1,3-dioxole (**7**), 1,3-dioxol-2-one (**8**), 1,3-benzodioxole (**10**), 1,3-benzodioxol-2-one (**11**) and their substituted derivatives was discussed in CHEC-I. Among the new methods to the derived imines and thiones, those based on the tin compounds (**270**) and described in Section 3.10.8.2 are possibly the best. The diazo compound-based preparations of (**273**) and (**275**) (Section 3.10.8.2) represent useful approaches to 1,3-oxathioles, and the corresponding imines (**329**) and thiones (**324**) are probably also best prepared from the diazo compounds (**312**) as described in Section 3.10.8.3.

Most of the standard methods for access to the fully saturated 1,3-dioxolanes (**24**) and 1,3-oxathiolanes (**31**) and the derived -2-ones are well established and were fully discussed in CHEC-I. As befits their importance for asymmetric synthesis, efficient routes to a number of chiral 1,3-dioxolanes have been developed, including preparation of (**400**) from tartaric acid <84SC1087>, (**203**) from serine in three steps <85MIP8503704>, (**401**) from D-ribonolactone and either it or its enantiomer by Sharpless epoxidation <86AG(E)87>, and the bidentate diol ligands (**402**) <91C238>. Reliable procedures for the preparation of (*R*)-glyceraldehyde acetonide (**194**) <93OS(72)6> and its (*S*)-enantiomer <93OS(72)1> have been described. A new efficient procedure for the formation of (**403**) from the corresponding diol has also been reported <89OPP255>.



The formation of 1,3-dioxolan-4-ones (**298**) from the silyl compounds (**297**) as described in Section 3.10.8.2 offers a competitive alternative to the conventional method from the α -hydroxy acids, and a further mild method involves treatment of the latter with an aldehyde dimethyl acetal and pyridinium tosylate <91TL1441>. The 1,3-dioxolane-2,4-diones (**404**) are efficiently prepared from α -hydroxy acids and diphosgene, $\text{Cl}_3\text{COCOC}_3\text{Cl}$ <89H(29)975>. The first preparation of 4-methylene-1,3-dioxolan-2-one (**54**), mentioned in Section 3.10.3.3.1, proceeds in good overall yield from 3-chloropropane-1,2-diol. Derivatives of the isomeric 5-methylene-1,3-dioxolan-4-one system (**406**) can be prepared by Et_3N treatment of the compounds (**405**) obtained from β -chlorolactic acid and a carbonyl compound (Equation (77)) <85DOK(284)632, 85KGS1316>. Reaction of the bis(epoxide) (**407**) of butadiene with phosgene and pyridine gives (**408**) in 75% yield (Equation (78)) <93SC847>.



The parent 2-imino-1,3-dioxolane (**29**; $\text{R} = \text{H}$) was first prepared by reaction of the *N*-chloro analogue with NaNH_2 in liquid ammonia <74JOC3442> and the formation of *N*-substituted analogues is best achieved from the tin compound (**300**) and an isothiocyanate as described in Section 3.10.8.2. The sulfur analogue (**310**) similarly gives good yields of the 2-imino-1,3-oxathiolanes by reaction with isothiocyanates and of 1,3-oxathiolane-2-thione (**42**) with CS_2 . An early but efficient preparation of 1,3-oxathiolan-2-one (**32**) involves reaction of the sodium salt of 2-thioethanol with ethyl chloroformate and thermal cyclization of the resulting thiocarbonate <61JOC5122>. 1,3-Oxathiolane 3-oxide (**38**) is prepared in 83% yield by NaIO_4 oxidation of the oxathiolane (**31**) <73IJS397>.

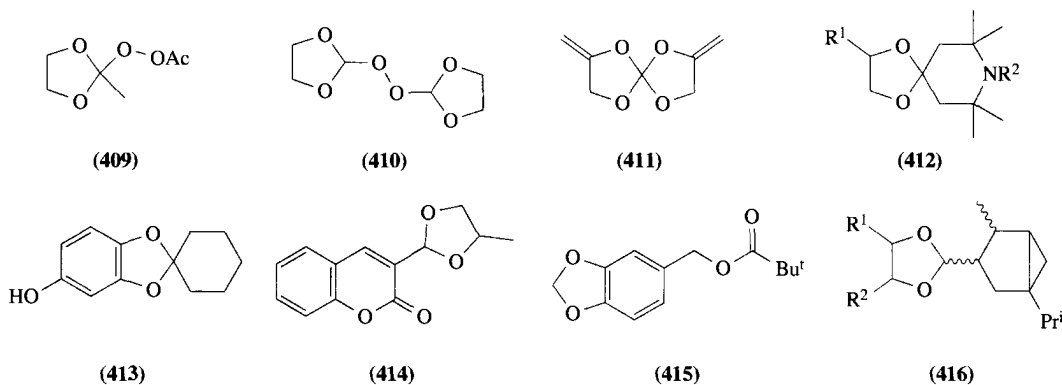
3.10.11 APPLICATIONS

3.10.11.1 Uses in the Polymer, Food, and Perfumery Industries

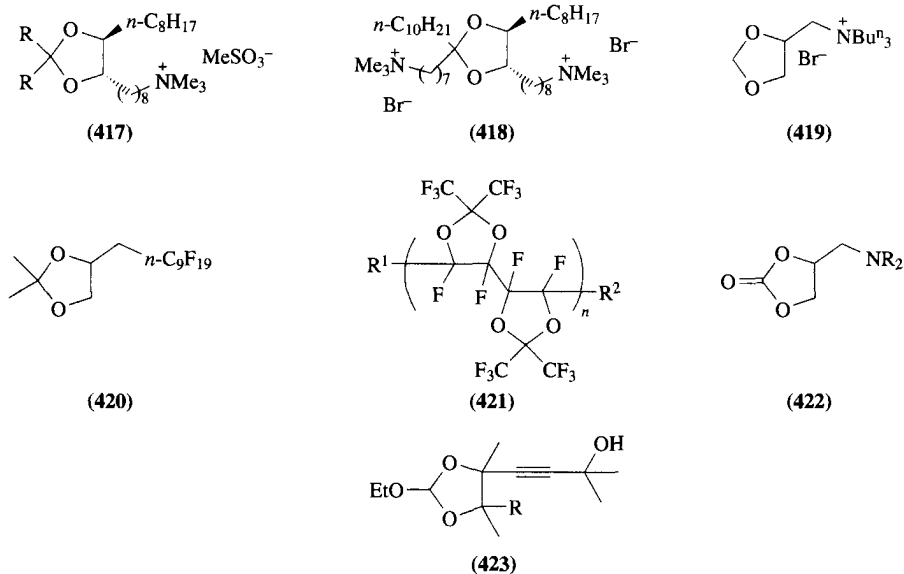
The kinetics of thermal decomposition of the dioxolane peroxyacetate (**409**) have been studied and its performance as a polymerization initiator evaluated <83ZPK2704>. The peroxide (**410**) has also been used as an initiator <84URP1068436>. The spiro bis(methylenedioxolane) (**411**) has been used as a monomer for radical polymerization <84JAP59161382>. A series of alkylidene bis(1,3-benzodioxol-2-ones) have found use as flame retardant polymer additives <82USP4329287> and piperidone ketals such as (**412**) are useful as light stabilizers for polymers <81JAP81138189>. The compounds (**413**) <83MIP533866> and (**414**) <93URP1806141> have been applied as food antioxidants. The benzodioxole-containing ester (**415**) has been used as a flavoring <84USP4430354> and compounds (**416**) are useful as perfume ingredients <83GEP3141327>.

3.10.11.2 Applications Based on Physical and Chiroptical Properties

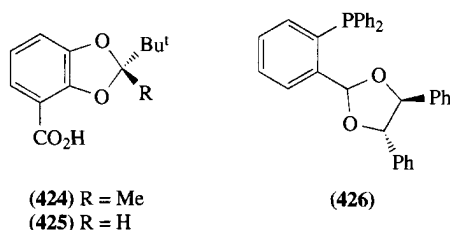
The ammonium salts (**417**) <90TL449> and (**418**) <93TL6985> have been introduced as cleavable surfactants which hydrolyze to give surfactants of higher critical micelle concentration. Dioxolane-



containing quaternary ammonium salts such as (419) are effective as phase-transfer catalysts <92ZOR2325>. Fluorinated dioxolane (420) is useful as a surface-tension lowering agent <83JAP5849376> and the fluorinated oligomers (421) have been evaluated as lubricants, hydraulic fluids, heat-transfer agents, plasticizers and surfactants <83USP4409393>. A range of aminomethyl dioxolanones (422) can be used as high dielectric constant solvents <86JAP6110573, 86JAP6136276>. The acetylenic alcohols (423) have found application for coal flotation <85URP1198074>.

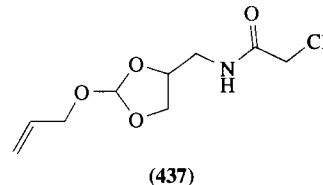
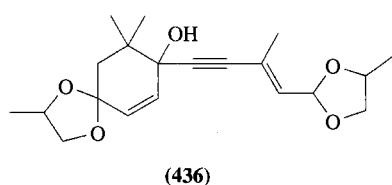
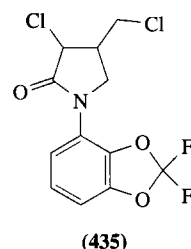
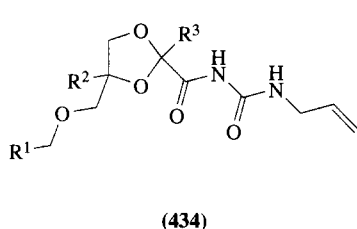
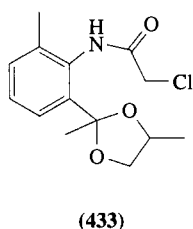
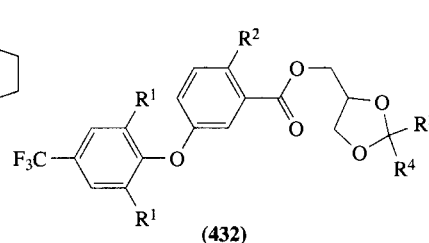
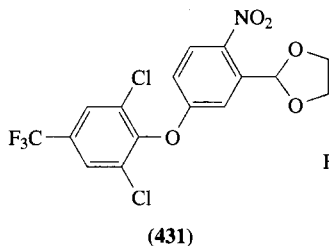
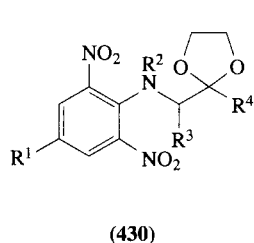
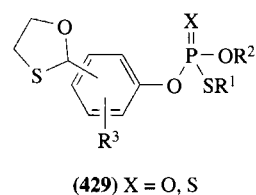
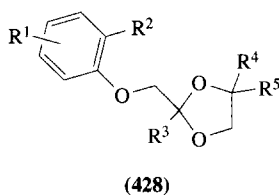
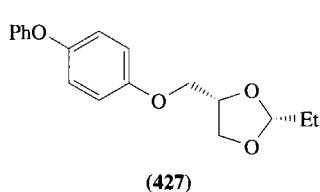


The benzodioxole carboxylic acid (424) has been used as a chiral derivatizing agent to allow determination of the *ee* of alcohols and amines by NMR and HPLC <89TL5277> and the analogue (425) has been used for this purpose <92JAP04346982> and as a derivatizing agent for TLC resolution of amino acids <93TA1431>. The chiral dioxolane diols (402; R = Ph, 1-naphthyl) have been applied both as NMR shift reagents <92HCA438> and as hosts for solid host-guest complexes <92JOC6825>. Dioxolanes such as (426) are effective ligands for palladium-catalyzed malonate alkylation with allylic acetates <94SL551>.



3.10.11.3 Agrochemical and Pesticidal Applications

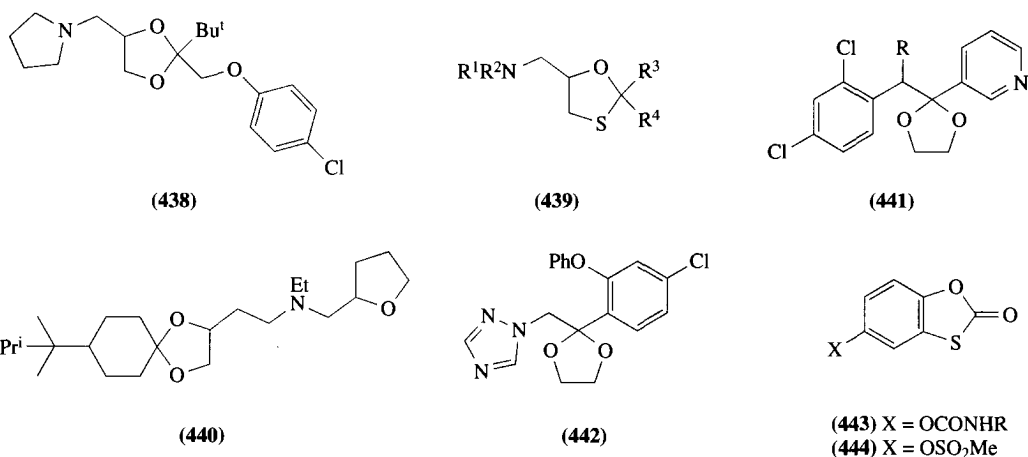
A range of 1,3-dioxolanes bearing aryloxymethyl groups either at the 4-position as in (427) <92EUP501912> or at the 2-position as in (428) <93EUP559612> have been used as pesticides, and 1,3-oxathiolane-containing compounds of the type (429) have insecticidal and acaricidal activity <81USP4262012>. Effective 1,3-dioxolane-containing herbicides include (430) <83USP4397677>, (431) <82GEP3118371>, (432) <81USP4293329>, (433) <82BEP891302> and (434) <81BRP1596292>, and the 2,2-difluoro-1,3-benzodioxole (435) is also active in this application <93MIP9324483>. A range of 1,3-enyne-containing dioxolane compounds such as (436) have proved effective as plant growth regulators <83EUP78509, 83GEP3143720, 83GEP3143722>. Simple dioxolanes such as (437) are used as herbicide antidotes, protecting crops from injury by herbicides <83EUP92517, 83USP4406686>.



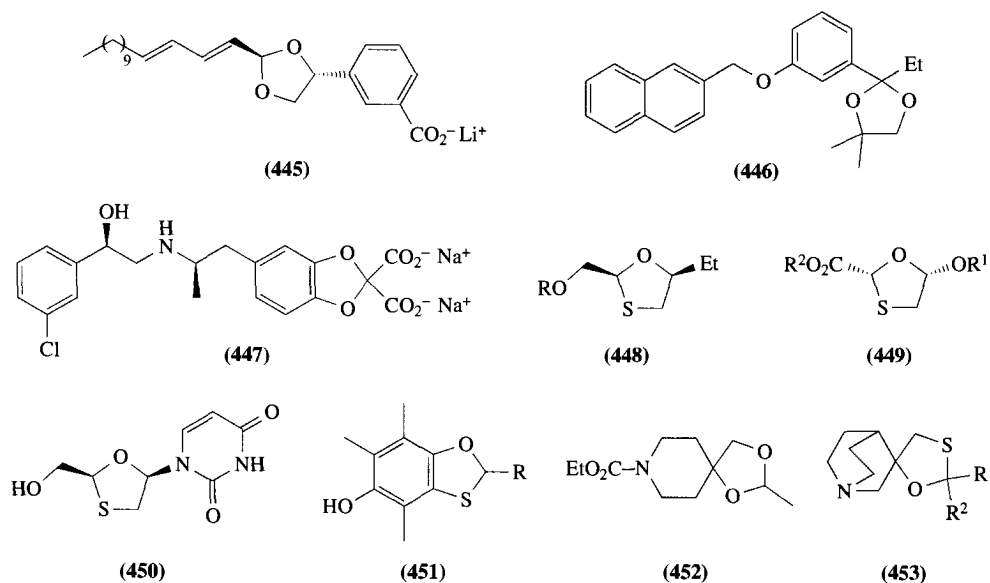
A variety of 4-aminomethyl-1,3-dioxolanes such as (438) have fungicidal activity <83GEP3305769, 85GEP3328151> and the corresponding oxathiolanes (439) are also effective <85GEP3324769>. Further examples of agricultural fungicides include (440) <93MIP9302074> and (441) <82EUP62238> and compounds of the latter type are also microbicides <84EUP129507>. A range of 2-triazolylmethyl-1,3-dioxolanes such as (442) have been used as fungicides and bactericides <84JAP59139380, 86GEP3529646, 86JAP6137783>. The simple 1,3-benzoxathiol-2-ones (443) <82USP4349685> and (444) <85JAP6006680> also show fungicidal activity.

3.10.11.4 Medical and Pharmaceutical Applications

The perfluorinated bis(dioxolane) (421; $R^1 = R^2 = F$, $n = 1$) has been used as a ^{19}F NMR imaging agent for tumors <91USP5070213>. The long-chain dioxolane (445) inhibits leukotriene- B_4 production in tumor cells <90EUP379191> and (446) is an inhibitor of 5-lipoxygenase <90EUP375457>. Benzo-

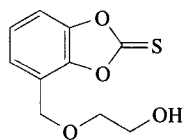
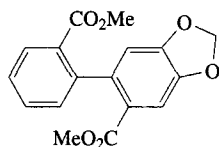
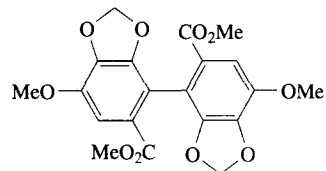
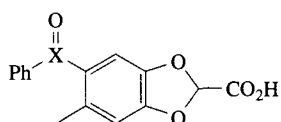


dioxole-2,2-dicarboxylates such as (447) and the corresponding dimethyl esters are effective anti-obesity agents <92JMC3081, 92USP5106867, 94EUP608568>. A range of 1,3-oxathiolane derivatives such as (448) <91S1046>, (449) and its enantiomer <93MI 310-06, 94MI 310-01> have been prepared in enantiomerically pure form with a view to synthesis of nucleoside analogues such as (450) <94MIP9414802>. The benzoxathioles (451) have promising antiasthmatic activity <90JMC1491>. Spiro dioxolanes such as (452) <86EUP189370> and oxathiolanes such as (453) <86JAP61280497> have been patented for the treatment of Alzheimer's disease.

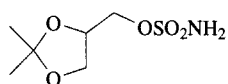
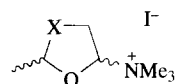
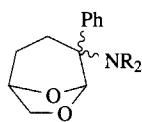
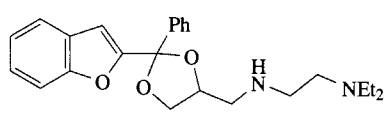
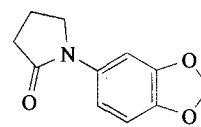


The benzodioxole-2-thione (454) has been used for the treatment of liver disease <93JAP0543570> and a range of benzodioxole compounds such as (455) and (456) are effective liver disorder improvers <85JAP60209582, 92JAP04193875, 92JAP04202153, 92JAP04202192>. A variety of simple benzodioxole-2-carboxylic acid derivatives such as (457) and (458) have been examined in detail as diuretic and uricosuric agents <82EUP64026, 82EUP64027, 84EUP107622, 84EUP107623, 85USP4517184, 86USP4600709>. Dioxolane sulfamates such as (459) are useful as anticonvulsants <86USP4591601>. The different possible enantiomers and diastereomers of the dioxolane, oxathiolane, and its *S*-oxides (460) have been separated and evaluated for their cholinergic agonist activity <86JMC1610, 87JMC1934>. The bicyclic dioxolane (461) has central nervous system (CNS) activity <94AP(327)405>. The 2,4-bis-(alkylidene)-1,3-oxathiolan-5-ones (107) mentioned in Section 3.10.6.2 have been found to have activity as *in vivo* chymotrypsin inhibitors <82JAP57193474>, antiinflammatory agents <85JAP60146887>, and antihypertensives <83JAP58164587>. A series of 2-benzofuryl-4-aminomethyl-1,3-dioxolanes such

as **(462)** affect the cardiovascular system and offer protection against fibrillation, arrhythmia, and angina <82MIP505979, 82MIP506904>. The methylenedioxyphenylpyrrolidinone **(463)** inhibits blood platelet aggregation <84GEP3325653>.

**(454)****(455)****(456)**

(457) X = C
(458) X = SO

**(459)****(460)** X = O, S, SO, SO₂**(461)****(462)****(463)**

3.11

1,2-Dithioles

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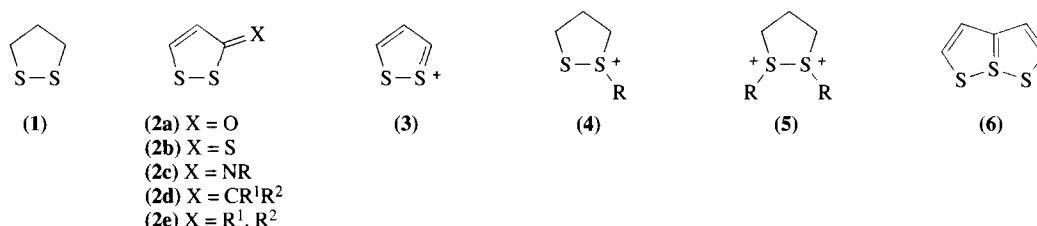
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3.11.1 INTRODUCTION

The chemistry of the 1,2-dithioles and related compounds was covered in the first edition of *Comprehensive Heterocyclic Chemistry* (CHEC-I), <CHEC-I(6)783> and a review, published in 1990, of some systems containing the 1,2-dithiolane ring <90SR257>. Reviews of other 1,2-dithioles were published in the early 1980s <80SR1, 82AHC(31)63>. Since 1985 there has been a marked increase in published applications of 1,2-dithioles.

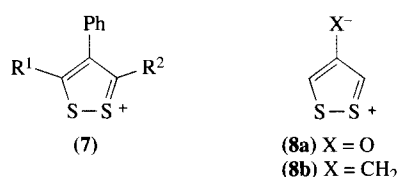
The system possesses two adjacent sulfur atoms in a five-membered ring, with varying degrees of unsaturation. A number of systems containing the fully saturated 1,2-dithiolane system (**1**) are known. While the partially unsaturated 1,2-dithiole system (**2**) is very common as are its derivatives, 1,2-dithiole-3-ones (**2a**), 1,2-dithiole-3-thiones (**2b**), 3-imino-1,2-dithioles (**2c**), and 1,2-dithiole-3-ylidene (**2d**) types. Only a few 1,2-dithioles of type (**2e**) are known. Cationic species include the 1,2-dithiolium system (**3**) and the saturated cations (**4**) and (**5**). The 1,2-dithiole system is an integral part of the 1,2-dithiolo[2,3-*b*]-1,2-dithiole system (**6**), also known as the 1,6,6a λ^4 -trithiapentalene system, covered in CHEC-I <84CHEC-I(6)1049>.



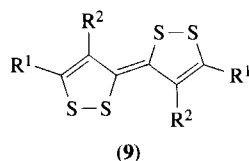
Benzo-, hetero-, cyclopenta-, and other fused derivatives of these are known, especially of systems (**2**)–(**6**).

3.11.2 THEORETICAL METHODS

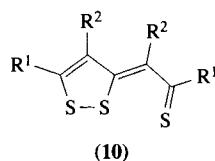
For 1,2-dithiolium ions (**3**), LCGO methods or CNDO/2 (complete neglect of differential overlap) methods suggested only a minor participation of sulfur *d*-orbitals <72TL4165, 73T2339>. In 1991 MNDO (modified neglect of differential overlap) calculations were performed on an excited singlet state of the 4-phenyl-1,2-dithiolium ion (**7**) <91DOK(321)331>. PPP (Pople–Pariser–Parr) type calculations have examined acyclic to ring preferences, color to structure relationships, and substituent effects of 1,2-dithiolium-4-olates (**8a**) and 1,2-dithiolium-4-methylides (**8b**) <87PS(31)109, 88CCC2096>.



A CNDO calculation of electronic spectra for 1,2-dithiole-3-ones (**2a**) and 3-thiones (**2b**) gave good agreement with other data <71BSB311, 72JST(14)95>, and some correlation of the first and second HOMOs and the nucleophilic reactivity of the thione function <92MI 311-01>. Earlier LCAO methods for thiones (**2b**) gave a linear correlation of *n*– π^* transitions, and information on the effect of aryl substituents and the exocyclic sulfur electron density <82AHC(31)63>, and an SCF–LCAO method matched observed and calculated spectra <69T5485>. In some studies of the bis-1,2-dithiole-3-ylidenes (**9**), the LCAO–MO coefficient was determined, and the electrical conductivity was correlated with the electronic structure and overlap of frontier MOs <82CA(97)71636>.

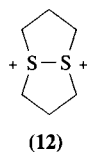
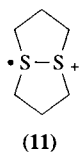


Ab initio 3-21G* and 6-31G* calculations on trithiapentalenes favor a bicyclic structure (6), whereas a monocyclic dithiole structure (10) is favored by SCF calculations <91JA6449>.



A comparison of 1,2-dithiolanes (1) with acyclic dithiols by a molecular mechanics MM2(85) method indicated that the greater stability of the ring, compared with acyclic 1,3-dithiols, is due to the relief of steric interactions, but MM2 methods poorly reflected the experimental value of the dihedral angle <90JA6304>. Conformational studies using a Gaussian 80 program showed that the addition of two hydrogen atoms to the cyclic disulfide caused structural and conformational change, and increased the S—S bond distance <90TCA1667>. *Ab initio* calculations, with a STOG-3G basis set, on the bicyclic ions (11) and (12) predicted the general trends in the conformational changes in their formation from a dithiacyclooctane <89JPC6052>.

Ab initio calculations of ^{35}S nuclear quadrupole coupling constants (NQCC) of some 1,2-dithiols (2), using a TZVP basis set, gave qualitative agreement with data by the CI method <92ZN(A)203>.

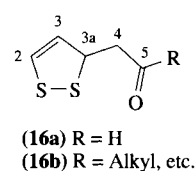
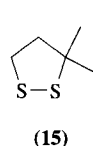
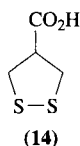
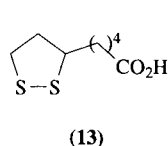


3.11.3 EXPERIMENTAL STRUCTURAL METHODS

3.11.3.1 X-ray Methods

Structural determinations of two 1,2-dithiolanes, lipoic acid (13), and asparagusic acid (14) showed S—S bond distances in the range of acyclic disulfides <90SR257>. Similar ranges are found for simple 1,2-dithiols (2) <B-66MI 311-01>. The interaction of an acyclic atom, especially of oxygen or sulfur, with a ring sulfur atom, can drastically alter S—S bonds, to lengths described as covalent, hypervalent, and nonbonded <B-85MI 311-01>, but interactions described as hypervalent should be viewed with reservation <90JA1434>. The S—S bond distance of unsubstituted 1,2-dithiole-3-thione (2b) <85AX(C)1768> is similar to that observed for 5-(4-methoxyphenyl)-1,2-dithiole-3-thione <85AX(C)1242> and some 3,4-bismethylthio derivatives (15) and (16) <91AX(C)1905>. The dimensions of (2b) are shown in Figure 1. An x-ray structure of a dithieno[4,5-c]-1,2-dithiole-3-thione shows a strong network of close nonbonded S—S interactions <92T8143>.

Simple 1,2-dithiolium salts have shorter S—S bond distances, of the order of 2.02 Å.



3.11.3.2 Neutron, Electron Diffraction, and Microwave Spectroscopy

No data appears to be available.

3.11.3.3 NMR Spectroscopy

3.11.3.3.1 Proton spectra

Protons in 1,2-dithiolanes (1) absorb in typical aliphatic regions <90SR257>. The protons adjacent to sulfur absorb at lower field. For example, for the 1,2-dithiolane (15), δ values are 2.09 ppm (C4)

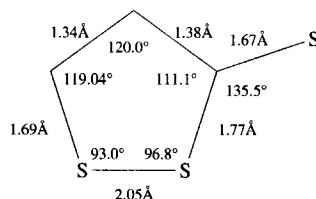


Figure 1 Bond lengths and angles of 1,2-dithiole-3-thione.

and 3.36 ppm (C(5)). Protons in 1,2-dithiole-3-ones (**2a**) absorb at higher field than in 1,2-dithiole-3-thiones (**2b**). Thus, in unsubstituted 1,2-dithiole-3-one (**2a**), the δ values are 8.30 ppm (H(5)) and 6.60 ppm (H(4)). In unsubstituted 1,2-dithiole-3-thione (**2b**), these are 8.30 ppm and 7.15 ppm respectively. Protons on imines (**2c**) absorb at similar ranges <80CPB487>. In 1,2-dithiole-3-thiones, the J values are ~ 5.4 Hz.

In the unsubstituted 1,2-dithiolium ion (**3**), the 3(5) protons absorb at 10.7 ppm, and at 8.88 ppm (C(4)). The J values (~ 5 Hz) are fairly typical for such ions.

3.11.3.3.2 Carbon-13 spectra

The ^{13}C chemical shifts in the unsubstituted ion are at 176.72 ppm (C(3), C(5)), and 142.68 ppm (C(4)). Electron-releasing substituents raise these values <82AHC(31)63>. The ^{13}C chemical shifts for the unsubstituted-1,2-dithiole-3-thione (**2b**) are 216.7 ppm (C(3)), 140.2 ppm (C(4)), and 155.1 ppm (C(5)) <75CJC836>. Similar ranges are found for other 1,2-dithiole-3-thiones. The ^{13}C shifts of the C(3) in 1,2-dithiole-3-ones are in the range of 193 ppm <82AHC(31)63, 89MRC498>. The α effects of phenyl groups at C(5) (~ 18 ppm) are twice those at C(4) (~ 9 ppm). Data for the aldehyde (**16a**) is: 145.71 ppm (C(2)), 126.72 ppm (C(3)), 172.04 ppm (3a), 109.89 ppm (C(4)), and 181.12 ppm (C(5)) <77OMR(9)546>. Comparisons of a series of thiones and thione- S -oxides (**2**; X = SO) show that the latter have increased electron density on the ring <81PS(12)115>. The ^{13}C chemical shifts in 1,2-dithiolanes are ~ 41 ppm (C(3), C(5)) and 56 ppm (C(4)).

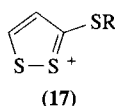
A linear correlation of ^1H and ^{13}C shifts of adjacent ring positions and between the ring and some substituents in 1,2-dithiol-3-ones (**2a**), 1,2-dithiole-3-thiones (**2b**), and 1,2-dithiolium ions (**3**), indicated that the changes in the electron distribution in the ring were responsible for the shift effects <87PS(29)187>, and ^{13}C NMR spectroscopy was used to confirm the structure of the 1,2-dithiolo[1,2-*a*]dium ion (**5**) <89G617>.

The ^{33}S nuclear quadrupoles of some dithioles have been examined <92ZN(A)203>. The principal axes of the NQCC are almost radial and tangential at the sulfur atoms, and with the greater value at the external bisector of the S-S-C angle.

3.11.3.4 Mass Spectroscopy

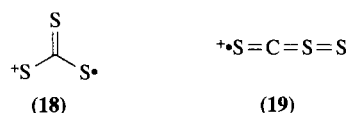
3.11.3.4.1 1,2-Dithiolium salts

3-Alkylthio-1,2-dithiolium salts (**17**) also lose alkyl groups to form thiones (**2b**) under the conditions of mass spectroscopy. For other 1,2-dithiolium salts (**3**), radicals are initially formed whose masses correspond to the molecular ions. Certain 1,2-dithiolium salts (**3**) form 1,2-dithiole-3-thiones under mass spectrometry conditions, presumably by thermal degradation <80SR1>.



3.11.3.4.2 1,2-Dithioles

1,2-Dithiole-3-ones (**2a**) and 1,2-dithiole-3-thiones (**2b**) also form intense parent ions <82AHC(31)63>. For most of these, the first fragmentation processes are loss of CO and CS respectively, to form 1,2-dithietes, and further loss of S to form thiirenes. Other fragmentation processes involve an initial loss of HS₂, and methyl-1,2-dithiol-3-ones rearrange to 1,2-dithiolium ions (**3**) <72ACS250>. Acylmethylene-1,2-dithioles (types (**16b**)) show α -cleavage at the carbonyl group, and M—OH or M—SH peaks for certain aryl derivatives <80SR1>. The electron impact spectrum of unsubstituted 1,2-dithiole-3-thione (**2b**) gives the CS₃ radical cation as two distinct species, (**18**) and (**19**) <90JA3750>.



If 3(5) substituents are present, 3-alkylidene-1,2-dithioles (**2d**) can be formed under the conditions of mass spectroscopy. Otherwise carbenes are formed which can dimerize to form bis-1,2-dithiol-3-ylidenes (**9**) <82SUL9>.

3.11.3.4.3 1,2-Dithiolanes

For 1,2-dithiolanes, peaks corresponding to the parent ion are common. These are intense, explained by reduced repulsion of the sulfur atoms <80CB3208>.

3.11.3.5 Electron Scanning Chemical Analysis and PE Spectroscopy

3.11.3.5.1 1,2-Dithiolium ions

For 1,2-dithiolium cations (**3**), the S2p binding energies (~165 eV), were equal for both sulfur atoms, indicating an almost equal charge distribution. These values lie between those of 1,2-dithiolanes (**1**) and sulfonium ions <74JHC105>.

3.11.3.5.2 1,2-Dithioles

For 1,2-dithiole-3-thiones (**2b**), the thione sulfur atom has a binding energy close to that in dithiocarboxylic esters, indicating substantial positive charge in the 1,2-dithiole ring. A high intensity band at 8.42 eV, using the He(1 α) photon energy, was assigned to at least two electronic transitions <75MI 311-01>. The results were compared to CNDO calculations <82AHC(31)63>. Both 1,2-dithiole-3-ones (**3a**) and -3-thiones (**3b**) had S2p binding energies of approximately 164 eV.

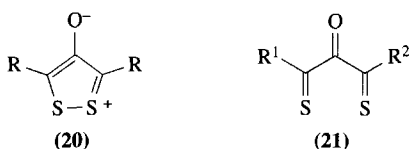
3.11.3.5.3 1,2-Dithiolanes

A Δ IE value, of the energy splitting, of approximately 1.7 eV was determined for 1,2-dithiolanes <80CB3208>.

3.11.3.6 IR and Raman Spectroscopy

3.11.3.6.1 1,2-Dithiolium salts

No data appears to be available for 1,2-dithiolium salts, but for mesoionic 1,2-dithioles, IR studies indicate that the cyclic structure (**20**) is favored over an acyclic structure (**21**), except where R is an amino substituent <87PS(31)109>.



The Raman spectrum of the dithiolodithiolodiiium salt (**12**) shows S—S str. absorptions at 446 cm^{-1} , and the spectrum of the radical cation (**11**) is mainly composed of bands below 500 cm^{-1} <89JPC6052>.

3.11.3.6.2 1,2-Dithioles

1,2-Dithiole-3-ones (**2a**) show C=O str. absorptions in the range of 1640–1670 cm^{-1} , suggesting considerable ionic character of the bond <82AHC(31)63>. 1,2-Dithiole-3-thiones (**2b**) have absorptions around 1170 cm^{-1} (C=S str.), and the 3-imines (**2c**) absorb around 1590–1605 cm^{-1} (C=N str.). Carbonyl absorptions in the ketones of type (**16**) are at much lower frequencies than normal ranges, due to S—O interactions. These may be due to either sulfur polarizability, or hypervalent interactions <91JA6449, 94SR317>.

3.11.3.6.3 1,2-Dithiolanes

These methods have limited applications to 1,2-dithiolanes <90SR257>. Owing to the weakness of S—S str. absorptions, Raman spectroscopy is preferred.

3.11.3.7 UV and Visible Spectroscopy

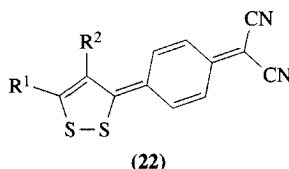
3.11.3.7.1 1,2-Dithiolium salts

Absorption bands of some phenyl substituted 1,2-dithiolium salts (**3**) have been used to confirm their decomposition reactions with nucleophiles, proceeding via 1,2-dithioles <81CJS202>. Simple mesoionic compounds (**20**) show large negative solvatochromic effects, related to the ring charge transfer of the lowest excited π - π^* transition. In contrast, for compounds with 3,5-bis(dimethylaminophenyl) substituents, colors are determined by electronic transitions of polymethine-type chromophores <87PS(31)109, 87ZC28>.

3.11.3.7.2 1,2-Dithioles

The spectra of many 1,2-dithiole-3-ones (**2a**) and -3-thiones (**2b**) have been reported <64JC153>. The unsubstituted-1,2-dithiole-3-one shows two maxima at 226 nM and 310 nM, and the

unsubstituted thione at 229 nM, 251 nM, 336 nM, and 415 nM. Some 5-aryl and -diazinyl 1,2-dithiole-3-thiones also absorb in these regions <85T3705>. Intramolecular charge transfer in 1,2-dithioles of the type (22) allows a photoinduced color response, of use in optical filters <88GEP3636157>.



3.11.3.7.3 1,2-Dithiolanes

1,2-Dithiolanes absorb at longer wavelengths than acyclic disulfides, due to the altered S–S dihedral angles <90SR257>. Calculations suggest that the two HOMOs are the bonding and antibonding π orbitals. The LUMO is an antibonding σ^* orbital between the two sulfur atoms and the excitation is of a π^- electron into this. Electron-withdrawing groups at C(3) or C(5) in 1,2-dithiolanes slightly reduce wavelengths of λ_{max} , while electron-releasing groups increase λ_{max} , in contrast to acyclic disulfides.

3.11.4 THERMODYNAMIC ASPECTS

3.11.4.1 1,2-Dithiolium Salts

1,2-Dithiolium cations are aromatic 6π systems and as such are very stable, except to nucleophilic reagents. This also holds for fused systems. A calculated aromaticity index, based on bond lengths, gave a value of 62 for (3) and 85 for (20; R = Ph). The corresponding value for thiophene is 66 <85T1404>. In general, although the mesoionic cyclic structures (20) are more stable than the acyclic isomers (21), this is affected by substitution <87PS(31)109>. The 1,2-dithiolium ion (3) is also more stable than an acyclic isomer <86CA(105)41972>.

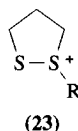
3.11.4.2 1,2-Dithioles

Likewise, the 1,2-dithiole rings in types (2a–e) and (3) are essentially planar <85AX(C)1768>. 1,2-Dithiole-3-ones and -3-thiones can be prepared under rigorous conditions and they are much more stable than the 1,2-dithiolanes. Delocalization of π electrons in these structures is suggested by their heats of formation <82AHC(31)63>. The 1,2-dithioles (2e) have somewhat intermediate character.

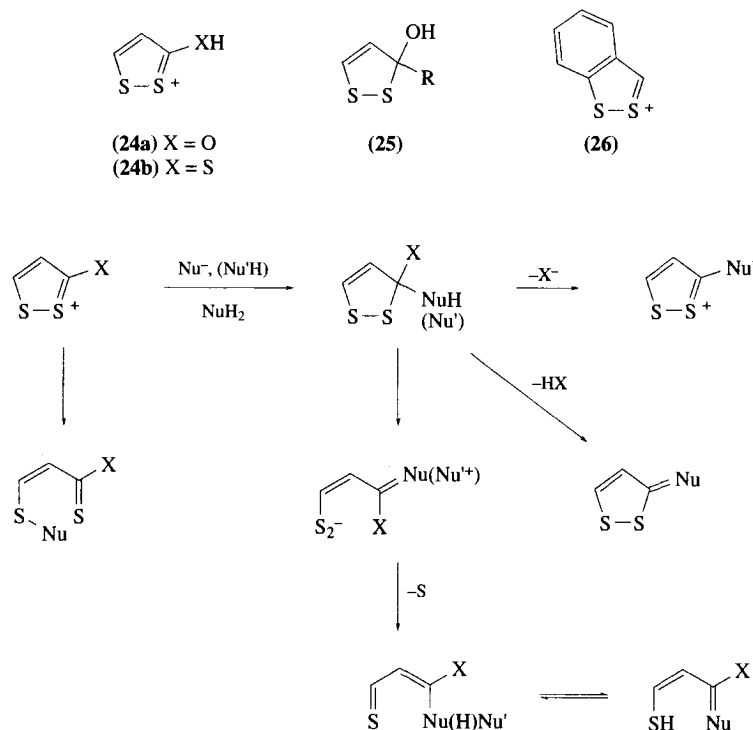
3.11.4.3 1,2-Dithiolanes

1,2-Dithiolanes have a greater reactivity than acyclic disulfides, which is attributed to some repulsion of the lone pairs on the adjacent sulfur atoms <90SR257>. In some *S*-methylated derivatives (23), there is also some repulsion <85JA2807>. The calculated values of strain energies correlated with experimental values <90JA6296>.

3-Hydroxy- and 3-thiol-1,2-dithiolium salts (24a) and (24b) respectively are protonated forms of



1,2-dithiole-3-ones (**2a**) and 3-thiones (**2b**) respectively, and are stable. 3-Hydroxy-1,2-dithioles (**25**) rapidly undergo ring opening and degradation (Scheme 1) <81CJS202>.



Scheme 1

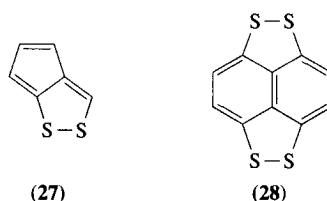
The chromatographic behavior of some 1,2-dithiole-3-thiones (**2b**) has been investigated <83JLC1291>. Usually these compounds chromatograph readily.

1,2-Dithiolanes (**1**) and 1,2-dithioles (**2**) are typical covalent compounds and are soluble in most typical organic solvents. 1,2-Dithiolium salts (**3**) have limited solubility in nonpolar solvents, but lower members dissolve in water. Others dissolve in polar organic solvents.

3.11.5 REACTIVITY OF FULLY CONJUGATED RINGS

3.11.5.1 General Summary

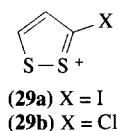
The 1,2-dithiolium ion (**3**) has a fully conjugated ring. The benzo- (**26**), or other fused derivatives, and certain fused 1,2-dithiole derivatives, for example, types (**27**) and (**28**), are also fully conjugated, but their reactivities are more comparable to those of 1,2-dithiole-3-ylidenes (**2d**). 1,2-Dithiolium ions (**3**) react readily only with nucleophiles, and often in the least hindered 3 (or 5) position to form 1,2-dithioles (**2**). These may reform 1,2-dithiolium salts by loss of a leaving group, or form an exocyclic double bond, for example, to form systems (**2a-d**), or undergo ring opening to form acyclic disulfide ions, which lose sulfur to form thiones or thiol tautomers (Scheme 1). In certain other cases the attack appears to occur at ring sulfur. An initial coordination of certain nucleophiles to a ring sulfur, prior to attack at a ring carbon, has been suggested <88CJC2339>.



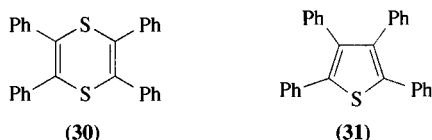
3.11.5.2 Reactions of 1,2-Dithiolium Salts

3.11.5.2.1 Thermal and photochemical reactions

1,2-Dithiolium cations (**3**) form radicals under the thermal conditions of mass spectroscopy (Section 3.11.3.4), and carbenes may be involved in the formation of 1,2-dithiole-3-thiones and thieno[3,2-*b*]thiophenes by thermolysis of 2-iodo-1,2-dithiolium salts (**29a**) <81LA1729>.



Photolysis of 3,5-diphenyl-1,2-dithiolium-3-olate (**20**; R = Ph) gave the dithiin (**30**) and the thiophene (**31**) <82JCS(P1)1885>, but thermolysis formed 2,3,5,6-tetraphenyl-1,4-benzoquinone <78AJC297>.



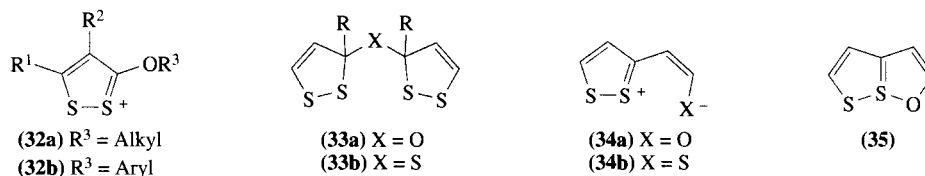
3.11.5.2.2 Electrophilic attack at carbon and sulfur

1,2-Dithiolium salts, being cations, are resistant to electrophilic attack on the ring.

3.11.5.2.3 Nucleophilic attack

(i) With oxygen nucleophiles

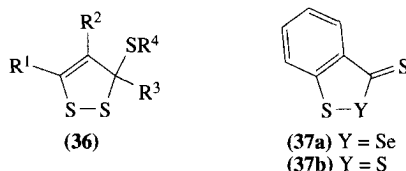
Little new data has been reported on nucleophilic attack by oxygen. 1,2-Dithiolium cations (**3**) are readily attacked by oxygen nucleophiles at C(3) (or C(5)) (Scheme 1) to form 1,2-dithioles and further enethiol products <65JCS32>. These intermediates have also been confirmed by spectroscopy <81CJS202>. When the 1,2-dithiolium salts bear a replaceable substituent at C(3), for example, halogen, they react with alcohols or phenols to form 3-alkoxy- or 3-aryloxy-1,2-dithiolium salts (**32a**) and (**32b**) respectively. With water, 1,2-dithiole-3-ones (**2a**) or bis-1,2-dithiol-3-yl ethers (**33a**) are formed. The interaction of substituents with a ring sulfur in 3-thioacylmethyl- and 3-acylmethylene-1,2-dithioles (**10**) and (**16**) respectively can be regarded as a special case of attack of nucleophilic ions (**34a**) and (**34b**) respectively on a ring sulfur of a 1,2-dithiolium ion, possibly interpreted as forming the bicyclic structures types (**6**) and (**35**) respectively.



(ii) With sulfur nucleophiles

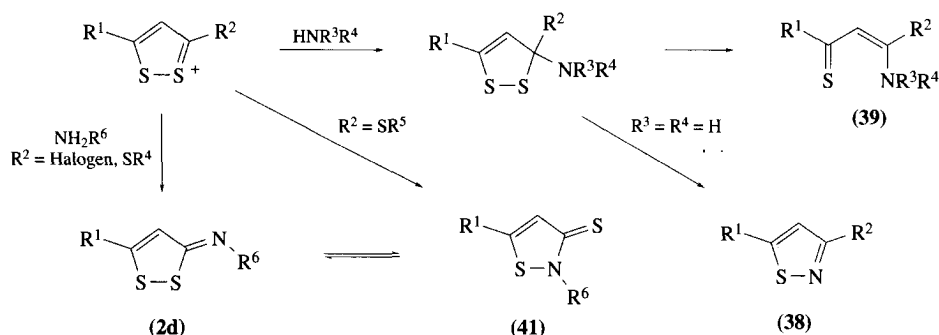
Nucleophilic attack with sulfur is somewhat similar to that with oxygen. Thiols or hydrogen sulfide react at C(3) of the 1,2-dithiolium cation to form 3-alkylthio-1,2-dithioles (**36**) and bis(1,2-dithiol-3-yl)sulfides (**33b**) respectively <65JCS32, 67CC353, 72JCS(P1)2305>. Thiols may displace halogen

at C(3) or C(5) to form 3-alkylthio-1,2-dithiolium salts (**19**) or 1,2-dithiole-3-thiones (**2b**). Hydrosulfide ions attack similarly, with eventual formation of 1,3-dithiones by ring opening $\langle 81\text{CJS}202 \rangle$. The regeneration of 1,2-dithiole-3 thiones (**2b**) from their mercury(II) complexes by sulfide ion can be regarded as a nucleophilic attack at C(3). Hydroselenide ion attacks a benzo-1,2-dithiolium salt to form a benzothiaselenothione (**37a**) $\langle 82\text{H}(19)657 \rangle$.



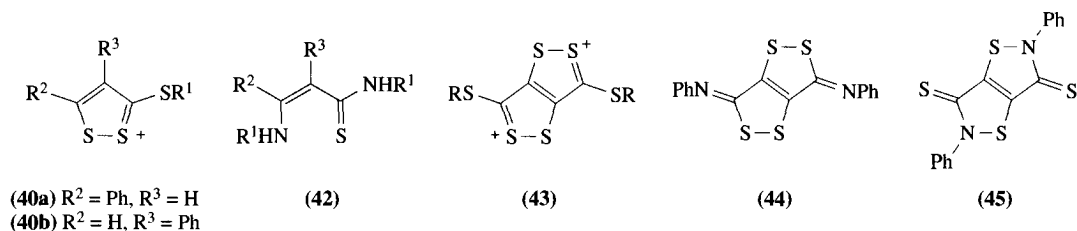
(iii) *With nitrogen nucleophiles*

Nitrogen nucleophiles react at C(3) (C(5)) to form 1,2-dithioles. The further products of the reactions depend on the substitution pattern of the dithiolium ring, the actual nucleophile, and occasionally the reaction medium. Dithiolium salts with nonreplaceable substituents react with ammonia to form isothiazoles (**38**) and with primary or secondary amines to form aminothiones (**39**) (Scheme 2) $\langle 65\text{JCS}32, 80\text{AHC}(27)151 \rangle$.



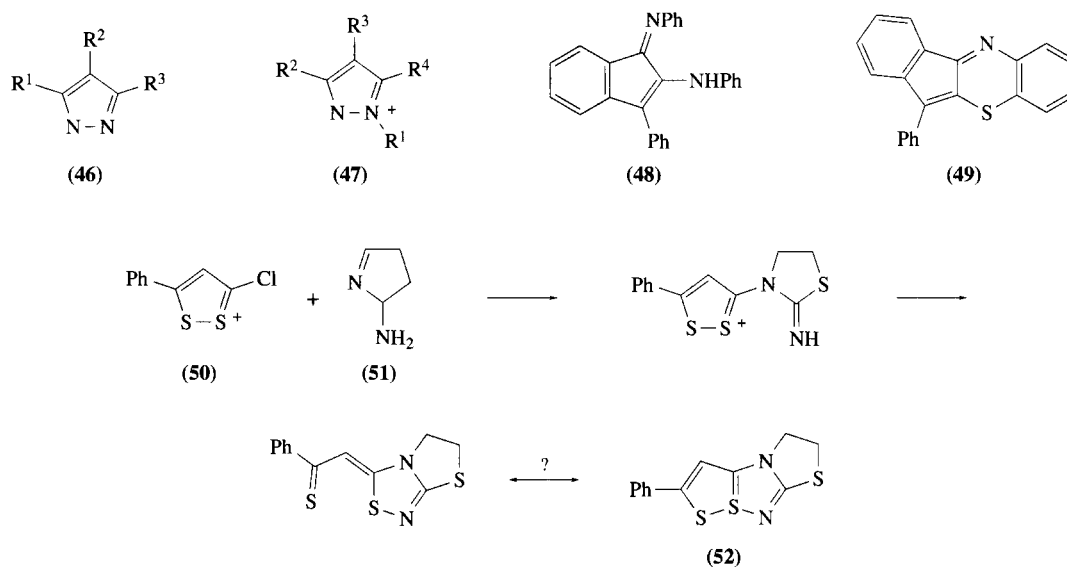
Scheme 2

The 1,2-dithiolium cations (**3**) react at either C(3) or C(5), not necessarily where there is a replaceable substituent. Further reactions involve either retention of the ring by loss of a substituent, or ring opening. Thus the 3-alkylthio-5-phenyl-1,2-dithiolium salt and the 4-phenyl- isomer (**40a**) and (**40b**) respectively react with amines at C(3) and C(5) respectively $\langle 72\text{CJC}2568, 72\text{CR}(C)1215, 75\text{ZC}478, 82\text{JCS}(P1)499, 86\text{T}839, 86\text{TL}159 \rangle$. Aliphatic amines usually give isothiazoline-3-thiones (**41**), 1,2-dithiole-3-thiones (**2b**), and aminothioamides (**42**), rather than 3-imino-1,2-dithioles (**2d**). Thus, the 1,2-dithiolodithiole[5,4-*d*]-1,2-dithioledium salt (**43**) reacted with aromatic amines to give mixtures of dithiolodithioles (**44**) and isothiazoloisothiazoles (**45**) $\langle 88\text{EGP}254008, 90\text{JPR}387 \rangle$.



1,2-Dithiolium salts react with hydrazines similarly to amines, but further cyclization gives pyrazoles (**46**) or pyrazolium salts (**47**). When there are replaceable substituents, hydrazones and azines are formed. A mesoionic 1,2-dithiole-3-olate (**20**; R = Ph) reacts similarly at C(3) with aniline, but with eventual formation of the products (**48**) and (**49**) $\langle 87\text{CJC}2830, 92\text{T}8127 \rangle$. The reaction

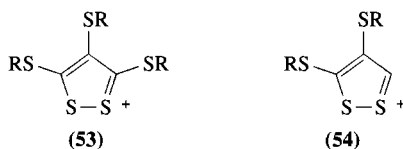
of a 3-chloro-5-phenyl-1,2-dithiolium cation (**50**) with an aminothiazoline (**51**) to form an isothiazolothiadiazole (**52**), can be rationalized by a nucleophilic attack of a nitrogen at a ring sulfur atom (Scheme 3) <82JCS(P1)499>.



Scheme 3

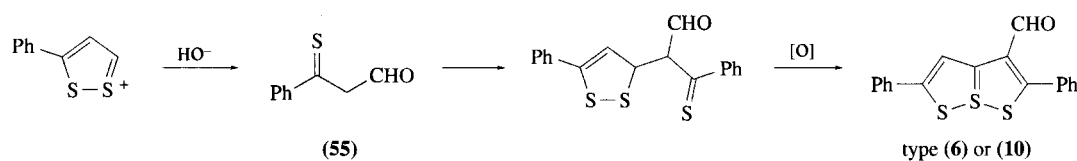
(iv) With hydrogen nucleophiles

The 3,4,5-trisalkylthio-1,2-dithiolium ion (**53**) reacts successively with sodium borohydride and acid to form the 3,4-bisalkylthio-1,2-dithiolium ion (**54**) <87CS261>, consistent with a hydride attack at C(3).

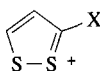


(v) With carbon nucleophiles

The reaction with carbon nucleophiles appears to occur predominantly at C(3) (C(5)). A number of ketones or vinyl ethers react at C(3) to form 3-acylmethylene-1,2-dithioles (**16**) by dehydrogenation of the initially formed product. With 3-aryl-3-thiopropional (**55**), arising from an initial decomposition of some of the 1,2-dithiolium salt, condensation gives thiones, which further dehydrogenate to trithiapentalenes (Scheme 4). The compounds (**16**) are also formed from 3-halo- or 3-alkylthio-1,2-dithiolium salts (**56a,b**) by loss of hydrogen halide or alkanethiol respectively, by reaction of compounds with reactive methylene groups, for example, 3-ketoacids, related compounds <70JCS(C)1202>, and their anions.



Scheme 4



(56a) X = halogen

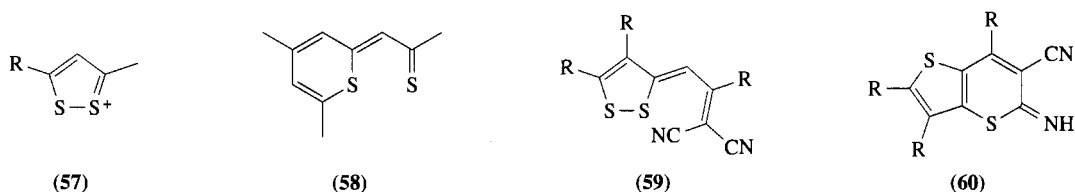
(56b) X = SR

(56c) X = SBr

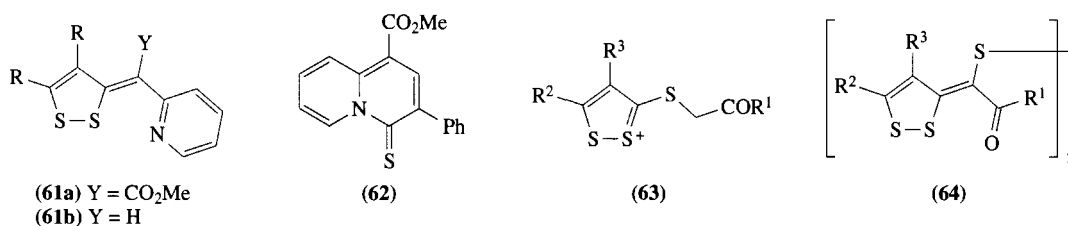
(56d) X = NR₂

When the dithiolium salt lacks a leaving group, ring opening and recyclization of intermediates can give thiopyrans or thiophenes. The latter reaction may involve intermediates similar to those in the reactions of dithiolium salts with ammonia to form isothiazoles, or proceed by an initial attack of a carbanion on ring sulfur <76JPR(318)221, 80AHC(27)151>.

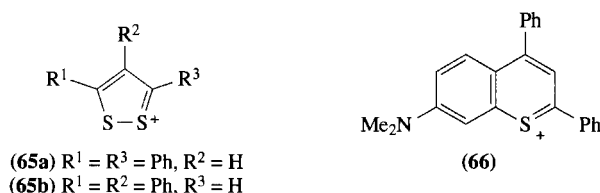
The self-condensation of the 3-methyl-1,2-dithiolium ions (57), promoted by base or an Au(I) species, gives thiopyrans (58) <77JCS(P1)1511, 88CC22>. The methylene groups can be conjugatively activated, as for the formation of a 1,2-dithiol-3-ylidenebutenenitrile (59) from a 3-alkylthio-1,2-dithiolium <81BSF113, 82SUL1>. The other reaction product (60) appears to arise from an attack of the nucleophile at the alternative position (C(5)).



Methyl pyridine-2-acetate and other related compounds react with 3-alkylthio-1,2-dithiolium salts at the least hindered C(3) or C(5) position. From the former, 1,2-dithiole-3-ylidenepyridines (61) are formed. From the latter, ring opening and recyclization gives quinolizinethiones (62) <88CJC2830>. The anions of cyclopentadienes and similar azoles act as carbon nucleophiles giving 3-cyclopentadienylidene-1,2-dithioles <86T839>. Reactive methylene groups may be situated on a side chain. For example, episulfide intermediates, formed from the dithiolium salts (63) by reaction with a base, can extrude sulfur or form disulfide bonds to form the dithioles of type (16) and (64) <70JCS(C)1202, 92CJC2290, 93CA(118)191593>.

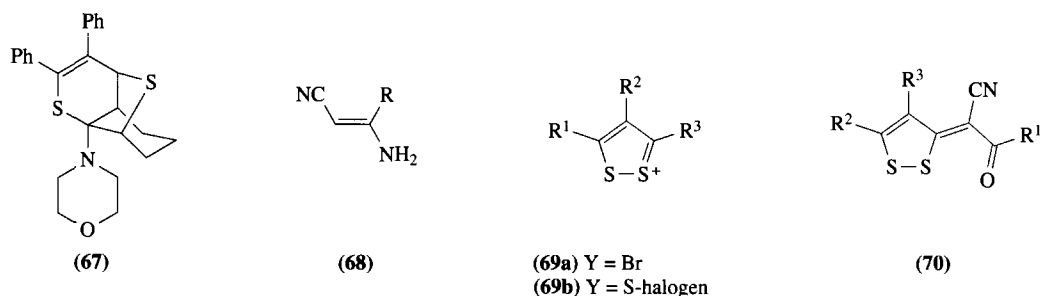


N,N-dimethyl aniline acts as a carbon nucleophile, and attack on the 3,5-diphenyl-1,2-dithiolium ion (65a) forms the benzothiopyrylium system (66). When the dithiolium salt has replaceable substituents, 3-(4-dimethylaminophenyl)-1,2-dithiolium salts are formed <66AHC(7)39>.

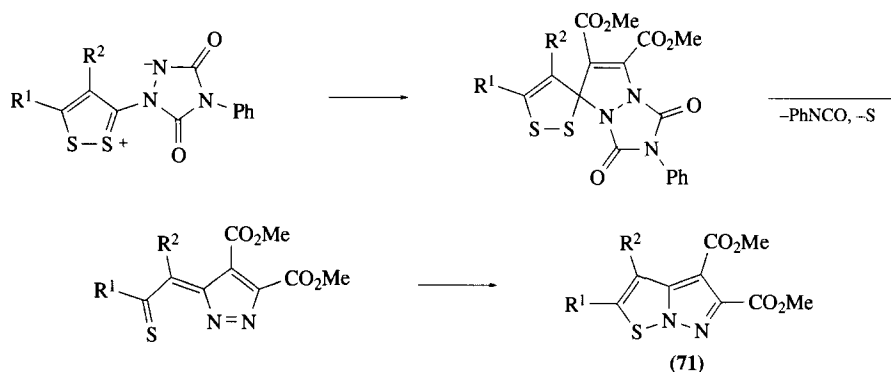


Enamines react conjugatively. Thus, treatment of the 4,5-diphenyl-1,2-dithiolium ion (65b) with morpholinocyclohexene gives the polycyclic structure (67) by an initial attack at C(3). However, a subsequent attack is at S(2) of a now uncharged 1,2-dithiole ring by an attached

morpholinocyclohexene <81LA1729>. Also, the reaction of a β -aminonitrile (**68**) on a 3-bromo-1,2-dithiolium ion (**69**) gave a 3-acylmethylene-1,2-dithiole (**70**) <91PS(63)109>.



The initial attack at C(3) on a 1,2-dithiolium ring by a carbon nucleophile, arising from reaction of an exocyclic amidic anion on DMAD explains the formation of the fused isothiazoloimidazole (**71**) (Scheme 5) <82ZOR2626>.



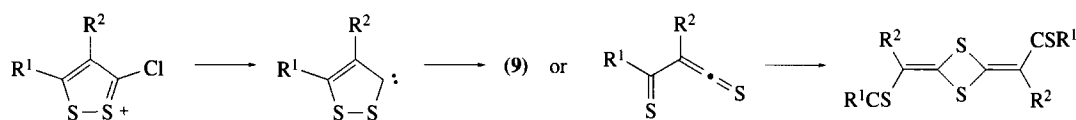
Scheme 5

(vi) With halogen nucleophiles

The reactions of 1,2-dithiole-3-thiones (**2b**) with various types of halogen reagents forming 3-halo-1,2-dithiolium cations (**29b**) <76PS(1)185> can be treated as a nucleophilic attack of a halide ion, or a halogen source on a type of initially formed 3-halothio-1,2-dithiolium salt (**69b**).

3.11.5.2.4 Reduction

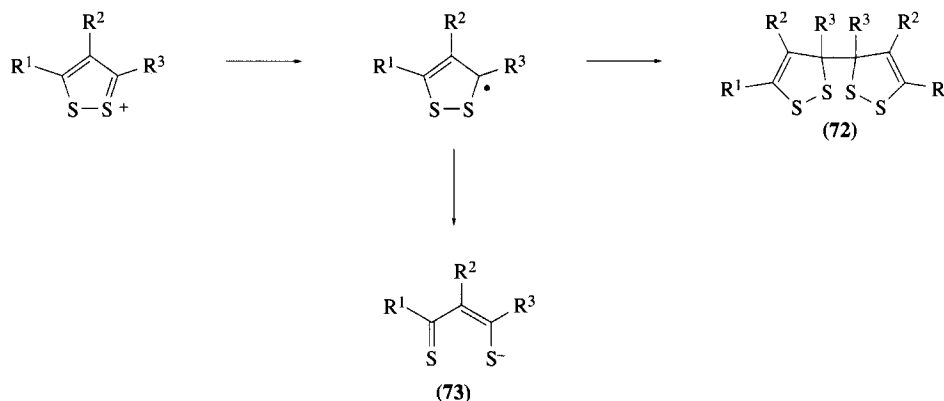
The reduction by, for example, Zn, Ag, or Ti(III) of 3-chloro-1,2-dithiolium salts (**29b**), probably by dimerization of carbenes, gives bis-1,2-dithiole-3-ylidenes (**9**) or, in some cases, acyclic products which dimerize to 1,3-dithietanes (Scheme 6) <81LA1928, 88BSF101>. Carbenes may also be involved in the formation of bis-1,2-dithiol-3-ylidenes (**9**) from trisalkylthio-1,2-dithiolium salts (**53**) <87EGP249481>.



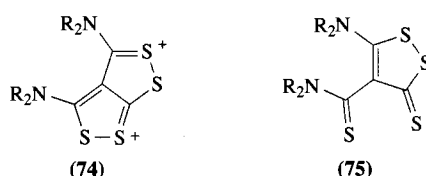
Scheme 6

The electrochemical reduction of 1,2-dithiolium salts (**3**) gives bis-1,2-dithiole dimers (**72**) via radicals, whose stability depends on their substitution <80SR1>. Further reduction gives a 3-thio-

enethiolate anion (**73**) (Scheme 7), and Cr(II) reduces 3,5-dimethyl-1,2-dithiolium cation to a 2,5-pentanedithionate anion <72AJC2547>. The diamino-1,2-dithiolo[3,4-*c*]dithiolodiiium cation (**74**) undergoes a two-electron reduction to the thioamide (**75**) <89SM537>.



Scheme 7

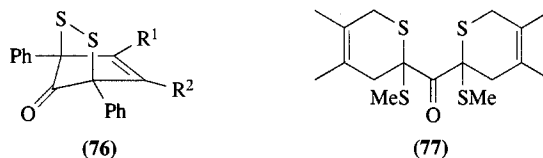


3.11.5.2.5 Deprotonation

The three or five protons on 1,2-dithiolium salts are exchanged by deuterium under various conditions <66AHC(7)31, 66T2119>. Probably carbene intermediates are involved in these, and in the conversion of 1,2-dithiolium salts (**3**) to the thiones (**2b**) by sulfur in pyridine <82AHC(31)63, 89CC1716>.

3.11.5.2.6 Reactions involving cyclic transition states

No data are reported for the ordinary 1,2-dithiolium systems (**3**), but the mesoionic system (**20**; R = Ph), behaving as a two-electron component, forms a 1:1 adduct (**76**) with 1,3-dienes. By contrast, the 3,5-bismethylthio- derivative (**20**; R = SMe) forms a 1:2 adduct (**77**) <84CC1682>, suggesting that it exists more as an acyclic form.



3.11.6 REACTIVITY OF CONJUGATED 1,2-DITHIOLES

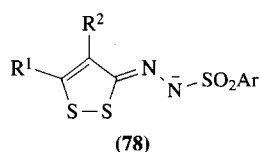
3.11.6.1 General Survey

To some extent, conjugated 1,2-dithioles behave as acyclic disulfides. 1,2-Dithioles with exocyclic double bonds at C(3) (types (**2a-d**)) are potentially aromatic and readily undergo reactions

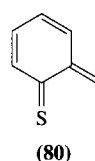
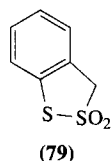
converting them to 1,2-dithiolium cations (**3**). The site of nucleophilic attack on 1,2-dithioles (**2**), especially the -3-thiones (**2b**), appears to depend on the ring substitution pattern, and the hard/soft character of the nucleophile <85T3705, 87T3421, 88JHC1223>.

3.11.6.2 Thermal and Photochemical Reactions

1,2-Dithiole-3-ones (**2a**) and 3-thiones (**2b**) are often synthesized under relatively drastic conditions <82AHC(31)63>, and are thermally fairly stable <65CRV237>. Desulfurization with copper powder gives a variety of other heterocyclic systems <74TL4113, 81LA1729>. Possibly carbenes or carbenoids, dimerizing to bis-1,2-dithiole-3-ylidenes (**9**) are involved, as pyrolysis of bis-1,2-dithiole-3-ylidenes (**9**), and 1,2-dithiol-3-sulfonylhydrazides (**78**) gives similar results <75TL3473>.



Photochemical reactions on 1,2-dithiole-3-thiones (**2b**) commonly involve cycloadditions on the thione function, but benzo-1,2-dithiole-2,2-dioxide (**79**) forms a thioquinonemethide (**80**) <78JOC3374>.



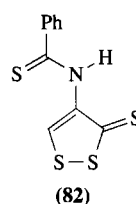
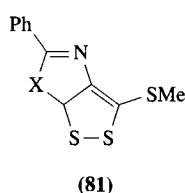
3.11.6.3 Electrophilic Attack

3.11.6.3.1 Electrophilic attack at carbon

Few examples of electrophilic attack at carbon are reported, not surprisingly, in view of the nucleophilicity of ring sulfur, -3-one, -3-thione, and other functions. Under certain conditions the 1,2-dithiole-3-one ring may be halogenated at the 4-position <65CRV237, B-67MI 311-001>.

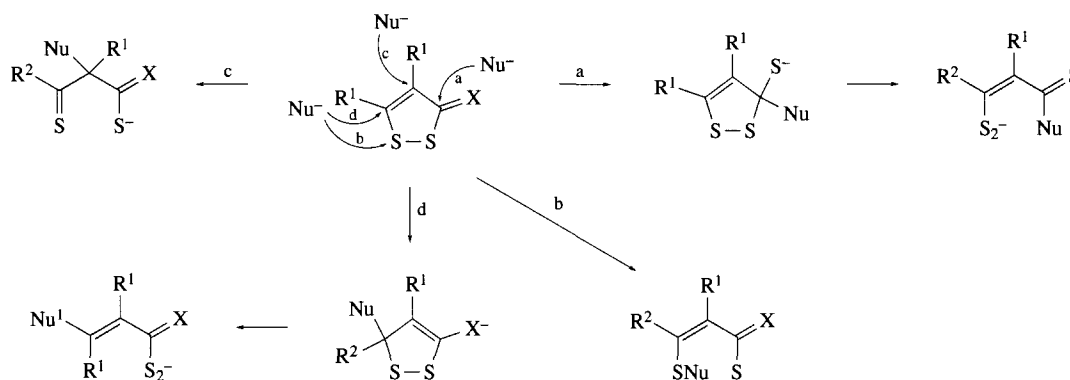
3.11.6.3.2 Electrophilic attack at ring sulfur

1,2-Dithiole-3-ones (**2a**) react with chlorine, sulfonyl chloride, and sulfenyl chlorides at ring sulfur to form acyclic products <74IZV643>. The reaction of a fused 1,2-dithiole (**81**) and a 4-acylamino-1,2-dithiole-3-thione (**82**) with iodomethane both formally require an electrophilic attack on a ring sulfur <66AJC503>.



3.11.6.4 Nucleophilic Attack

For 1,2-dithiole-3-thiones (**2b**), the exact position of the attack, whether S(2), C(3), C(4), or C(5), appears to depend on the substitution pattern of the ring, and on the hard/soft character of the nucleophile (Scheme 8) <85T3705, 87T3421, 88JHC1223>.

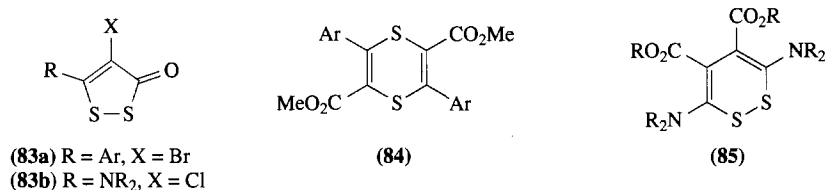


Scheme 8

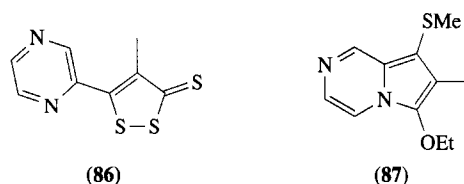
3.11.6.4.1 Nucleophilic attack at carbon

(i) By oxygen nucleophiles

1,2-Dithioles are attacked at C(3) by hydroxide ion. Ring halogen substituents can be displaced with or without ring opening <84FRP2541679>. This gives acyclic products with eventual loss of sulfur, but also with the formation of other systems. For example, the halogenated dithioles (**83a,b**) give the 1,4-dithiin (**84**) and 1,2-dithiin (**85**) respectively on treatment with base <82AHC(31)63, 84PS(20)117>.

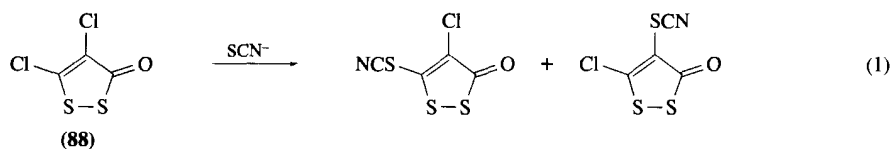


Ethoxide ion attacks “Oltipraz” (**86**), a 1,2-dithiole-3-thione, at C(5), or possibly at C(3) <85T3705>. Ring opening and recyclization forms a pyrrolodiazine, isolated as the compound (**87**). With the bulkier *t*-butoxide ion, the attack is at C(4).



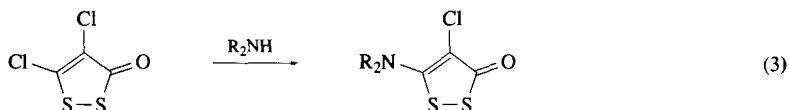
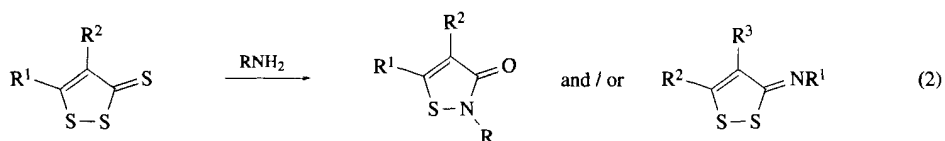
(ii) By sulfur nucleophiles

Thiolate ions react at C(4) or S(2) <85T3705>, and thiocyanate can displace halogen substituents at C(4) or C(5) in dichloro-1,2-dithiole-3-ones (**88**) (Equation (1)) <82AHC(31)63, 85JAP(K)6001181>.



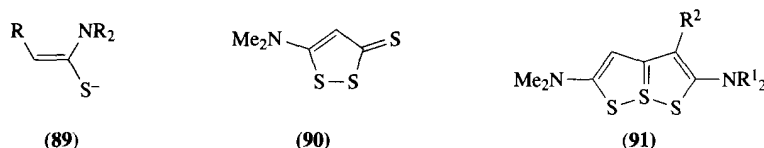
(iii) *By nitrogen nucleophiles*

1,2-Dithiole-3-ones and -3-thiones behave like acyclic ketones and thiones, forming imines, oximes, and hydrazones, etc. <65CRV237>, but ring opening <79BCJ3640> and recyclization to, for example, isothiazoles is common with fused dithioles and aromatic amines (Equation (2)) <78CB2716, 82JHC1393, 90JPR387, 91JCS(P2)1763, 91JPR19>. When the ring contains replaceable substituents, aminodithioles are formed (Equation (3)) <84FRP2541575, 84FRP2541679>.



(iv) *By carbon nucleophiles*

While the aminoenethiolate anion (89) reacted at C(3) of a thione (90), with the eventual formation of a trithiapentalene (91) <83URP1004387>, other enamine types, for example, enethiolate anions and anions of acenaphthenone, reacted at the C(5) of thiones, with eventual formation of thiopyran-2-thiones <77BSF1142, 82AHC(31)63>. However, the products of these reactions also appear to depend on the actual nature of the nucleophile, as Grignard reagents react as thiophiles, attacking at S(2) of 1,2-dithiole-3-ones (Section 3.11.6.4.2.iv). Phosphonium ylides and other carbanions attack at C(3) of dithiole-3-ones and -3-thiones to form 3-alkylidene-1,2-dithioles (2d) <66AHC(7)39, 71AHC(13)161, 78SC315>.



(v) *By phosphorus nucleophiles*

Phosphorus nucleophiles appear to attack at ring sulfur (Section 3.11.6.4.2(v)).

3.11.6.4.2 Nucleophilic attack at ring sulfur

(i) *By oxygen nucleophiles*

No data is reported.

(ii) *By sulfur nucleophiles*

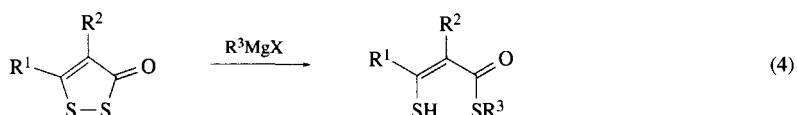
Sulfur nucleophiles give reduced products consistent with either nucleophilic attack at a sulfur atom or electron transfer reactions <90PS(53)425>. The dithiolate anions formed by these reactions can be characterized as nickel complexes <89JAP(K)63222188>. Thiocyanate ion attacks at S(2) in 1,2-dithiole-3-thiones <88JHC1223>.

(iii) *By nitrogen nucleophiles*

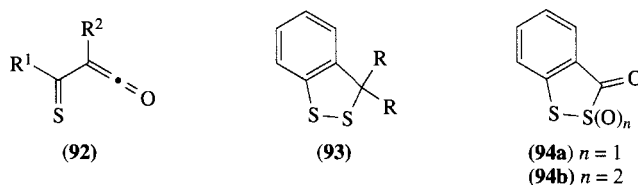
No data is available.

(iv) *By carbon nucleophiles*

Grignard reagents commonly react at S(2) of 1,2-dithiole-3-ones, with ring opening (Equation (4)) <73LA247, 74LA1261, 82AHC(31)63>.

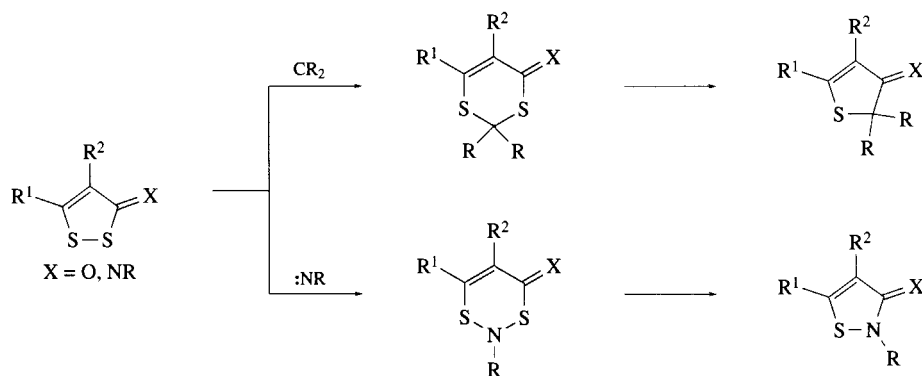
(v) *By phosphorus nucleophiles*

Phosphorus nucleophiles attack at S(2), leading to acyclic products. Thus, 1,2-dithiole-3-ones give thioacylketenes (**92**), and benzo-1,2-dithiole (**93**) forms the thioquinone methide (**80**) <70JOC3259, 76TL2961, 82AHC(31)63>, but ring contraction to thietanes can occur with 1,2-dithiolones (**2a**) and imines (**2c**) <75TL3473, 81LA1928, 86CB162>. By contrast, 1,2-dithiole-3-thiones dethionate to bis-1,2-dithiole-3-ylidenes (**9**) <85CS167>. The benzo-1,2-dithiol-3-one-*S,S*-dioxide (**94a**) and -*S*-oxide (**94b**) are sulfurizing agents, acting by attack of phosphorus(III) species on S2 <90JA1253, 92OPP488>.

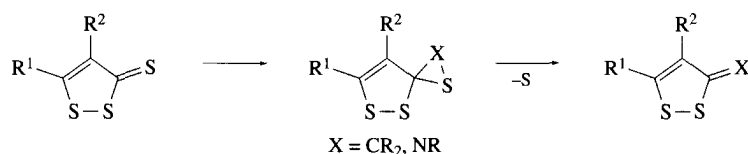


3.11.6.5 Reaction with Nitrenes and Carbenes

Most 1,2-dithioles react with carbenes and nitrenes at the S—S bond, leading to insertion, and possible further loss of sulfur to form thiophenes or isothiazoles respectively (Scheme 9) <74T4113, 76CJC3879>. 1,2-Dithiol-3-thiones (**2b**) usually react at the thione function, with the formation of thiiranes or thiaziranes respectively, which can extrude sulfur to form 3-methylene (**2d**) or 3-imino-1,2-dithioles (**2c**) respectively (Scheme 10). The reaction of α -thiocarbenes with the thione group of 1,2-dithiole-3-thiones (**2b**) is possibly implicated in their conversion to trithiapentalenes (**6**) <82AHC(31)63>.



Scheme 9

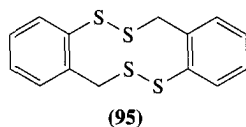


Scheme 10

3.11.6.6 Oxidation and Reduction

Various types of 1,2-dithioles (**2**) undergo oxidative electron transfer under chemical or electrochemical conditions to form 1,2-dithiolium ions (**3**) <66AHC(7)39>. The electrochemical reduction of dithiolethiones gives two waves, attributed to a reversible single electron reduction, followed by a cleavage of the S—S bond, or to a two-electron reduction of the thione group, and a catalytic wave <63RP117, 83JEC313>. A two-electron reduction of 1,2-dithiole-3-thiones (**2b**) gave a dianion which could be intercepted <86JHC1603>.

1,2-Dithioles of various types react in THF with excess lithium metal to give reactive soluble lithium complexes, corresponding to ring reduction products <84CB42> and 1,2-dithiole-3-thiones form acyclic reduction products with sulfide ions <73BSF721>. Reduction of benzo-1,2-dithiole-3-thione (**37b**) with $LiAlH_4$ gave the tetrathiecine (**95**) <82AHC(31)63>.



3.11.7 REACTIVITY OF NONCONJUGATED SYSTEMS, 1,2-DITHIOLES TYPE 2D, 1,2-DITHIOLANES, 1,2-DITHIOLANUM, AND 1,2-DITHIOLANEDIUM SALTS

3.11.7.1 General Survey

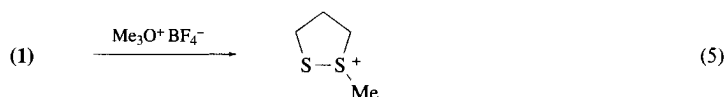
In all of these reactions involving nonconjugated systems, the predominant reactivity is at ring sulfur.

3.11.7.2 Thermal and Photochemical Reactions

1,2-Dithiolanes (**1**) are relatively unstable and polymerize readily by initial fission of the S—S bond under both photochemical and thermal conditions <90SR257>. In ethanol, photolysis gives mercaptosulfenic acids or derivatives. Lipoic acid (**13**) forms various oligomers, depending on the solvent used.

3.11.7.3 Electrophilic Attack at Sulfur

The sulfur is nucleophilic and is alkylated easily to form 1,2-dithiolanium ions (Equation (5)) <85JA2807, 85PS(23)169>.



3.11.7.4 Nucleophilic Attack at Sulfur

3.11.7.4.1 By oxygen nucleophiles

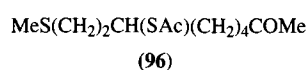
Little data is available on attack by oxygen nucleophiles, but it would be expected that the reactivity would be comparable to that of acyclic disulfides. Some dithiolodithiolanediium salts are attacked by water at the sulfur atom, with scission of the S—S bond <93T1605>.

3.11.7.4.2 By sulfur nucleophiles

Thiolate and thiocyanate anions cause ring opening of dithiolanes by attack at sulfur $\langle 85\text{CA}(102)5680, 88\text{JOC}396 \rangle$ and hydrosulfide ion is a reductant to lipoic acid, by either nucleophilic attack or electron transfer $\langle 84\text{ICA}33 \rangle$. Elemental sulfur or certain other sulfur nucleophiles cause ring expansion to 1,2,3-trithiolanes $\langle 90\text{SR}257 \rangle$. 1,2-Dithiolanium salts undergo attack at sulfur by sulfide ions with reversible ring opening $\langle 85\text{JA}2807 \rangle$.

3.11.7.4.3 By carbon nucleophiles

Alkyl lithium reagents, Grignard reagents, and cyanide ion attack 1,2-dithiolanes at a sulfur atom $\langle 84\text{JCS(P1)}523, 88\text{CL}1339 \rangle$. For example, lipoic acid (**13**) forms the acyclic product (**96**) on sequential treatment with methyl lithium and acetic anhydride. Dithiolanium salts are also attacked by alkenes, with ring expansion $\langle 82\text{JA}3231 \rangle$.

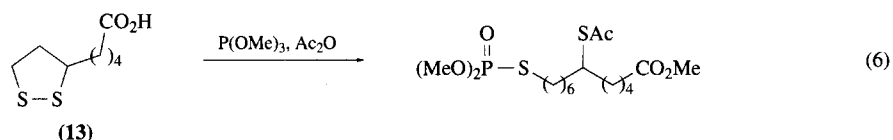


3.11.7.4.4 By nitrogen nucleophiles

Dithiolodithiolandium salts are attacked by aniline at a sulfur atom, with scission of the S—S bond $\langle 93\text{TI}605 \rangle$.

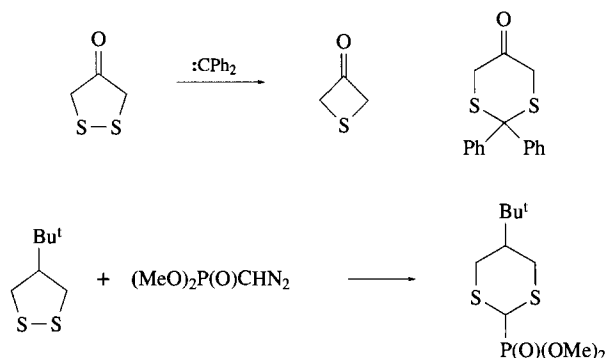
3.11.7.4.5 By phosphorus nucleophiles

Phosphorus(III) species react at sulfur, with ring opening (Equation (6)) $\langle 84\text{JCS(P1)}523 \rangle$.



3.11.7.5 Reaction with Carbenes

Carbenes undergo insertion reactions at the disulfide bond to form 1,3-dithianes or cause desulfurization (Scheme 11) $\langle 85\text{TL}5817, 87\text{PAC}983 \rangle$.



Scheme 11

3.11.7.6 Reduction

Under polarographic conditions, 1,2-dithiolanes are reduced to 1,3-dithiols <90SR257>, but debate surrounds their reducibility under other conditions. The treatment of some dithiolodithioldium salts with carbanions gives dithiacyclooctanes by electron transfer, rather than ylide formation <93T1605>.

3.11.7.7 Deprotonation

In view of the acidity of sulfur α -hydrogen atoms, the C(3) hydrogen in 1,2-dithiolanes should be removable by an appropriate base, but no studies are reported. Evidently anions attack predominantly at a ring sulfur atom.

3.11.8 REACTIVITY OF SUBSTITUENTS ON RING CARBONS

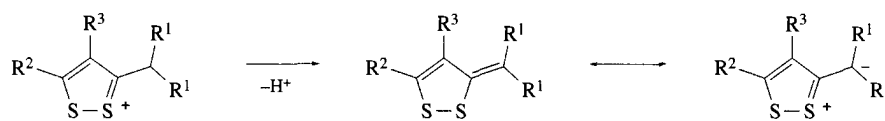
3.11.8.1 Reactivity of Substituents on 1,2-Dithiolium Salts

3.11.8.1.1 General survey

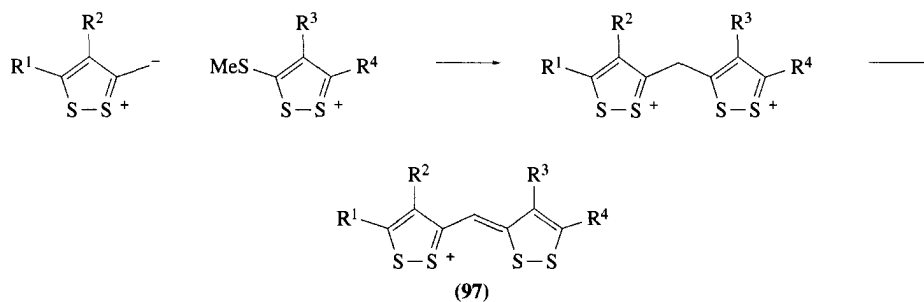
In common with other cationic heterocyclic systems, the dithiolium ring enhances the reactivity of substituents to bases or nucleophilic reagents, and reduces the reactivity to electrophilic reagents.

3.11.8.1.2 Alkyl substituents

3-Alkyl substituents readily deprotonate to form 3-alkylidene-1,2-dithioles (**2d**) which can be isolated, but in other cases react as anions because of contributing resonance structures (Scheme 12). Thus, protons on alkyl substituents are readily exchanged by deuterium. The anions can attack other 1,2-dithiolium salts. When there are replaceable substituents at C(3), cyanines (**97**) are formed (Scheme 13). Otherwise ring opening and recyclization gives 2-thioacetylmethylenethiopyrans (**58**) <77JCS(P1)1511, 88CC22>. Condensations of 3-methyl and other alkyl substituents with carbonyl compounds form 3-alkenyl-1,2-dithiolium salts <64CI(L)461, 66ZC321, 80AHC(27)151>.



Scheme 12



Scheme 13

3.11.8.1.3 Aryl substituents

As expected, an aryl substituent is more readily substituted by electrophilic reagents than the cationic heterocyclic ring <61JA2934, 74CR(C)237>.

3.11.8.1.4 Vinyl substituents

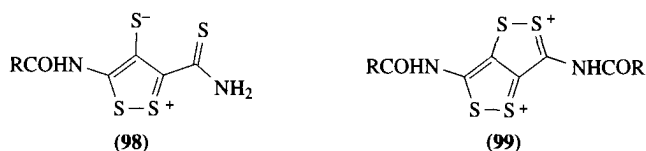
While a number of substituted vinyl- or alkenyl-1,2-dithiolium salts are known, no study is reported on particular properties.

3.11.8.1.5 Carboxy substituents

A limited number of dithioles with carboxy and other substituents are known, but an oxidation of 1,2-dithiole-3-thione-5-carboxylic acid with peracetic acid caused decarboxylation <60CI(L)1568>, suggesting that 3- or 5-carboxy-1,2-dithiolium cations decarboxylate readily.

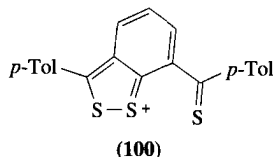
3.11.8.1.6 Hydroxy and thiol substituents

Dithioles with hydroxy and thiol substituents are protonated forms of 1,2-dithiole-3-ones (**2a**) and -3-thiones (**2b**) respectively, which are regenerated on deprotonation. The reactions with nucleophiles of 3-alkoxy and 3-alkylthio-1,2-dithiolium salts give dealkylation products only in minor amounts. Instead, nucleophilic attack occurs on the ring (Section 3.11.4.2(iv)). A 1,2-dithiolium-4-thiolate (**98**) readily acylates on an amine function to form a 1,2-dithiolo-1,2-dithiole (**99**). This unusual reactivity is explained by the relative preferences for cyclic and acyclic forms of mesoionic forms <91EGP293120>.



3.11.8.1.7 Thiones

The exocyclic thione function in the dithiolium salt (**100**) can interact with the sulfur atom on a dithiolium ring, leading, when there are appropriate substituents, to NMR symmetry <69CC83>.



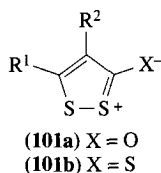
3.11.8.1.8 Amino substituents

Little data is reported on amino substituents, but 3-amino compounds readily deprotonate to 1,2-dithiole-3-imines (**2c**).

3.11.8.2 Reactivity of Substituents on Neutral 1,2-Dithioles

3.11.8.2.1 General survey

Because of structural contributors such as **(101)**, ring substituents on dithiole rings with exocyclic double bonds at C(3) or C(5) should have a reactivity similar to that of 1,2-dithiolium salts **(3)**.

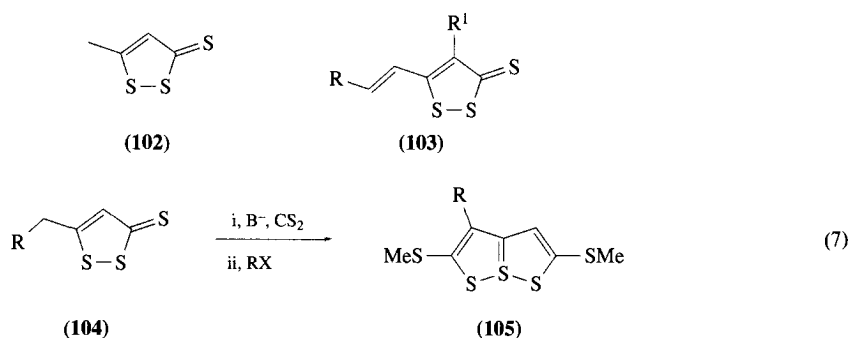


3.11.8.2.2 Benzenoid substituents

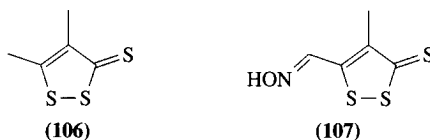
No systematic study of benzenoid substituents has been reported.

3.11.8.2.3 Alkyl groups

5-Alkyl groups on 1,2-dithiole-3-thiones react fairly readily with carbonyl groups to form 5-vinyl-1,2-dithioles <87EUP256929, 92JAP(K)04117377>. For example, 5-methyl-1,2-dithiole-3-thione **(102)** reacts with aldehydes or acetals to form 5-vinyl-1,2-dithiole-3-thiones **(103)** <82AHC(31)63, 92SUL227>. Carbanion formation, reaction with carbon disulfide, and further elaboration converts the dithiole-3-thione **(104)** into a trithiapentalene **(105)** (Equation (7)).



Owing to the lability and electrophilicity of the ring, reactions on alkyl groups such as oxidation or halogenation are likely to be unsuccessful, but exocyclic alkylidene groups are readily attacked by electrophilic reagents, such as nitrous acid and diazonium salts <80AHC(27)151>, and 4,5-dimethyl-1,2-dithiole-3-thione **(106)** reacts at the C(5) methyl with sodium nitrate in acetic acid to form an oxime **(107)** <93IP9219613>.



3.11.8.2.4 Aryl substituents

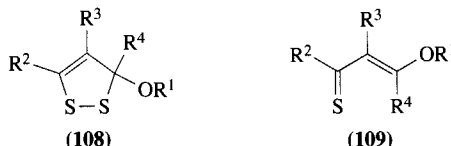
Little reactivity of aryl substituents is described.

3.11.8.2.5 Carboxy substituents

A number of types of 1,2-dithiole carboxylic acids are known. These have typical carboxylic acid reactivity <67ZC275, 72BSF1840, 73BSF721>. No significant newer work is reported.

3.11.8.2.6 Oxygen substituents

1,2-Dithiole-3-ones (**2a**) react with strong alkylating agents, for example, triethyloxonium fluoroborate to form 3-alkoxy-1,2-dithiolium salts. *O*-Acylation can be performed with acetic anhydride in perchloric acid <65LA(688)150, 69ZN(B)577>. Many types of thionating agents convert 1,2-dithiole-3-ones (**2a**) into 3-thiones (**2b**). 3-Alkoxy-1,2-dithioles (**108**) are pseudobases that convert into 1,2-dithiolium salts in acid <65JCS32>, but can lose sulfur to form acyclic products (**109**).



Various reagents, including oxalyl chloride and thionyl chloride, convert 1,2-dithiole-3-ones (**2a**) and -3-thiones (**2b**) into 3-chloro-1,2-dithiolium salts, types (**56a**), some via cyclic intermediates <87PS(31)109>. The oxygen atom on 1,2-dithiolium-3-olates (**20**) can be protonated or alkylated to form 4-hydroxy or 4-alkoxy-1,2-dithiolium salts respectively <86MCLC373>.

3.11.8.2.7 Amino and imino groups

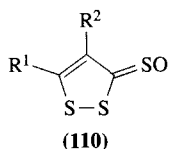
A few 5-amino-1,2-dithiole-3-thiones are described <83BSF277, 83EUP72743>. These have typical 1,2-dithiole-3-thione reactivity. 3-Iminodithioles (**2c**) protonate or alkylate to give 3-amino-1,2-dithiolium salts. They also participate in reactions with alkynoic esters similar to those of -3-thiones (Section 3.11.8.2.8). The nature and amount of interaction of certain exocyclic nitrogen atoms, for example, on a pyridine ring, with the dithiole ring are still unclear <94SR317>.

3.11.8.2.8 Thio- and thiol substituents

1,2-Dithiole-3-thiones (**2b**) readily alkylate to form 3-alkylthio-1,2-dithiolium salts (**19**). Aryl halides are usually unreactive but react photochemically to form 3-arylthio-1,2-dithiolium salts <82AHC(31)63>.

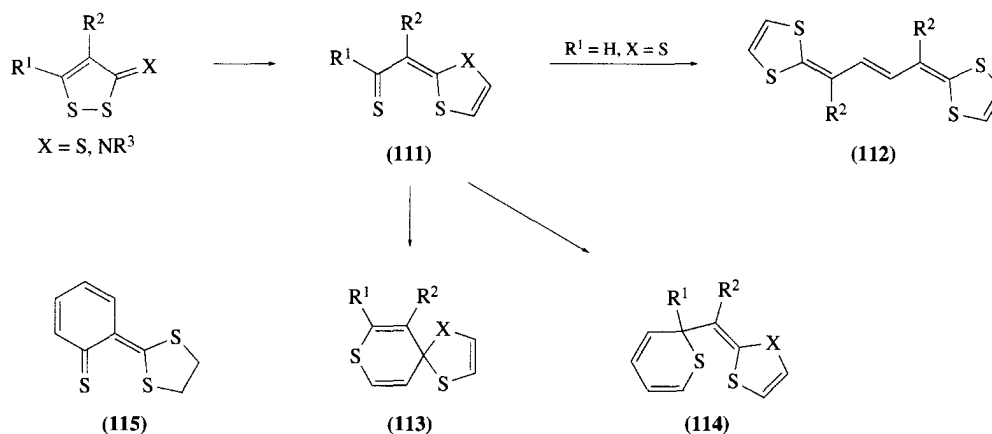
Chlorine reacts with the thione function forming 3-chloro-1,2-dithiolium chlorides (**56a**). These are also obtained with thionyl chloride, oxalyl chloride, and phosphoryl chloride <70LA(742)103, 88BSF101>. With bromine, products are formed whose reactions are consistent with 3-bromothio-1,2-dithiolium bromides (**56c**). 1,2-Dithiole-3-thiones (**2b**) are converted to the corresponding -3-ones (**2a**) with potassium permanganate or mercury(II) acetate.

Aldehyde and ketone functions, and thione and thials, if suitably placed, can strongly interact with the ring sulfur <B-85MI 104-01> by hypervalent or possibly polar effects <94SR317>. The exocyclic thione function is readily oxidized by, for example, peracetic acid. Thione-*S*-oxides (**110**) have been isolated. The reaction with more oxidizing agent under acidic conditions is a valuable synthesis of 3-unsubstituted-1,2-dithiolium salts (**3**), but in some cases 1,2-dithiole-3-ones (**2a**) are products <81PS(12)115, 82AH(31)C63, 92T8143>. The electrochemical oxidation of thiones gives disulfide dications <82AHC(31)63>.



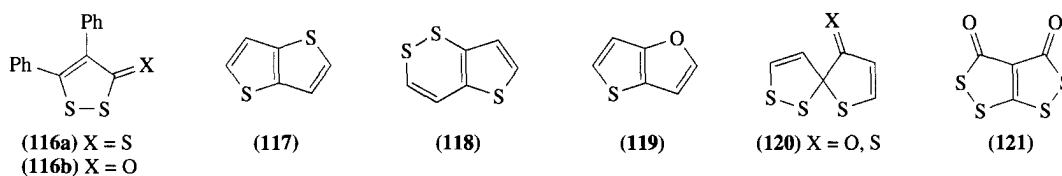
The reactions of alkynes, alkynoic esters, ynamines, and dehydrobenzene with 1,2-dithiole-3-thiones (**2b**), and occasionally 1,2-dithiol-3-imines (**12c**), has been extensively studied <82AHC(31)63>. The initial products for thiones are 3-thioacetylmethylene-1,3-dithioles or thiazoles (**111**), which can react further to form di- or tri- adducts (**113**) and (**114**) respectively. Other rearrangements can give trithiapentalenes (**6**). Thials, formed from reactions of 5-unsubstituted-1,2-dithiole-3-thiones, can dimerize to products (**112**) with loss of sulfur (Scheme 14). Similar types of reactions have been observed with 1,2-dithiole-3-thiones (**2b**) reacting with alkenes and ketenes, especially under

photochemical conditions. Rate constants for the formation of the adducts have been determined $\langle 82\text{SUL}53 \rangle$. The photochemical reaction of benzo-1,2-dithiole-3-thione (**113**) with alkenes gives *o*-thioquinone methides (**115**).

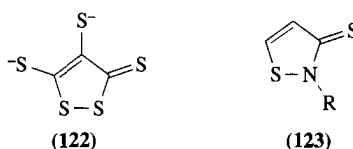


Scheme 14

The thione function acts as a nucleophile to cyclopropenethione and cyclopropenone to form a number of products. Thus 4,5-diphenyl-3-thione (**116a**) reacts with cyclopropenethione to form the thienothiophene (**117**) and a thienodithiin (**118**). With cyclopropenone, the furothiophene (**119**) and 4,5-diphenyl-1,2-dithiole-3-one (**116b**) are isolated. Other products are thienospiro-1,2-dithioles (**120**) $\langle 82\text{LA}315 \rangle$. Fluxional behavior of the dithiole-1,2-dithiole (**121**) has been suggested $\langle 89\text{CC}1716 \rangle$, and related systems exhibit valency tautomerism $\langle 82\text{AHC}(31)63 \rangle$.



1,2-Dithiole-3-thione-4,5-dithiolate anions (**122**) form metal chelates and can be easily alkylated $\langle 85\text{CS}167, 87\text{CA}(106)26239, 87\text{ICA}251 \rangle$. 1,2-Dithiole-3-imines (**2c**) and isothiazoline-3-thiones (**123**) interconvert via Dimroth-type rearrangements under thermal, photochemical, or Lewis acid conditions $\langle 90\text{JPR}387 \rangle$.



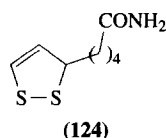
3.11.8.3 Reactivity of Substituents on 1,2-Dithiolanes

3.11.8.3.1 Alkyl and aryl substituents

No data is reported. As with other dithioles, the reactivity of the ring to oxidative or reductive conditions and to electrophilic, nucleophilic, and radical reagents overshadows the reactivity of alkyl substituents. No data is reported for aryl substituents.

3.11.8.3.2 Carboxylic acids and derivatives

Carboxylic acids and their derivatives appear to have fairly typical acid properties, for example, the amide (**124**) of lipoic acid can be dehydrated to a nitrile <86TL2203>.



3.11.9 REACTIVITY OF SUBSTITUENTS ON RING SULFUR

3.11.9.1 Reactivity of *S*-substituents in 1,2-Dithioles

The only examples of reactivity of *S*-substituents in 1,2-dithioles are *S*-oxides. No chemistry of the oxygen atom is reported.

3.11.9.2 Reactivity of *S*-substituents in 1,2-Dithiolanes and 1,2-Dithiolanium Salts

The only reported examples of reactivity of *S*-substituents in 1,2-dithiolanes and 1,2-dithiolanium salts are *S*-oxides and *S*-alkyl groups. The dithiolodithiolodinium salt (**12**) undergo attack by acetic acid at a carbon adjacent to a sulfonium sulfur, similar to Pummerer-type rearrangements <89G617>, but reacts differently with water (Section 3.11.7).

3.11.10 SYNTHESIS

3.11.10.1 Direct Synthesis

3.11.10.1.1 Direct synthesis by formation of one bond

(i) Between two sulfur atoms

Many 1,2-dithiole types are made by S—S bond formation (as shown in Figure 2) from appropriate substrates. These include the oxidation of 1,3-dithiols <89JAP(K)0145380>. However, the bond can also be formed by the internal displacement of a nucleofuge on a sulfur atom by thiolate <85KGS1493, 90SR257, 92EUP293120>.

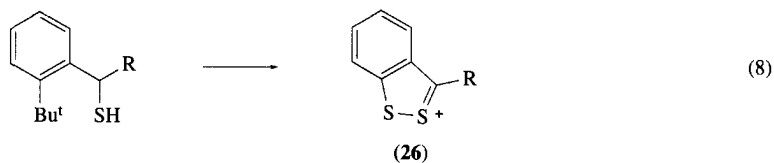


Figure 2 Formation of a sulfur to sulfur bond.

Dithiacyclooctanes provide 1,2-dithiolano[1,2-*a*]dithiole radical cations (**4**) and dications (**5**), and benzo derivatives <81JPC3767, 84CC1151, 86H(24)17, 87JOC4254, 89G617>. The method also provides monocyclic 1,2-dithioles (**2**) <85CC1704, 86CB2582>, benzo- and naphtho- fused systems <65JOC3997, 78JOC3374, 85KGS1493>, and a dithiolopyridine <86CB2582>.

1,2-Dithiolium salts are prepared by oxidation of 1,3-dithio- compounds, or of certain arylthiols

in acidic media <76JCS(D)455, 79TL3339>. In a useful synthesis of benzo-1,2-dithiolium salts (**26**), one of the sulfur atoms is supplied by a *t*-butylthio- group (Equation (8)) <91CC540>.

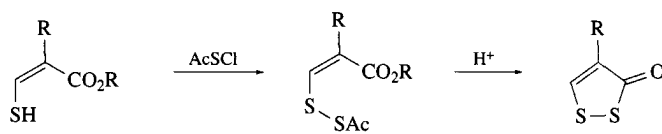


(ii) *Between a sulfur atom and a carbon atom*

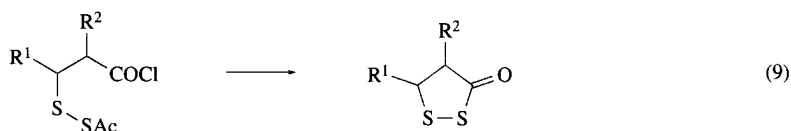
This method involving bond formation between a sulfur atom and a carbon atom (Figure 3) has been little used, but the structural requirements are present in the disulfides, formed by reaction of 2-mercaptoacrylic esters, or 2-mercaptobenzoic esters with chloroacetyl chloride. These cyclize in acids to 1,2-dithiole-3-thiones (Scheme 15) <B-66MI 311-01>. The 3-acyldithiopropanoyl chlorides cyclize to 1,2-dithiolane-thiones (Equation (9)) <74IZV700>.



Figure 3 Formation of a carbon to sulfur bond.



Scheme 15

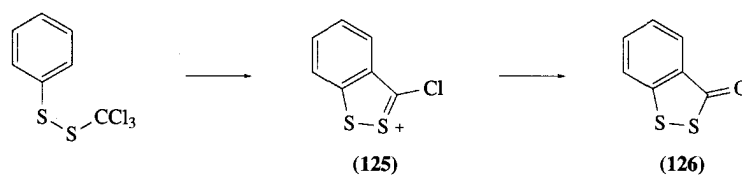


(iii) *Between two carbon atoms*

Only one example involving bond formation between two carbon atoms (Figure 4) is reported. Benzenethiol reacts with trichloromethanesulfonyl chloride to form a product which under Friedel-Crafts conditions cyclizes to 3-chlorobenzo-1,2-dithiolium chloride (**125**). This is hydrolyzed to benzo-1,2-dithiole-3-one (**126**) (Scheme 16) <B-66MI 311-01>.



Figure 4 Formation of carbon to carbon bond.



Scheme 16

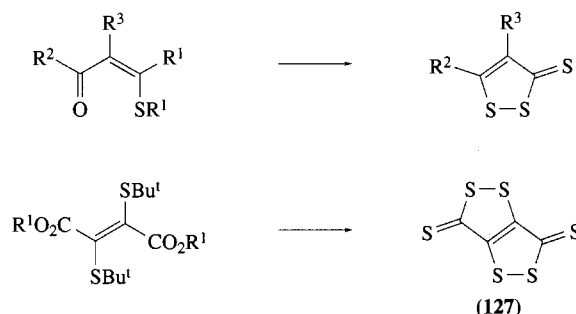
3.11.10.1.2 Direct synthesis by the formation of two bonds

(i) From [4 + 1] units

This method involving [4 + 1] units (Figure 5) is exemplified by a C_3S unit reacting with a sulfur source. The thionation of 1,1-bis(alkylthio)alkene-3-ones or 3-ketoacids is widely used in the preparation of 1,2-dithiole-3-thiones (Scheme 17) and can be used for many structural types <82AHC(31)63, 89JAP(K)01319478, 93MIP 311-01>. It has also been applied to a dithiolodithiole (**127**) <83TL3577>.

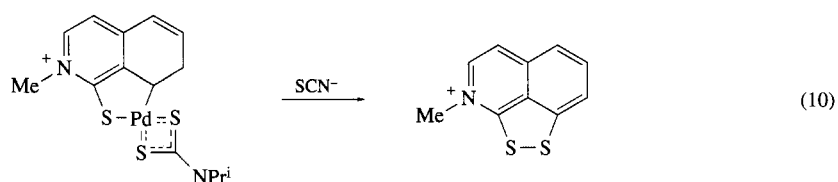


Figure 5 Formation of a carbon to carbon bond and a carbon to sulfur bond.



Scheme 17

The required C_3S unit also exists in 2-thio derivatives of benzoic acid. Thus, thionation of diphenyl disulfide-2,2'-dicarboxylic acid gives benzo-1,2-dithiole-3-thione (**37b**). This approach can be also applied to thienodithioles and to dithiopyridines <82AHC(31)63>. In a conversion of thiosalicylic acid to benzo-1,2-dithiole-3-thione, the extra sulfur atom is provided by thiolacetic acid <92OPP488>. The necessary units also appear in some palladium complexes, which by treatment with thiocyanate give benzo-1,2-dithiolium salts and other fused dithioles (Equation (10)) <90JCS(P1)2881>.



(ii) From [3 + 2] units

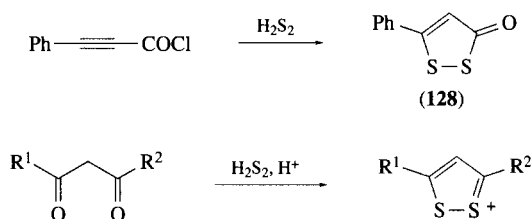
(a) From C_3 and S_2 units (Figure 6). 1,2-Dithiolanes are formed by reaction of 1,3-dihalopropanes or haloalkenes with disulfide ions (Equation (11)) <76JA252, 86EGP264734, 90SR257, 90ZOR1222>. At 500 °C, 1,2-dithiole-3-one (**2a**) is formed from propenol and methyl disulfide or trisulfide <88KGS999>. Dibutyldisulfide and dibutyltrisulfide are transformed into 5-methyl-1,2-dithiole-3-thione (**102**), although at this temperature it is unlikely that the S—S bond is transferred intact into the dithiol.



Figure 6 Formation of two carbon to sulfur bonds.



Hydrogen disulfide provides appropriate S_2 units and readily condenses with phenylpropynyl chloride to form 5-phenyl-1,2-dithiole-3-one (**128**). 1,3-Diketones or synthetic equivalents form 1,2-dithiolium salts (**3**) <57AG138, 62JCS5104>. Hydrogen polysulfide or diacetyl disulfide can usefully replace the hydrogen disulfide (Scheme 18).

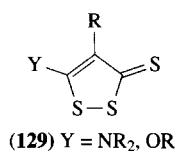


Scheme 18

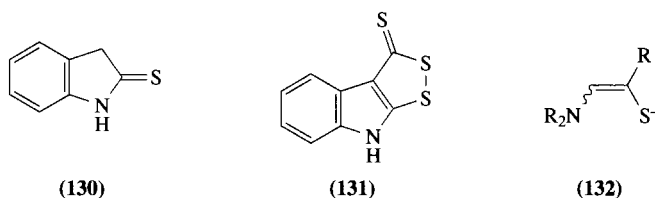
(b) *From C_2S and CS units.* α -Thio derivatives of enamines and enol ethers react with carbon disulfide to form 5-amino- or 5-alkoxy-1,2-dithioles (**129a**) and (**129b**) respectively (Figure 7) <81ZOR139>.



Figure 7 Formation of a carbon to carbon bond and a sulfur to sulfur bond.



Under basic conditions, carbanions derived from thiones, thionoesters, or thioamides react with carbon disulfide to give dithiocarboxylic acids, or derivatives that can be cyclized to 1,2-dithioles <76BCJ3128, 80LA483>. For example, the thioindoxyl (**130**) forms the dithiolindole (**131**) <82AHC(31)63>. The 3-aminocarbanions (**132**) give bis-1,2-dithiol-3-ylidenes (**9**), probably via 1,2-dithiole-3-thiones (**2a**) <82ZOR274>.



3.11.10.1.3 Direct synthesis by formation of three bonds

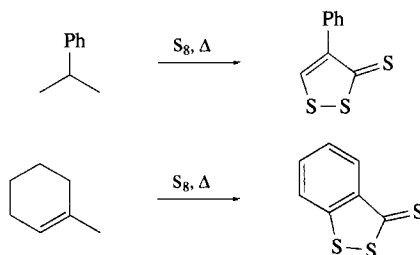
(i) From C_3 and two S units

The sulfurization of various three-carbon units by elemental sulfur (Figure 8) is a common method of 1,2-dithiole synthesis <82AHC(31)63, 89SUL31>. Under the reaction conditions (180–250 °C)

it is likely that various multisulfur species are involved. Because of the difficulty of identifying these, this method is treated here as involving discrete sulfur atoms (Scheme 19).

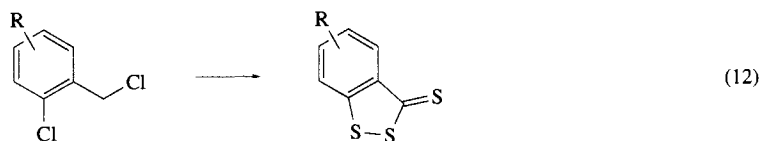


Figure 8 Formation of two carbon to sulfur bonds and a sulfur to sulfur bond.



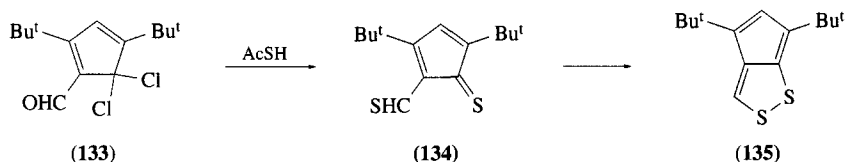
Scheme 19

Haloalkenes, or 2-halobenzyl halides, react with elemental sulfur to form 1,2-dithiole-3-thiones, sometimes with retention of halogen substituents (Equation (12)) <60AG629, 82EUP43936, 85EGP224320>, and 1,3-dichloropropane is converted by piperidinium tetrathiotungstate into 1,2-dithiolane <92JOC1699>. The preparation of a 1,2-dithiol-3-ylidenepyridylmethane (type **(61b)**) from a pyridinediyne and hydrogen sulfide involves two discrete sulfur atoms <92JOC3995>.



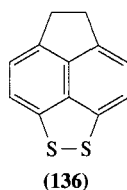
Various types of dithioles are formed from unsaturated esters and ketones. Dienoic acids and esters give 1,2-dithiole-3-ylidenes (**(3d)**) sometimes with dehydrogenation.

The reaction of 1,3-diketones and 3-ketoesters with phosphorus pentasulfide, sometimes also with sulfur, provides 1,2-dithiole-3-thiones <82AHC(31)63> with alkyl, aryl, or heterocyclic substituents. Acylphenols, ethers, and heterocyclic analogues can also be used. Other 1,3-diketones react with phosphorus pentasulfide to give materials (probably bis-1,2-dithiol-3-yl sulfides) (**(33b)**), from which 1,2-dithiolium salts (**(3)**) can be isolated by acid treatment <65LA(682)188, 76JA7629, 88JAP(K)63222188> and 3-amidoesters give dithiole-3-thiones with amine substituents <83EUP72743>. Treatment of the aldehyde (**(133)**) with thiolacetic acid gave the thionoal (**(134)**) which by an 8π electrocyclic process converted to a cyclopentadithiole (**(135)**) (Scheme 20) <85TL189>.



Scheme 20

A dilithio acenaphthylene reacts with elemental sulfur to form the fused derivative (**(136)**). Naphthaceno-fused 1,2-dithioles are formed from tetrachloronaphthacene and various sulfur transfer reagents, or by thionation of a naphthacenedione <90CA(112)178743>. Mesoionic 1,2-dithiolium-4-olates (**(20)**) are formed from 1,2,3-triketones and phosphorus pentasulfide, or various α,α' -halogenated ketones with potassium ethyl xanthate, or sulfur in dimethylformamide, or other sulfur transfer reagents <78AJC297, 87PS(31)109>.

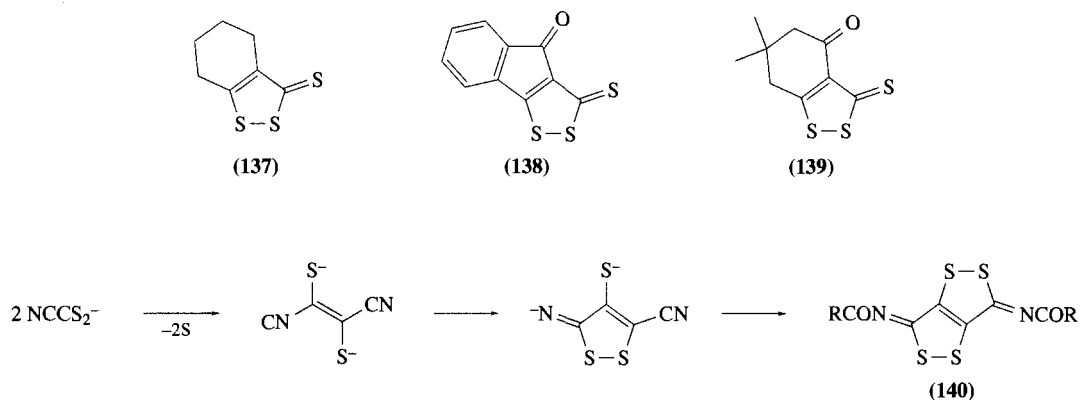


(ii) From C(2), CS, and S units (Figure 9)

Enamines react with carbon disulfide and elemental sulfur to give 1,2-dithiole-3-thiones via 3-iminodithioic acids <82AHC(31)63>. The reaction can give other products and the yields are rather low, but the mild conditions of the reaction, contrasted with thermal reactions of elemental sulfur, do not cause dehydrogenation. Thus, 1-morpholinocyclohexene gives tetrahydrobenzo-1,2-dithiole-3-thione (137). By contrast, the direct sulfurization of methylcyclohexene gives benzo-1,2-dithiole-3-thione (37b). More recently, enaminones have been used for the preparation of some 4-acyl-1,2-dithioles (138) and (139) <90H(31)1, 91JHC1245>. Compounds with activated methylene groups, on treatment with carbon disulfide in base, give dithiocarboxylate ions, which react with sulfur to form dithiole-3-thiones <63ZC26>. The necessary two-carbon fragment is also provided by dehydrobenzene or arylsulfonylimines <70TL629, 78JCS(C)1017>. The formation of the dithiole ring in the fused dithiolodithiole (140) from cyanodithioformate and an acyl halide is likely to involve combinations of C(2), CS, and S units (Scheme 21) <81EGP148341>.



Figure 9 Formation of a carbon to carbon bond, a carbon to sulfur bond, and a sulfur to sulfur bond.



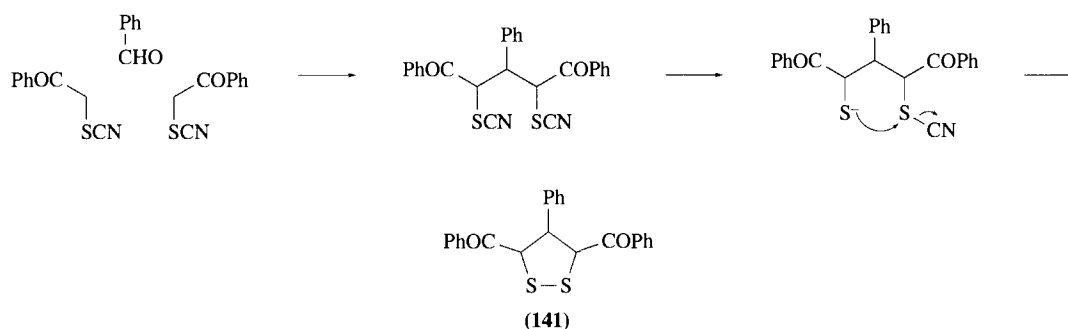
Scheme 21

(iii) From CS, CS, and C units (Figure 10)

A dibenzoyldithiolane (141) is formed from phenacylthiocyanate and benzaldehyde, most likely via the thiocyanate and hydrolysis (Scheme 22) <90EGP278340>.



Figure 10 Formation of two carbon to carbon bonds and a sulfur to sulfur bond.



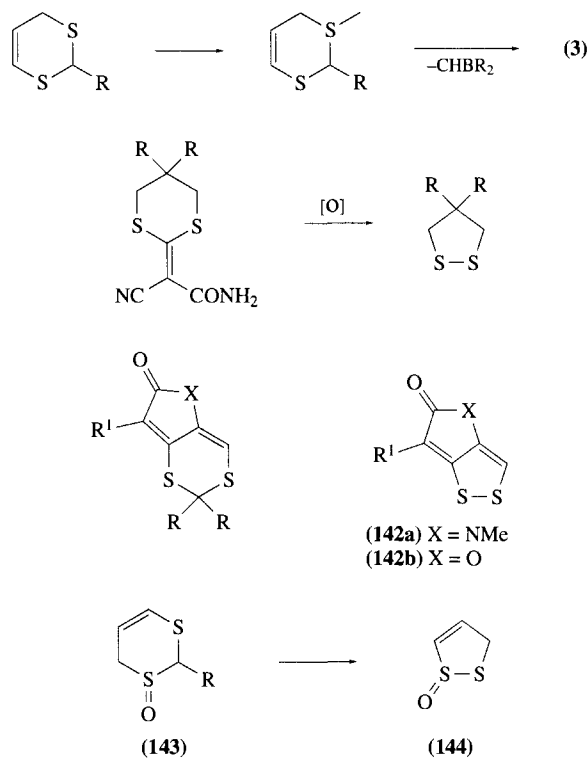
Scheme 22

3.11.10.2.1 From 1,2,3-trithianes

1,2-Dithiolanes and 1,2,3-trithianes readily interconvert by sulfur insertion or extrusion (90SR257). The desulfurization is also effected with P(III) species and phosphorus ylides (91S785).

3.11.10.2.2 From 1,3-dithianes and 1,3-dithienes

1,2-Dithiolanes and 1,2-dithiols can be made from 1,3-dithianes or 1,3-dithienes respectively, by oxidation in the presence of acid, or from 1,3-dithiane-*S*-oxides and acids. Bromine may also be used (Scheme 23) ^{<87JAP(K)6261977, 87JOC4337, 88ACS(B)629, 90SR257>}. This method has been used to prepare some 1,2-dithiolo[4,3-*b*]pyrrole antibiotics (**142a**) and a furan analogue (**142b**) ^{<92LA473, 93LA305>}.

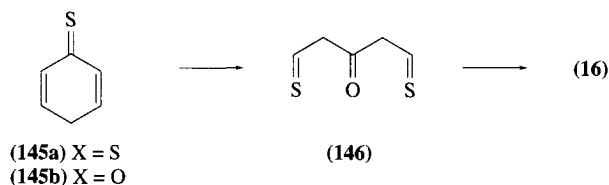


Scheme 23

A 1,2-dithiene-*S*-oxide (**143**) is reported to undergo conversion to a 1,2-dithiole-*S*-oxide (**144**) by a nucleophilic induced ring opening [⟨89JA8268⟩](#).

3.11.10.2.3 From pyrans and thiopyrans

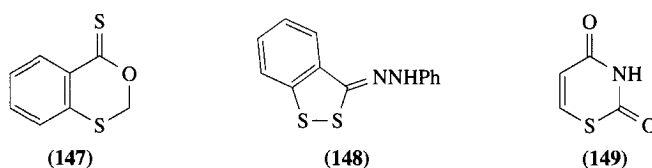
4*H*-Thiopyran-4-thiones (**145a**) and 4*H*-pyran-4-thiones (**145b**) undergo ring opening by hydro-sulfide or hydroxide respectively, to form acyclic products (**146**), which on reoxidation are converted to 3-acylmethylene-1,2-dithioles (**16**) (Scheme 24) <70JCS(C)2412>.



Scheme 24

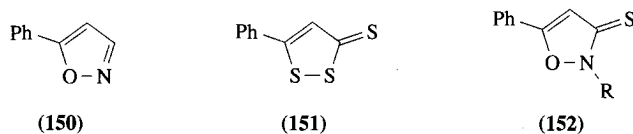
3.11.10.2.4 From 1,3-thioxins and 1,3-thiazines

5,6-Benzo-1,3-thioxin-4-thione (**147**) reacts with phenylhydrazine to form the phenylhydrazone (**148**), probably by initial nucleophilic attack at the thione function <80T3309>, and 1,3-thiazine-2,4-dione (**149**) reacts with phosphorus pentasulfide to form 1,2-dithiole-3-thione (**2**) <82AHC(31)63>.



3.11.10.2.5 From isoxazoles

Isoxazoles possess suitable three-carbon units for conversion to the 1,2-dithiole skeleton. Thus, 5-phenylisoxazole (**150**) is thionated to 5-phenyl-1,2-dithiole-3-thione (**151**) <58AC(R)577>, and isoxazoline-3-thiones (**152**) form 1,2-dithiole-3-imines by reaction with hydrogen sulfide <80CPB487>.

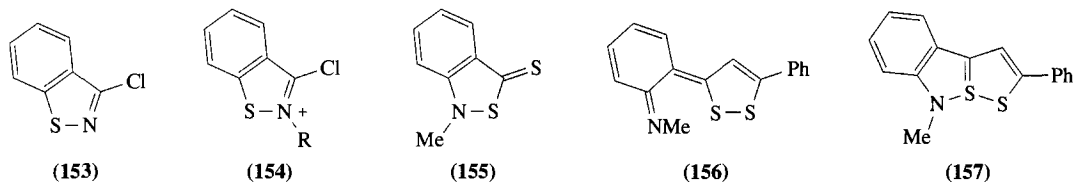


3.11.10.2.6 From isothiazoles

Various 1,2-dithiole-3-imines (**2c**) and isothiazoline-3-thiones (**41**) interconvert via Dimroth-type rearrangements (Section 3.11.5.2.3(iii)), and other interconversions of isothiazoles and 1,2-dithioles are common. *N*-Arylisothiazolium salts react with sulfur in pyridine to form 1,2-dithiole-3-aryl-imines. The reaction may involve ring opening to a β -thio ketimine via a carbene, but Dimroth-type rearrangements of isothiazoline-3-thiones to dithioleimines cannot be excluded <67CB2435, 73CJC3081>. Also, isothiazolium salts form bis-1,2-dithiole-3-yl sulfides (**33b**) with hydrogen sulfide <72JCS(P1)2305>, probably via nucleophilic attack on sulfur <73CJC3081>.

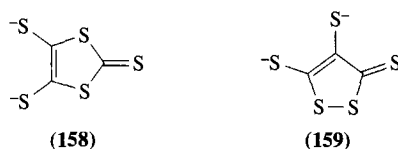
3-Chloro-benzisothiazoles (**153**) or benzisothiazolium (**154**) salts react with thiolacetic acid to give 1,2-dithioles, and benzo-1,2-dithiole-3-thiones are formed from benzisothiazoline-3-thiones with hydrogen sulfide. An isothiazoline-3-thione (**155**) reacted with phenylethyne to form what may

be described as either the fused system (**157**) or as a 1,2-dithiole (**156**). This rearrangement probably proceeds similarly to that described for the reaction of 1,2-dithiole-3-thiones and alkynes (Section 3.11.8.2.8) <87CJC1247>.



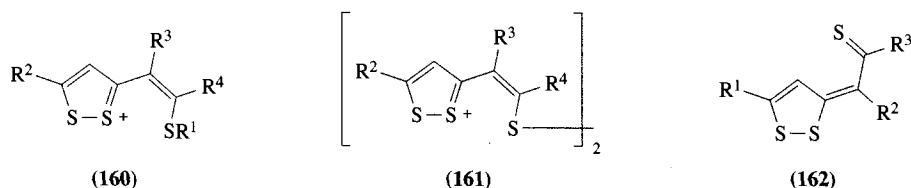
3.11.10.2.7 From 1,3-dithioles

1,3-Dithiole-3-thione-4,5-dithiolates (**158**), prepared by chemical or electrochemical reduction of carbon disulfide in dimethylformamide, themselves rearrange at higher temperatures to 1,2-dithiole-3-thione-4,5-dithiolates (**159**) <92CCR99>. These can be alkylated, acylated, and otherwise characterized <88CS167>. Also, photochemical rearrangement of some mesoionic 1,3-dithioles gives 1,2-dithioles <80CA(92)197661>.



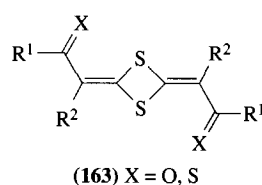
3.11.10.2.8 From trithiapentalenes

These compounds, usually represented as having a central tetravalent sulfur, can also be regarded as 1,2-dithiole derivatives, i.e. the bonding in sulfur compounds described as tetravalent may also be interpreted in terms of ionic bonding and negative hyperconjugation <90JA1434, 93JPC3176>. Several reactions convert them into more typical 1,2-dithioles. For example, they are converted by alkylation into 3-(3-alkylthiovinyl)-1,2-dithiolium salts (**160**), and by mercury(II) acetate into 3-acylmethylene-1,2-dithioles (**16**) <68JOC2915>. Electrochemical oxidation forms bisdithiolium disulfides (**161**), photolysis forms an (*E*)3-thioacetylmethylene-1,2-dithiole (**162**) <82AHC(31)63>, and tin radicals and tungsten or gold complexes form 1,2-dithioles <82JCS(P1)431, 83CC289, 88CC22>.



3.11.10.2.9 From 1,3-dithietanes

2,4-(Dibenzoyl- (or bithiobenzoyl-) methylene)-1,3-dithietes (**163**) possess suitable C_3 units and form 1,2-dithiole-3-thiones on thionation <81LA1729>.



3.11.10.3 Syntheses of Particular Classes of Compounds

3.11.10.3.1 1,2-Dithiolanes and other saturated derivatives

The most practical methods of syntheses of 1,2-dithiolanes and other saturated derivatives appear to be those involving sulfur to sulfur bond formation by oxidative ring closure of dithiols, or thiolate displacement of a leaving group attached to another sulfur. This can be applied to many types <90SR257>, but in view of the availability of 1,3-dithianes, syntheses by their oxidative ring contraction offer attractive alternatives.

3.11.10.3.2 1,2-Dithiolanium salts and 1,2-dithiolo-1,2-dithiolodiiium salts

S-Alkyl-1,2-dithiolanium salts (**23**) are best made by alkylation of 1,2-dithiolanes <85PS(23)169>. Only one method for the dithiolodiiium salts is described, that of acid treatment of dithiacyclooctane-S-oxides.

3.11.10.3.3 1,2-Dithioles

For 1,2-dithiole-3-ones and 3-thiones, the sulfurization of various unsaturated esters to 1,2-dithiole-3-ones, and with phosphorus pentasulfide to 3-thiones is a very versatile method. It is less applicable to 5-unsubstituted types, although the parent 1,2-dithiole-3-thione can be made from tetramethoxypropane and phosphorus pentasulfide <77S802>. 1,2-Dithiole-3-thiones (**2b**), including compounds lacking 5-substituents, can be made by sulfurization of 3-substituted propanes or propenes, but the harsh conditions of this reaction render it unsuitable for many types.

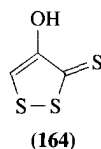
1,2-Dithiole-3-thiones can be made from 1,2-dithiole-3-ones by thionation, and the reverse process is effected by mercury(II) acetate.

3.11.10.3.4 1,2-Dithiolium salts

The oxidation of the 3-thiones with peracetic acid is a valuable route to 3- (or 5-) unsubstituted 1,2-dithiolium salts <66AHC(7)39, 80AHC(27)151>. Otherwise syntheses based on 1,3-diketones can be used. Hydrogen disulfide is inconvenient to make and syntheses based on sequential treatment with phosphorus pentasulfide and acid are limited and messy, but little attention has been paid to diacyldisulfides as potential S₂ sources. The 1,2-dithiole-3-thiones also provide routes to 3-alkylthio-1,2-dithiolium salts (**19**) by alkylation, to 3-halo-1,2-dithiolium salts (**56a**) by treatment with various halogenating reagents, and to amino-1,2-dithiolium salts (**56d**) or iminodithioles by reaction of alkylthio- or halo- compounds with amines. The latter route is preferred to avoid isothiazole formation. Polythio- derivatives of 1,2-dithioles, of interest in electronic applications, are best made by rearrangement of 1,2-dithiole-3-thione-4,5-dithiolate anions.

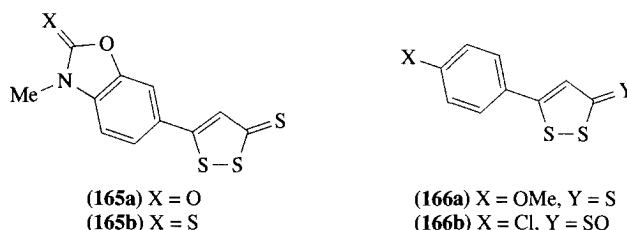
3.11.11 IMPORTANT COMPOUNDS AND APPLICATIONS

Many 1,2-dithiolanes are naturally occurring <84CA(101)126818, 89CA(110)93733, 90SR257>. Alkyl-1,2-dithiolanes, present in anal gland secretions of mustelids, have been proposed for crop protection <90SR257>. Various hydroxy-1,2-dithiolanes (**164**) have proven insecticidal properties <89TL3671, 92CA(117)247107>, and a 1,2-dithiolan-4-yl nucleoside has been patented as an antitumour agent <89JAP(K)0183902>.



1,2-Dithiolane-4-carboxylic acid (asparagusic acid) (**14**) is thought to act in biological systems as a substrate of a dehydrogenating enzyme, and to stimulate pyruvate oxidation. Lipoic acid (**13**) is involved, among other biological processes, in the oxidative decarboxylation of 3-ketoacids, oxidative phosphorylation, and in photosynthesis <90SR257>. Cyclic disulfide anions of lipoic acid can effect two-electron reductions of flavins <84CJC962>. Lipoic acid has been proposed as an anti-retroviral agent <91EUP427246>, various lipoic acid derivatives have radioprotective properties <82CA(97)140957, 83CA(98)30646, 85CA(102)131949>, and polymers containing lipoic acid have been suggested as electron transfer catalysts <87MM962, 89CA(110)95809>. Some streptomyces species produce pyrrolo[3,2-*c*]-1,2-dithiole antibiotics (**143a**), whose syntheses, and properties are currently being explored <86GEP3602148, 92LA473, 93CA(118)22076>. They act as inhibitors of actinomycetes <86JAB609> and have been proposed as agrofungicides <89JAP(K)0122879>.

The 1,2-dithiole-3-thione "Oltipraz" (**86**) has schistosomicidal activity. It appears to deplete glutathione stores of schistosomes by inhibition of glutathione *S*-transferase <85T3705, 92CA(116)187565>. The dithiole-3-thiones (**165**) are active against schistosomes in mice <86CA(105)35192>. 5-(4-Methoxyphenyl)-1,2-dithiole-3-thione (**166a**) protects against liver damage by carbon tetrachloride and inhibits platelet aggregation <88CA(108)105945, 92AF318>, and 5-(4-chlorophenyl)-1,2-dithiole-3-thione-*S*-oxide (**166b**) has been proposed as a liver protective agent <89EUP343303>. Other dithiole-3-thiones protect against aflatoxin-induced hepatocarcinogenesis <92CA(116)168174>, and are chemoprotective and radioprotective <90CAN17>, immunomodulators <88EUP236929>, and antirheumatic agents <84FRP2541679, 84FRP25415750>. Other pharmaceutical uses are for the prevention of hair loss in chemotherapy, for dandruff control, and combined as a dipeptide amide, for artificial sweeteners <85GEP3509071, 87JAP(K)62175417, 89USP4797298>.



Many halogeno-1,2-dithioles act as fungicides and slimicides <88EUP277402, 88EUP282203, 88JAP(K)62292702, 90EUP338440>.

Various 1,2-dithiole derivatives, especially those with sulfur substituents, have been investigated for their charge transfer properties with electron acceptors <76JA252, 81CS65, 84CA(100)67757, 85MCLC315, 85MCLC357, 86T839, 86TL159, 87CS261, 90JPR821, 91CL871>. There are also battery applications <88EGP258107>.

1,2-Dithioles have also been patented for photographic applications <91JAP(K)03155538, 92EUP447105>, and alkoxy-1,2-dithiolium salts have been investigated for liquid crystal applications <86MCLC373, 90LC775, 91PS(59)541>. 1,2-Dithiole-3-thione-4,5-dithiolates (**122**) have been patented as corrosion inhibitors <87EGP246322>.

3.12

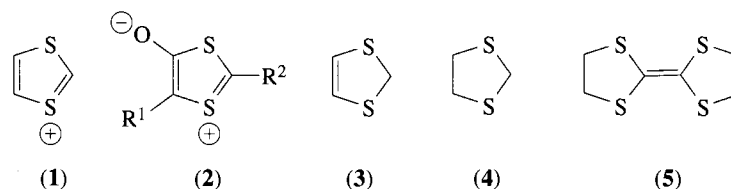
1,3-Dithioles

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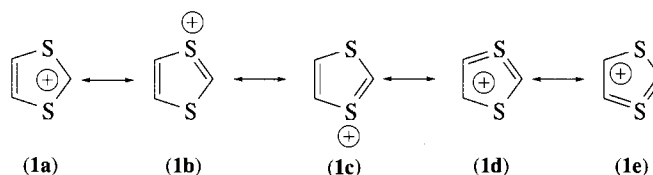
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3.12.1 INTRODUCTION

The synthesis and characterization of new heterocyclic systems has been a central research objective in contemporary organic chemistry. This chapter deals with 1,3-dithiole compounds such as 1,3-dithiolylum ions (**1**), mesoionic 1,3-dithiol-4-ones (**2**), 1,3-dithioles (**3**), 1,3-dithiolanes (**4**), and the tetrathiafulvalene (TTF) system (**5**); all of these compounds have gained a central position in the chemistry of new conducting solids.



The chemistry of the 1,3-dithiolylum, 1,3-dithiole, 1,3-dithiolane, and the tetrathiafulvalene system has been subject to excellent reviews <66AHC(7)39, 70QRS275, 74ACR232, 76S489, 77AG534, 79ACR79, 80AHC(27)151, 83UK1301, 84ACR227, 85MI 312-01, 86T1209, 87SR155, 92HOU(E14a/3)403, 93HOU(E8a)630, 93SR245, 95S215>. The 1,3-dithiolylum ions of the parent compound (**1**) possess a 6 π -electron system and thus exhibit Hückel-type aromatic properties. They can be represented as resonance hybrids (**1a**)–(**1e**). (Scheme 1).



Scheme 1

According to IUPAC rule C-83 the ionic system (**1**) has been named 1,3-dithiolylum although it is often referred to in the literature as “1,3-dithiolium.”

3.12.2 THEORETICAL METHODS

An understanding of certain chemical and physical properties of sulfur-containing heterocycles has been offered by quantum chemical calculations. Some earlier computational results by the Hückel LCAO-MO method have already been summarized <65AHC(5)1>. In addition, π -electron densities and reactivity indices of 4-aryl-1,3-dithiolylum ions have been calculated <65ZC23, 70CPB865>. Simple LCAO-MO calculations for the 1,3-dithiole-2-thione, benzo-1,3-dithiolylum ion, 1,3-dithiole-2-one, and 1,3-dithiolylum ions indicate that the lowest electron density was found at the 2-position of the 1,3-dithiolylum cation, and showed that the C(4)—C(5) bond order corresponded approximately to that of an isolated C=C double bond. A delocalization energy of 440 kJ mol⁻¹ (15 kcal mol⁻¹) has been calculated for this cation. It was found for the benzo-1,3-dithiolylum ion that electrophilic attack should take place at the 4-position whereas nucleophilic substitution takes place at the C(2) position <66AHC(7)39>.

Charge densities have been calculated for thiazolylum, 1,3-dithiolylum, and imidazolium ion (by π -electron SCF-MO) using the zero differential overlap approximation (Table 1) <71JHC551>; it was found that the highest charge densities are at the heteroatoms of the ions. The difference in energy for an ion and its corresponding carbene predicts the rates of ionization of the H—C(2) bond and was found to be imidazolium < thiazolylum < 1,3-dithiolylum.

These theoretical findings are in excellent agreement with experiments showing thiazolylum ions are deuterated at the 2-position about 300 times faster than imidazolium ions.

Nonempirical calculations of the dithiolylum ion using a linear combination of Gaussian orbitals with and without *d*-orbitals revealed that the carbons at the 2-, 4-, and 5-positions possess a negative charge, whereas almost all of the positive charge is shared by the sulfur and the hydrogen atoms <72TL4165>.

Since nucleophilic addition occurs exclusively at the 2-position, one must assume that the presence of the nucleophile would be expected to induce an opposite polarization.

Table 1 π -Electron SCF-MO computed charge densities <71JHC551>.

Atom	Imidazolium ion		Thiazolylum ion		1,3-Dithiazolylum ion	
	Ion	Carbene	Ion	Carbene	Ion	Carbene
1	0.41	0.30	0.38	0.04	0.44	0.06
2	0.15	-0.40	0.13	-0.30	0.09	-0.09
3	0.41	0.30	0.45	0.36	0.44	0.06
4	0.02	-0.10	0.09	0.02	0.02	-0.01
5	0.02	-0.10	-0.05	-0.13	0.02	-0.01

UV transition energies of the 1,3-dithiolylum ions have been calculated by the Pariser–Parr–Pople (PPP) method with neglect of the d -orbitals <68JPC3975, 68TCA319>. Excellent agreement between the observed and the calculated UV transition energies for the 1,3-dithiolylum ion was observed by a semiempirical PPP variable integral method <71TCA216>. In addition, good agreement between experimental values and predictions by the PPP method was found for the influence of alkyl substituents on the UV transitions of the 1,3-dithiolylum ions <71T4705>. These compounds possess two UV absorption maxima of approximately equal intensities. The long wavelength band corresponds to a $\pi \rightarrow \pi^*$ transition with a transition moment in the direction of the twofold symmetry axis of (1), whereas the $\pi \rightarrow \pi^*$ transition of the second band is polarized perpendicular to the first one <71T4705>.

In addition, introduction of a mercapto or methylsulfanyl moiety at the 2-position of the 1,3-dithiolylum ion is known to drastically change the UV absorption spectrum; instead of two maxima in the parent ion there are now three absorption maxima. These findings are consistent with the calculations <68TCA319>.

For the fluorescent 2,5-diphenyl-1,3-dithiolylum perchlorate the absorption behavior has also been satisfactorily interpreted by PPP calculation.

3.12.3 EXPERIMENTAL METHODS

3.12.3.1 X-ray, Neutron, and Electron Diffraction

Several x-ray crystal structure determinations on 1,3-dithioles and 1,3-dithiolanes have been carried out. Representative data are provided in Tables 2 and 3. Most of these analyses refer to the (dibenzo)-tetrathiafulvalene or (dibenzo)-tetrathiafulvalenium system <74CSC23, 79MI 312-01, 80K507, 81AX(B)1716, 81BCJ2408, 81MCLC295, 81MI 312-01, 82AX(B)1632, 82CJC2057, 82CSC835, 82CSC1841, 82JCP(77)318, 82JCS(P2)593, 82MCLC137, 82MCLC163, 83BCJ405, 83CL581, 83CL759, 83JA297, 83MCLC181, 83MI 312-03, 83MI 312-04, 83SM101, 84CL1, 84CL957, 84CSC190, 84CSC1331, 84CSC1334, 84JA7644, 84JOC726, 84K1089, 84MCLC33, 84MCLC359, 84MI 312-01, 84NJC3, 85JA6184, 85MCLC361, 86BCJ301, 86CL2017, 86IZV342, 86JA1908, 86JA7853, 86MCLC393, 86MI 312-03, 86ZN(A)1319, 87CL459, 87MI 312-01, 88SM343, 90CC970, 90CSC2312, 92CC1410, 92CSC516, 94S460, 94S489>. Only a few structures are available for 1,3-dithioles <73CSC95, 80CSC615, 82AX(B)1525, 82MI 312-01, 82ZOB167, 84CSC190, 84CSC1221, 84JCS(D)3, 85CSC585, 95S521>. The structures of several complexes with metals have been determined, for example, with mercury <81IC3819>, iron <82JOM(233)C51, 84JOM(262)69>, chromium <83CB11>, and nickel <78DOK(241)862, 83CC110>. A few structures for 1,3-dithiolanes have been determined <78AX(B)3805, 80ACS(A)577, 81HCA1140, 82AX(B)1525, 82JHC459, 83JOC227, 84CSC198>.

It is of interest to note that tetrathiafulvalene (5) is not planar, but rather slightly distorted into a chair conformation <71CC889>. Also, the five-membered ring of the 1,3-dithiolane derivative (6) was found to be slightly puckered with C(4) and C(5) being above and below the plane defined by S(1)—C(2)—S(3) <54ACS1145>.

3.12.3.2 NMR Spectroscopy

Correlations have been established between the resonances of methyl protons in the ^1H NMR spectra of methyl-substituted 1,3-dithiolylum ions as well as resonances of ring protons with calculated π -charges of the ring carbons.

A linear relationship exists in 2π -substituted phenyl-derivatives of 4-phenyl-1,3-dithiolylum ions

Table 2 Bond lengths (Å) of some 1,3-dithiole and 1,3-dithiolane derivatives.

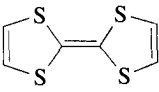
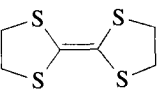
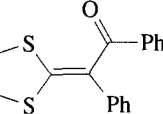
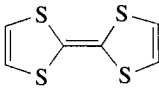
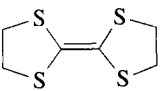
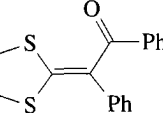
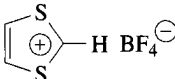
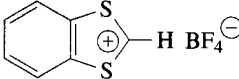
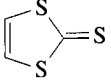
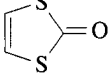
			
<i>Bond</i>			
S(1)—C(2)	1.756	1.82	1.72
S(1)—C(5)	1.732	1.84	1.83
S(3)—C(2)	1.758	1.86	1.76
S(3)—C(4)	1.729	1.89	1.80
C(4)—C(5)	1.314	1.52	1.54
References	71CC889	54ACS1145	67TL5311

Table 3 Bond angles (°) of some 1,3-dithiole and 1,3-dithiolane derivatives.

			
<i>Angle</i>			
S(1)—C(2)—S(3)	114.5	104	115.5
C(2)—S(3)—C(4)	94.3	102	96.7
S(3)—C(4)—C(5)	118.6	109	15.4
C(4)—C(5)—S(1)	118.0	100	108.3
C(5)—S(1)—C(2)	94.5	109	94.6
References	71CC889	54ACS1145	67TL5311

between the Hammett σ_p values and the H(5) resonance signal (71T4003). Proton NMR data of variously substituted 1,3-dithiolium ions has been compiled (66AHC(7)39, 80AHC(27)151). Due to the delocalization of the negative charge on O(4) and C(5), leading to an increased shielding of C(5), the H(5) resonance of 2-phenyl-1,3-dithiolium-4-olate appears at significantly higher field than in 1,3-dithiolium ions (Table 4). In addition, the ^1H NMR spectrum of 1,3-dithiolium tetrafluoroborate exhibits the H(2) signals about 2 ppm downfield from the H(4) and resonances. This finding has been explained in terms of lower electron density on the C(2) than on C(4) and C(5), respectively (66AHC(7)39).

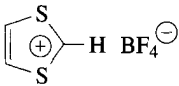
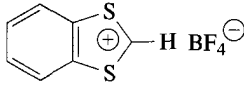
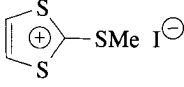
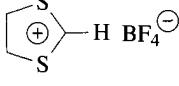
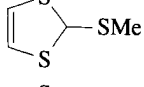
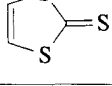
Table 4 Proton NMR spectral data of some 1,3-dithiole derivatives^a.

<i>Compound</i>	<i>H(2)</i>	<i>H(4); H(5) and aromatic</i>	<i>Solvent</i>	<i>Reference</i>
	11.65 11.50	9.67 8.06–8.26	CD ₃ CN CF ₃ CO ₂ D	76BCJ3567 76BCJ3567
		8.66–8.86		
		7.20	CS ₂	66AHC(7)39
		6.74	CS ₂	66AHC(7)39

^a δ in ppm relative to internal TMS.

Due to the greater delocalization of the positive charge in the 1,3-dithiolylum cation the C(2) resonance signal in the ^{13}C NMR spectra of the 1,3-dithiolylum ion at δ 179.5 ppm appears at higher field than in the 1,3-dithiolanylium ion (δ 221.2 ppm); the opposite is true for the C(4) resonances (Table 5).

Table 5 Selected ^{13}C NMR spectral data of some 1,3-dithiole derivatives^a.

Compound	C(2)(δ)	C(4)(δ)	Solvent	Reference
	179.5	146.2	$\text{CF}_3\text{CO}_2\text{D}$	77CL1133
	182.4	146.0	$\text{CF}_3\text{CO}_2\text{D}$	77CL1133
	166.4	139.7	$\text{CF}_3\text{CO}_2\text{D}$	77CL1133
	221.2	46.4	$\text{CF}_3\text{CO}_2\text{D}$	77CL1133
	61.2	115.4	CDCl_3	77CL1133
	140.7	133.7	$\text{SO}_2(-60^\circ\text{C})$	77JOC2237

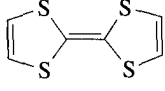
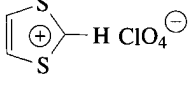
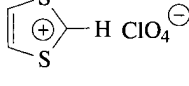
^a δ in ppm relative to internal TMS.

Spectroscopic data for 1,3-dithiole-2-thiones and 1,3-dithiole-2-ones and their corresponding saturated compounds have been compiled <81JPR737>. Calculated electron densities have been correlated with observed ^{13}C chemical shifts for the benzo-1,3-dithiolylum ion <77CL1133>.

3.12.3.3 UV and IR Spectroscopy

The UV absorption spectrum of 1,3-dithiolylum perchlorate in ethanol/perchloric acid shows two bands which are shifted to larger wavelengths in perchloric acid alone (Table 6). A bathochromic shift of the largest wavelength absorption at 305 nm is observed upon introduction of alkyl groups as in trimethyl-1,3-dithiolylum perchlorate <71T4705>.

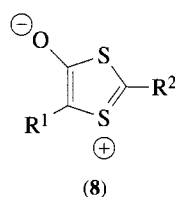
Table 6 UV Spectral data of some 1,3-dithiole compounds.

Compound	λ_{max} (nm) ($\log \epsilon$)	Solvent	Reference
	207 (3.13)	cyclohexane	71PMH(3)67
	247 (2.56) 303 (4.11) 317 (4.10) 368 (3.28)	cyclohexane	71JA2258
	4.50 (2.43) 212 (3.53)	ethanol/ HClO_4	71PMH(3)67
	254 (3.58) 242 (3.80) 264 (3.55)	HClO_4	71T4705

An essentially larger bathochromic shift of aryl groups introduced in position 2 is found and has been explained by the better delocalization of the positive charge $\langle 66\text{AHC}(7)39 \rangle$. A correlation exists between the Hammett σ_p constant and the wavenumber of the longest wavelength maximum of 2-(*p*-substituted phenyl)-1,3-dithiolylum ions; an enhanced bathochromic shift of the long wavelength absorption by electron-donating groups in the order $\text{H} < \text{Me} < \text{OPh} < \text{OH} < \text{OMe}$ was found $\langle 71\text{T4003} \rangle$.

Bathochromic shifts were also observed by introducing electron-donating moieties into the *p*-position of 2-phenyl groups, for example, in 2-phenyl-1,3-benzodithiolylum tetrafluoroborates $\langle 68\text{TL165}, 77\text{S263} \rangle$. As far as 1,3-dithiolylum-4-olates (**8**) $\langle 76\text{CB740}, 78\text{CB2021} \rangle$ are concerned electron donating, *p*-substituted phenyl groups at the 5-position cause a stronger bathochromic shift than in the 2-position, whereas electron-attracting, *p*-substituted phenyl groups have the larger shift effect at the 2-position (Table 7) $\langle 76\text{CB740}, 78\text{CB2021} \rangle$.

Table 7 UV Spectral data of some 1,3-dithiolylum-4-olates (**8**) in 1,4-dioxane.



R^1	R^2	λ_{max} (nm) ($\log \epsilon$)
Ph	4-NO ₂ -C ₆ H ₄	380 (4.11)
Ph	piperidino	478 (3.62)
Ph	Ph	553 (4.11)
Ph	4-MeO-C ₆ H ₄	563 (4.20)
Ph	4-Me ₂ N-C ₆ H ₄	599 (4.36)
H	Ph	483 (3.78)
Me	Ph	508 (3.90)
4-NO ₂ -C ₆ H ₄	Ph	550 (4.25)
4-MeO-C ₆ H ₄	Ph	570 (5.15)

The long wavelength absorption in the UV spectrum of tetrathiafulvalene (**5**) (Table 6) which exhibits three other absorptions has only low intensity ($\epsilon = 270$) and has been assigned to a $\pi \rightarrow \sigma^*$ transition $\langle 71\text{JA2258} \rangle$. The longest wavelength absorption of the mesoionic dithiolone shows hypsochromic shift with increasing polarity of the solvent; this negative solvatochromic effect correlates with solvent polarity parameters $\langle 76\text{CB740} \rangle$ and is in agreement with the highly mesoionic ground state of 1,3-dithiolylum-4-olates which possess dipole moments between 5.0 D and 5.98 D $\langle 76\text{CB740} \rangle$. In general, the deeply colored 2,5-diaryl-1,3-dithiolylum-4-olates show intense long wavelength $\pi \rightarrow \pi^*$ transitions between 553 nm and 599 nm (Table 7) being in agreement with PPP calculations assigning these bands to intramolecular charge transfer transitions $\langle 73\text{JPR690} \rangle$.

IR data for 1,3-dithiolylum cations have been reported $\langle 80\text{AHC}(27)151 \rangle$. The mesoionic 1,3-dithiolones (**8**) show substituent-dependent IR carbonyl stretching vibrations between 1612 cm^{-1} and 1558 cm^{-1} (Table 8), being well in agreement with the mesoionic structure of these compounds $\langle 76\text{CB740} \rangle$.

3.12.4 REACTIONS OF 1,3-DITHIOLYLUM IONS, MESOIONIC 1,3-DITHIOL-4-ONES, AND 1,3-DITHIOLES

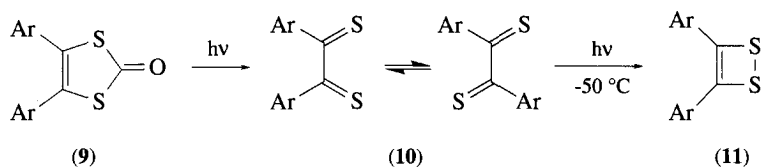
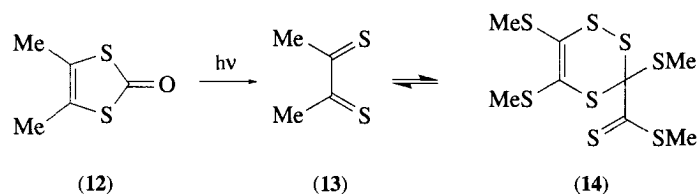
3.12.4.1 Thermal and Photochemical Reactions

A photochemical decarbonylation occurred upon photolysis of the 1,3-dithiol-2-one (**9**) to afford the dithione derivative (**10**) which upon further irradiation at -50°C yields a product believed to be a dithiete (**11**) (Scheme 2) $\langle 74\text{JA3502} \rangle$.

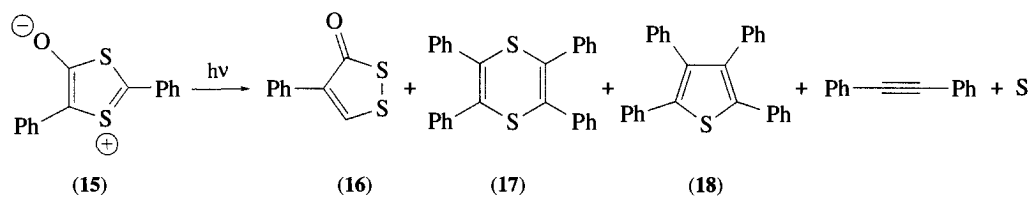
Similarly the dithiolone (**12**) gave the tetrathiooxalate (**13**), which is in equilibrium with its [4 + 2] dimer (**14**) (Scheme 3) $\langle 80\text{CB1898} \rangle$.

Table 8 Selected IR data of some 1,3-dithiolylum-4-olates (**8**).

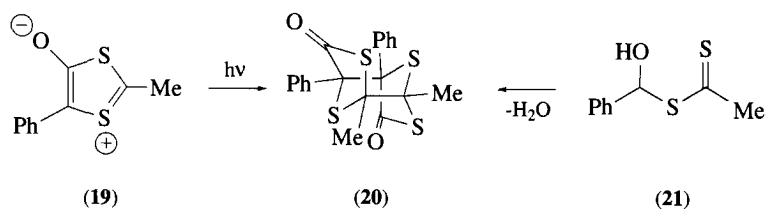
R^1	R^2	$\nu (C=O) (cm^{-1})$
Ph	Ph	1580
Ph	4-MeO-C ₆ H ₄	1576
Ph	4-NO ₂ -C ₆ H ₄	1596, 1578
Ph	4-Me ₂ N-C ₆ H ₄	1602, 1592
Ph	piperidino	1610, 1584
H	Ph	1600
Me	Ph	1576
4-NO ₂ -C ₆ H ₄	Ph	1597, 1589
4-MeO-C ₆ H ₄	Ph	1612, 1595

**Scheme 2****Scheme 3**

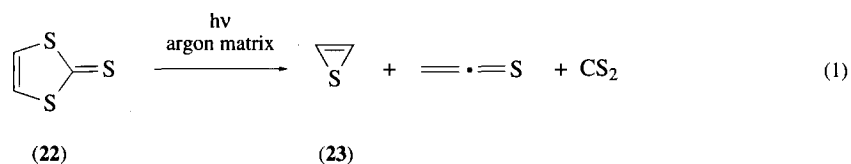
Photolysis of the 1,3-dithiolylum-4-olate (**15**), gave (**16**) together with a mixture of sulfur, diphenyl-acetylene, (**17**), and (**18**) (Scheme 4) <82JCS(P1)1885>.

**Scheme 4**

Dimerization occurred upon heating of the 1,3-dithiolylum-4-olate (**19**) to afford the dimeric (**20**) which was also independently prepared from (**21**) (Scheme 5) <79CB1650>; the structure of (**20**) was confirmed by x-ray analysis <78TL671>.

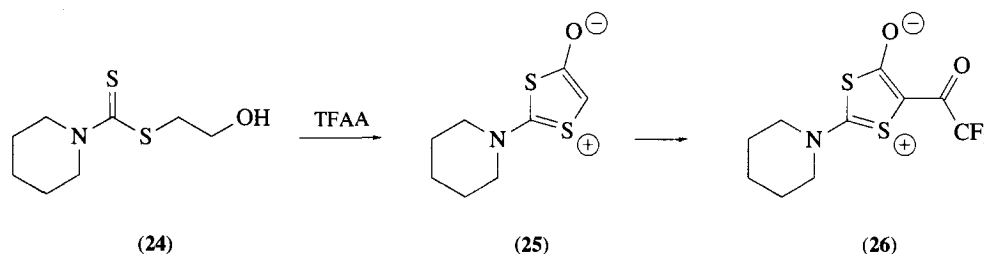
**Scheme 5**

Irradiation of the 1,3-dithiole-2-thione (**22**) afforded the antiaromatic thiirene (**23**) in an argon matrix (Equation (1)) <79NJC149>.



3.12.4.2 Electrophilic Attack at Carbon

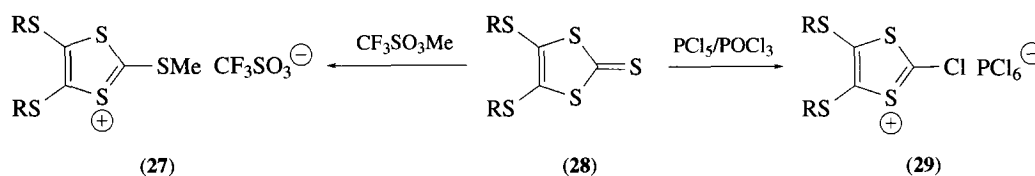
The attack of electrophiles at the ring carbons of 1,3-dithiolium ions is seldom observed. Thus, upon reaction of (**24**) with TFAA the intermediary mesoionic 1,3-dithiolone (**25**) is acylated in the 5-position to afford (**26**) (Scheme 6) <78CB2021>.



Scheme 6

3.12.4.3 Electrophilic Attack at Sulfur

Although alkylation of the thion moiety of 1,3-dithiole-2-thiones is energetically favored by the gain in energy due to aromatization of the 1,3-dithiole ring to a 1,3-dithiolium system, strong alkylating reagents must be applied, such as methyl fluorosulfate <80CB1898>, triethyloxonium tetrafluoroborate <74JA945>, methyl trifluorosulfonate <74JA945>, dimethoxycarbonium tetrafluoroborate <92JOC2374>, or triethyl orthoformate/boron trifluoride diethyl ether complex <89ZOR45>. Thus, 4,5-bis(alkylsulfanyl)-1,3-dithiole-2-thiones (**27**) were transformed into (**28**) by using methyl triflate (Scheme 7) <91JOC2720>. Compound (**27**) gave, upon reaction with phosphorus pentachloride in phosphorus oxychloride, the corresponding 2-chloro-4,5-bis(alkylsulfanyl)-1,3-dithiolium hexachlorophosphate (**29**) <84S319>.



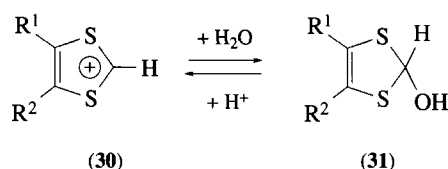
Scheme 7

3.12.4.4 Nucleophilic Attack at Carbon

1,3-Dithiolium salts as well as 1,3-dithiolium-4-olates react with a variety of C-, N-, O-, P-, and S-nucleophiles; as a 6π -electron system with a positively charged five-membered ring the reactions occur for the 1,3-dithiolium salts exclusively at the 2-position while the 1,3-dithiolium-4-olates undergo nucleophilic attack at the 4-position.

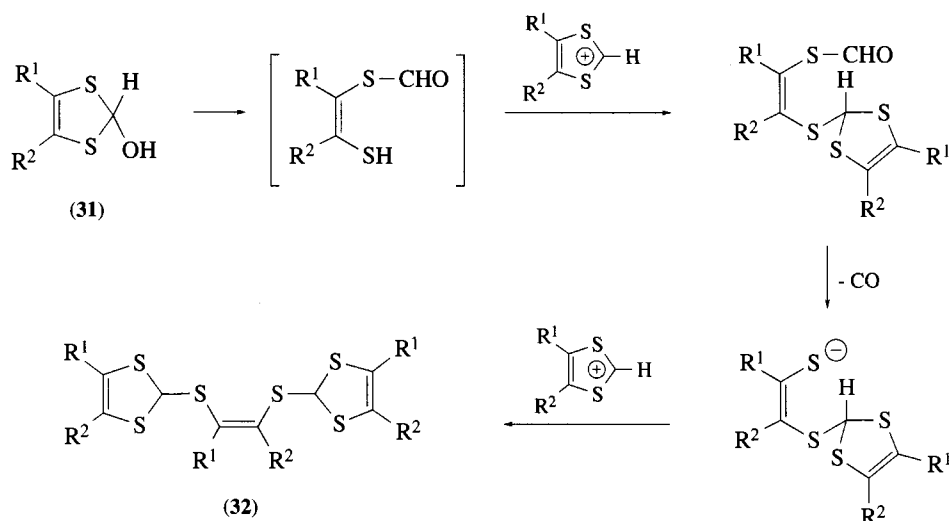
3.12.4.4.1 With O-nucleophiles

Hydrolysis of 1,3-dithiolium cations (**30**) leads to the corresponding 2-hydroxy-1,3-dithioles (**31**) (Scheme 8) which upon treatment with acid, afford again the educts <74RZC765, 82PJC991, 82PJC1313>.



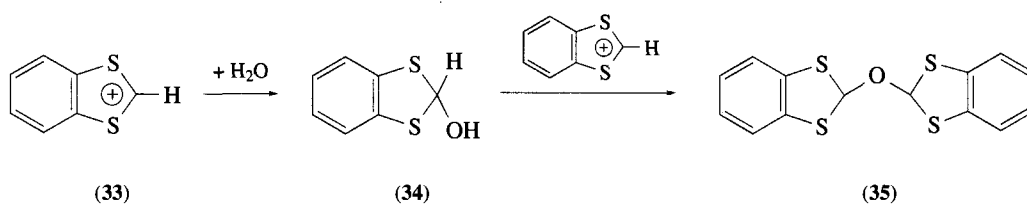
Scheme 8

The 2-hydroxy-1,3-dithioles (**31**) are quite unstable compounds leading, by reaction with excess of 1,3-dithiolium ions, to a variety of products (e.g., (**32**)) (Scheme 9) <74RZC765, 82PJC1313>.



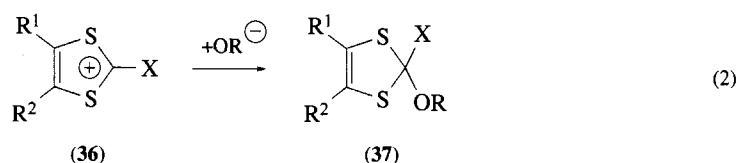
Scheme 9

In a similar way, the benzo-1,3-dithiolium salt (**33**) afforded via the corresponding 2-hydroxy compound (**34**) and finally (**35**) (Scheme 10) which reverts to (**33**) upon addition of acid <66AHC(7)39>.

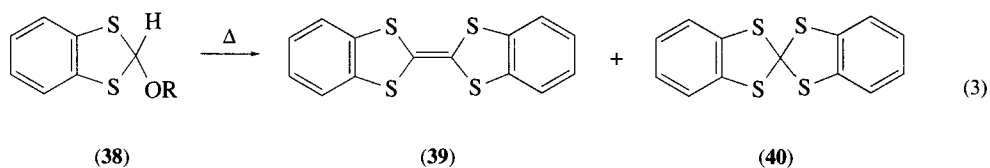


Scheme 10

The reaction between 1,3-dithiolium salts (**36**) with alcoholates or alcohols leads to stable 2-alkoxy-1,3-dithioles (**37**) (Equation (2)) <64ZC384, 66AHC(7)39, 74LA403, 76BCJ3567>, which are valuable starting materials for the synthesis of 2-aryl-1,3-dithioles <75S170, 90TL3051>.

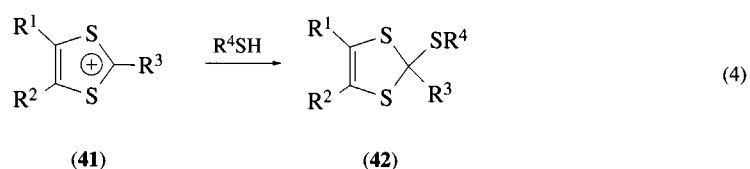


2-Alkoxy-1,3-benzodithioles (**38**) can be pyrolyzed (200°C, 2 h) into a mixture of the corresponding benzo-TTF (**39**) and the spiro-compound (**40**) (Equation (3)) <75S168>.

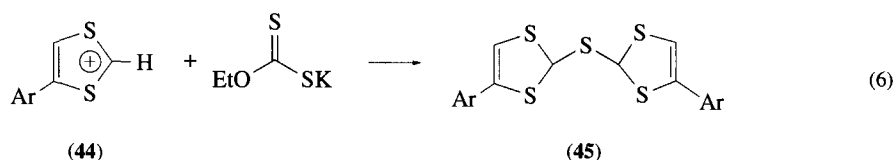
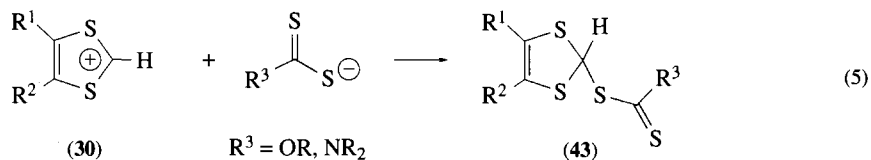


3.12.4.4.2 With S-nucleophiles

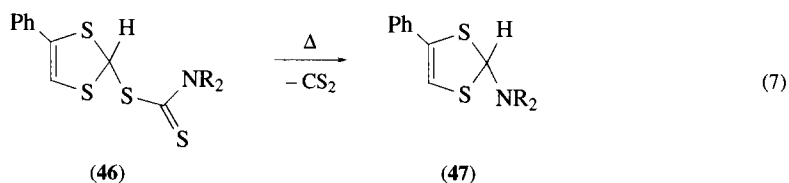
1,3-Dithiolylium salts (**41**) react with thiols leading to 2-alkylsulfanyl- or 2-arylthio-1,3-dithioles (**42**) (Equation (4)) <70RZC2319, 75S436, 76BCJ3567>.



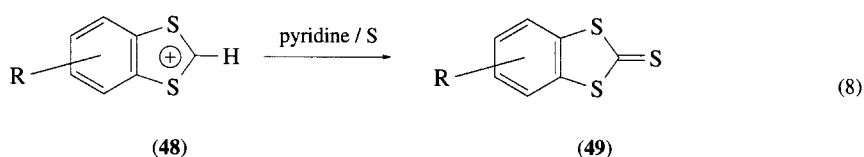
O-Alkyl-dithiocarbonate and dithiocarbamate anions react with 1,3-dithiolylium salts (**30**) in acetonitrile to give the corresponding 2-(alkoxy-thiocarbonylthio)- and 2-(amino-thiocarbonylthio)-1,3-dithioles (**43**) (Equation (5)) <76BCJ3567, 77JOC1543>, whereas 4-aryl-1,3-dithiolylium salts (**44**) afforded (**45**) upon reaction with an excess of potassium *O*-ethyl-dithiocarbonate in acetone (Equation (6)) <77JOC1543>.



The 2-(amino-thiocarbonylthio)-4-phenyl-1,3-dithioles (**46**) upon heating afford carbon disulfide and the *N*-substituted 2-amino-4-phenyl-1,3-dithioles (**47**) (Equation (7)) <77JOC1543>.

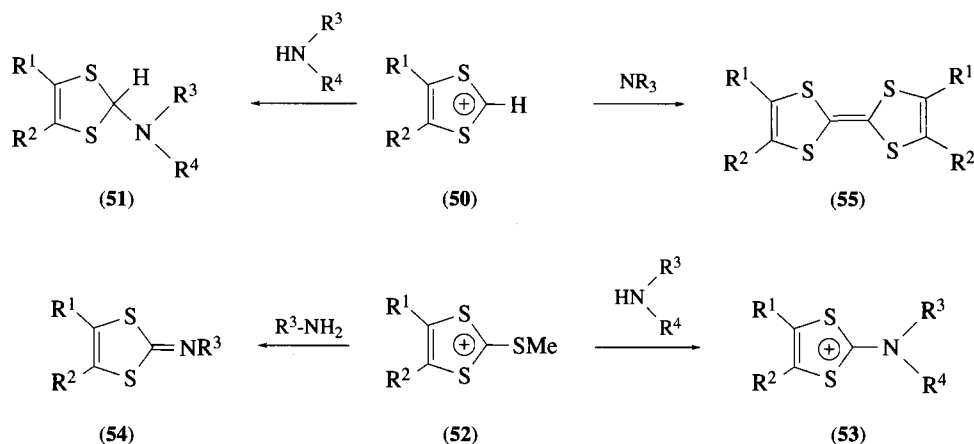


1,3-Benzodithiolylium salts (**48**) react with elemental sulfur in the presence of pyridine to give the corresponding 2-thiono-1,3-dithioles (**49**) (Equation (8)) <72RZC2377, 83TL2585>.



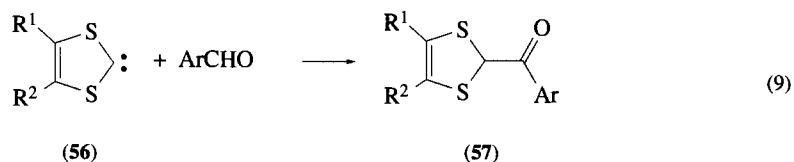
3.12.4.4.3 With *N*-nucleophiles

The reaction of 1,3-dithiolylium salts unsubstituted at position 2 (**50**) with secondary amines results in the formation of 2-amino-1,3-dithioles (**51**) (Scheme 11) <76BCJ3567, 76RZC1823>, whereas 2-methylsulfanyl-1,3-dithiolylium salts (**52**) give the corresponding 2-amino-1,3-dithiolylium salts (**53**) <64JOC2877>. 2-Methylsulfanyl-1,3-dithiolylium salts (**52**) react with primary amines to give 2-imino-1,3-dithioles (**54**) <65JOC1677, 71LA(754)46>. 1,3-Dithiolylium salts unsubstituted at position 2 (**50**) on reaction with tertiary amines via their carbenes give TTF (**55**) <75CL603, 78JCS(P1)468, 78JPR404>.

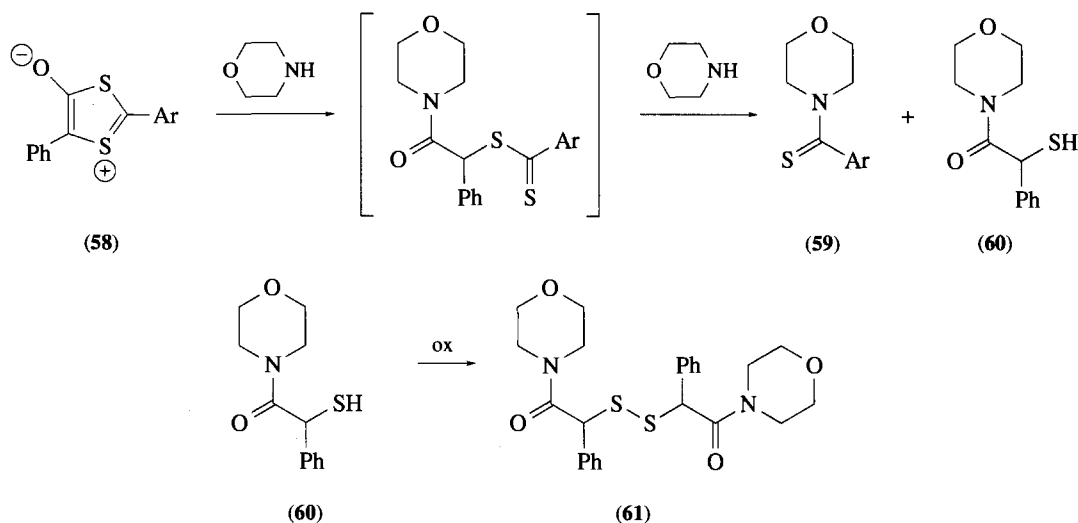


Scheme 11

The intermediary carbenes (**56**) can be trapped by the addition of aromatic aldehydes to yield 2-aryl-1,3-dithioles (**57**) (Equation (9)) <70RZC1823, 80PJC717>.

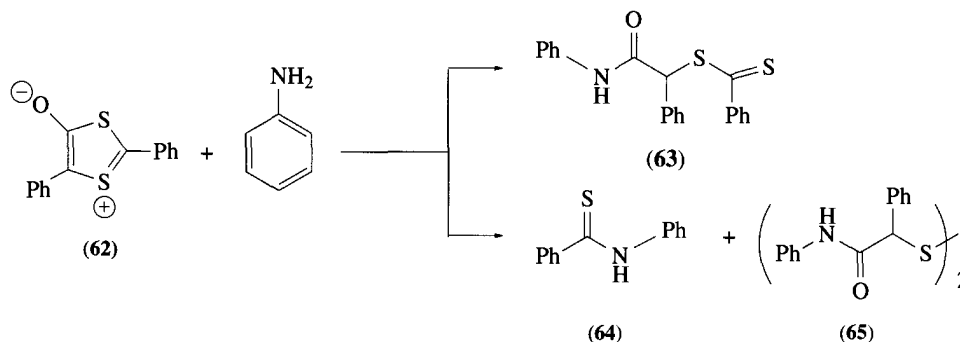


The 1,3-dithiolylium-4-olate (**58**) reacted with morpholine at the 4-position with formation of the thiobenzomorpholide (**59**) and the thiophenylacetomorpholide (**60**) (Scheme 12); the disulfide (**61**) is obtained from (**60**) by oxidation <78CB3178>.



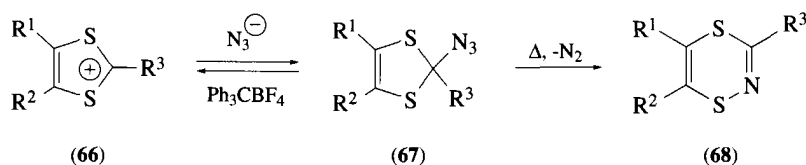
Scheme 12

The reaction of (62) with aniline affords, primarily by attack at the 4-position, a ring-opened intermediate which either recloses with liberation of H_2S to yield (63), or reacts with a second molecule of aniline to produce the thiobenzanilide (64) and the disulfide (65) (Scheme 13) <78CB3178>.



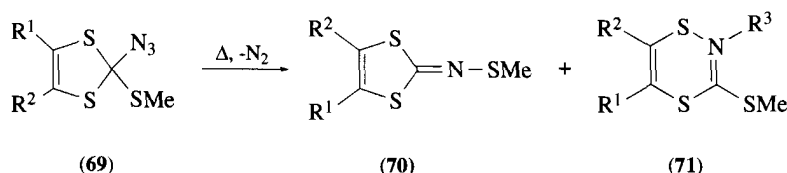
Scheme 13

1,3-Dithiolylium salts (66) give, on reaction with azide anion, 2-azido-1,3-dithioles (67) (Scheme 14) <76JPR127, 81JCS(P1)618>, which upon reaction with triphenylmethyl tetrafluoroborate afford azido-triphenylmethane and the corresponding 1,3-dithiolylium salt, whereas upon thermal treatment with liberation of nitrogen 1,4,2-dithiazines (68) were obtained <64JOC1708, 76JPR127, 80JOC2024>.



Scheme 14

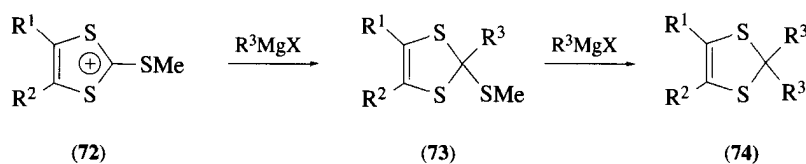
Under the same conditions 2-azido-2-methylsulfanyl-1,3-dithioles (69) afforded mixtures of 2-imino-1,3-dithiole (70) and the corresponding 1,4,2-dithiazines (71) (Scheme 15) <76JPR127>.



Scheme 15

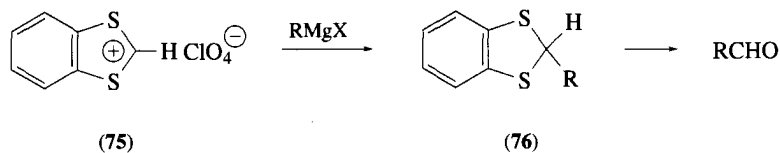
3.12.4.4.4 With C-nucleophiles

2-Methylsulfanyl-1,3-dithiolylium salts (72) react with Grignard reagents to form 2-alkyl-2-methylsulfanyl-1,3-dithioles (73) which react with an excess of the reagent to give 2,2-dialkyl-1,3-dithioles (74) (Scheme 16) <64ZC384>.



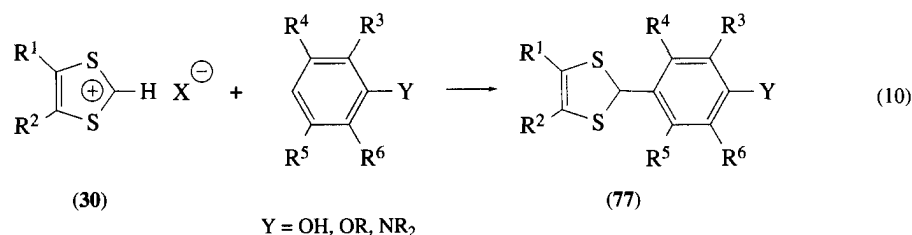
Scheme 16

1,3-Benzodithiolylium perchlorate (**75**) with Grignard reagents affords 2-substituted 1,3-benzodithioles (**76**) which can be hydrolyzed very easily to the corresponding aldehydes (Scheme 17) <76JCS(P1)1886>.

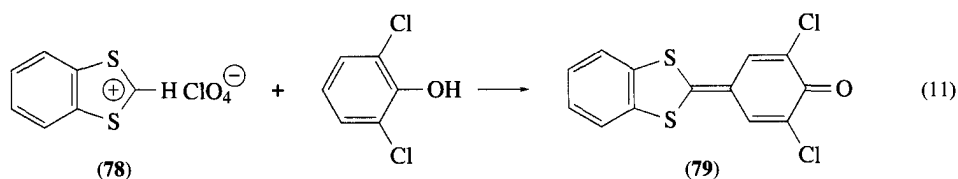


Scheme 17

Arylamines, phenols, and phenoethers react with their electron-rich *para*-position at C(2) of the 1,3-dithiolylium ion (**30**) leading to compounds of the type (**77**) (Equation (10)) <63HCA2167, 71T4003, 76BCJ3567, 77CL789, 80AHC(27)151, 81CC565>.

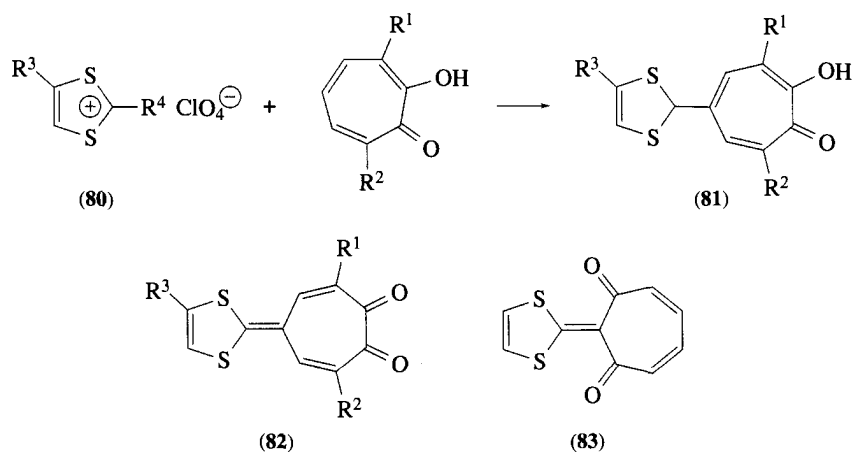


1,3-Benzodithiolylium tetrafluoroborate (**78**) upon reaction with an excess of 2,6-dichlorophenol finally affords (**79**) (Equation (11)) <77CL789>.



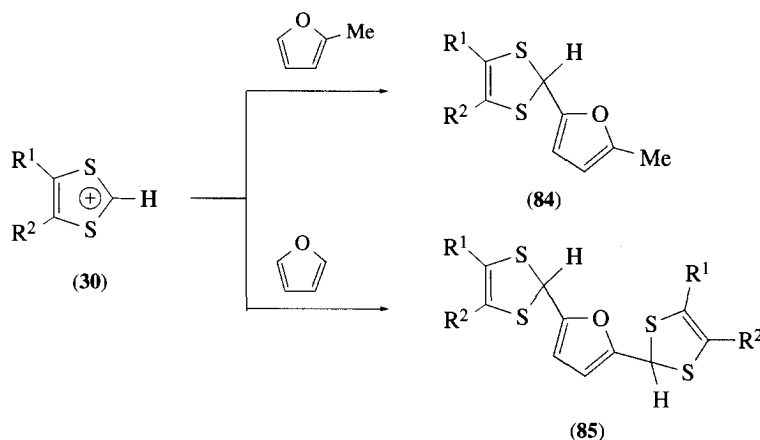
In an analogous manner 4-phenyl-1,3-dithiolylium perchlorate (**80**) afforded, upon reaction with tropolones, the 2-(4-hydroxy-5-oxo-1,3,5-cycloheptatrien-yl)-4-phenyl-1,3-dithioles (**81**), which can be transformed into (**82**) (Scheme 18) <77CL1505>.

The derivatives (**83**) were obtained from 2-methylsulfanyl-1,3-dithiolylium salts <77CL287,



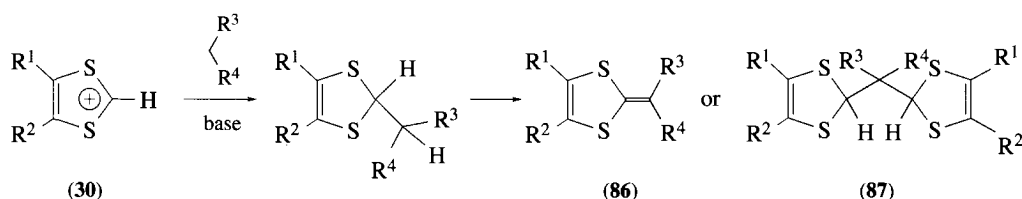
Scheme 18

81CL805). The reaction between 1,3-dithiolylum perchlorates (**30**) and methylfuran or furan gave the mono- or bis addition products (**84**) or (**85**) (Scheme 19) <78PJC2071>.



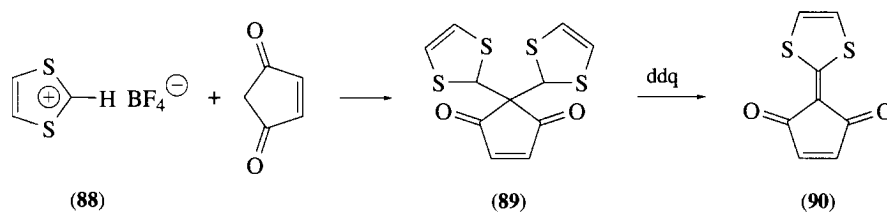
Scheme 19

Activated methylene groups may react with one or two molecules of 1,3-dithiolylum salts (**30**) to afford (**86**) or (**87**) (Scheme 20) <71TL1137, 72CPB1711, 80AHC(27)151>.



Scheme 20

In an analogous manner, from 1,3-dithiolylum tetrafluoroborate (**88**) and 2-cyclopentene-1,4-dione the product (**89**) was formed, which was oxidized using ddq to yield the dithiafulvalene derivative (**90**) (Scheme 21) <77CL77>.



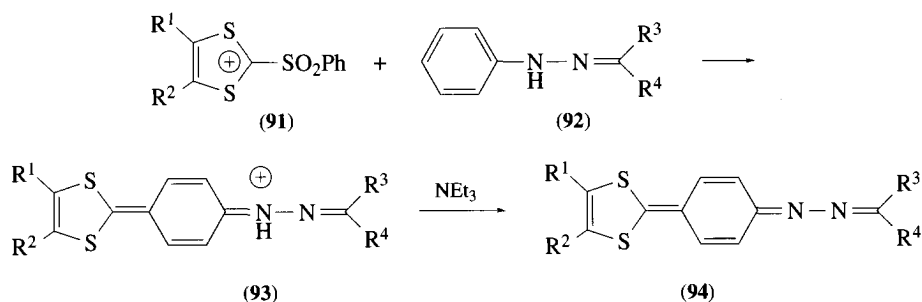
Scheme 21

The reaction of 2-methylsulfanyl- or 2-phenylsulfonyl-1,3-dithiolylum salts (**91**) with arylhydrazones (**92**) leads to compounds (**93**) which can be deprotonated with triethylamine to afford (**94**) (Scheme 22) <87ZC26>.

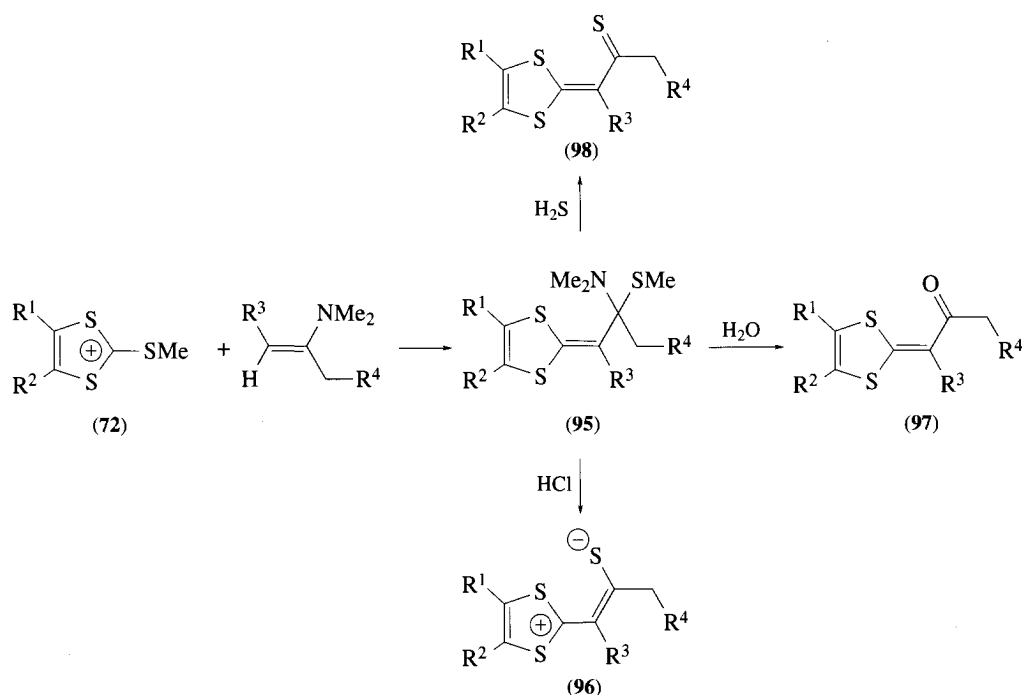
The reaction between sulfur ylides and 1,3-dithiolylum salts has also been described <77T1595>. The reaction between enamines and 2-methylsulfanyl-1,3-dithiolylum salts (**72**) affords an intermediary (**95**) which gave, upon reaction with hydrochloric acid, water, or hydrogen sulfide, the products (**96**), (**97**), and (**98**), respectively (Scheme 23) <75JPR137>.

3.12.4.4.5 Reductions

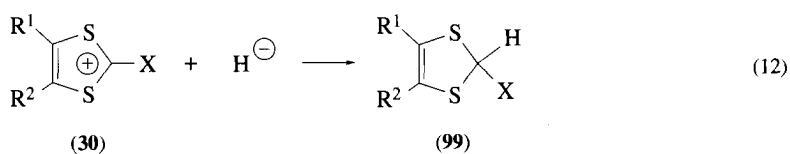
1,3-Dithiolylum salts (**30**) are easily reduced by sodium borohydride, lithium aluminum hydride, or sodium hydrogen sulfide to afford the corresponding 1,3-dithioles (**99**) (Equation (12)) <65JCS32, 69CPB1924, 74JOC3608, 76BCJ3567, 76S759, 77CC388, 77TL2579>.



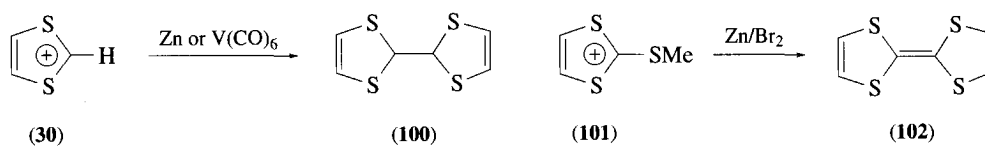
Scheme 22



Scheme 23



Reduction of 1,3-dithiolium salts (30) with zinc ^{<77JOC2778>} or hexacarbonyl-vanadate ^{<75JOC2002>} leads to dimerization affording (100); the reduction of 2-methylsulfanyl-dithiolium iodide (101) with zinc in the presence of bromine, however, gave the corresponding TTF (102) (Scheme 24) ^{<76ZC317>}. Dimers were also obtained by electrochemical reduction ^{<77MI 312-01>}.

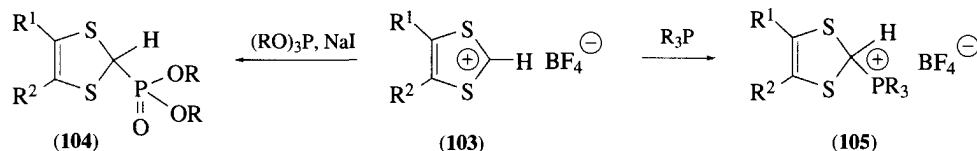


Scheme 24

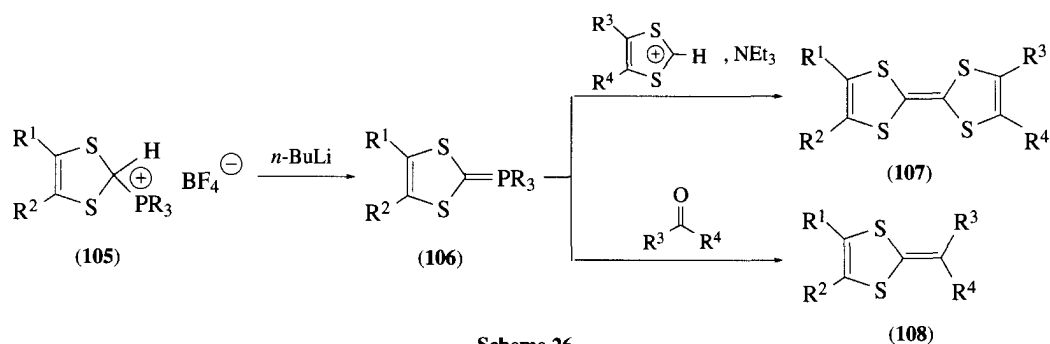
3.12.4.4.6 With P-nucleophiles

1,3-Dithiolylum salts (**103**) react with trialkylphosphite <76TL3695> to yield 2-dialkoxyphosphoryl-1,3-dithioles (**104**), whereas the reaction with phosphanes affords 2-phosphonio-1,3-dithiolylum salts (**105**) (Scheme 25) <76TL3695, 78JOC369, 80H(14)271, 80JOC2024, 84JPR479>.

The latter are valuable starting materials in reactions leading via (**106**) to compounds (**107**) and (**108**) (Scheme 26) <76TL3695, 78JOC369, 80H(14)271, 82TL1813, 84JPR479>.



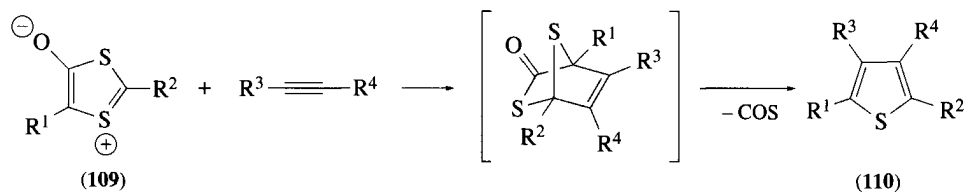
Scheme 25



Scheme 26

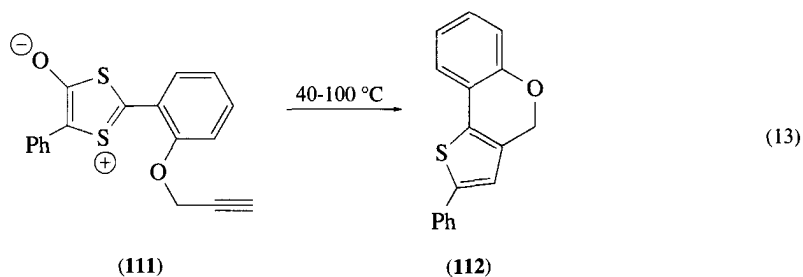
3.12.4.5 Cyclic Transition State Reactions

The 1,3-dithiolylum-4-olates (**109**) can be regarded as cyclic or masked 1,3-dipolar thiocarbonyl ylides, and hence they are valuable synthons for subsequent heterocyclic syntheses. Thus, thiophenes (**110**) are obtained from the reaction of 1,3-dithiolones with alkynes (Scheme 27) <68TL4747, 68TL4751, 69CC569, 76CB753, 76JOC1724, 78CB2021, 78CB2028>.



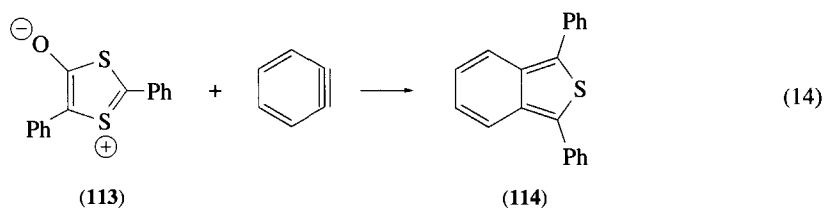
Scheme 27

The observed regioselectivities during these cycloadditions have been explained in terms of qualitative frontier molecular orbital perturbation theory <78CB2028>. An intramolecular cycloaddition has been observed for the 1,3-dithiolone (**111**) to afford the tricyclic thiophene derivative (**112**) (Equation (13)) <81LA347>.

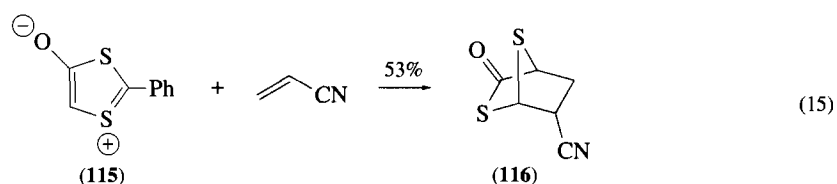


(13)

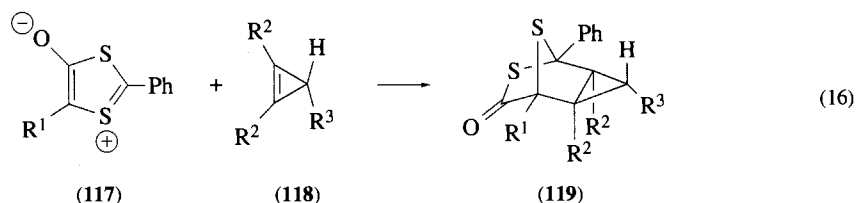
Benzyne as a dipolarophile afforded, with the 2,5-diphenyl-substituted 1,3-dithiolium-4-olate (**113**), the benzothiophene (**114**) (Equation (14)) <76JCS(P1)672>.



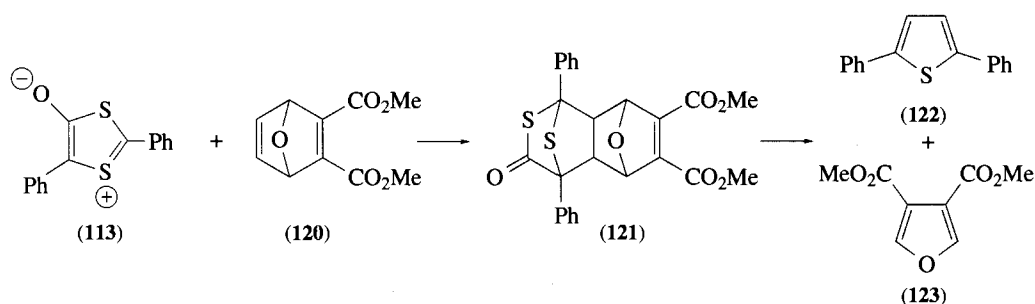
From the reactions of 1,3-dithiolium-4-olates, for example, (**115**), with alkenes like *N*-phenyl maleimide, acrylonitrile, ethyl acrylate, azirines, α -methyl-styrene, methyl cinnamate, tetracyanoethylene, or 2,3-dimethylbut-2-ene, the stable 1 : 1 adducts, such as (**116**), are obtained (Equation (15)) <76JOC1724, 78CB3029, 79HCA1236, 79LA360>.



Cyclic alkenes afforded, upon reaction with mesoionic 1,3-dithiolones (**117**), the primary cyclo-adducts. Thus, the cyclopropenes (**118**) gave the *exo* tricyclic compounds (**119**) (Equation (16)) <78CB3037>.

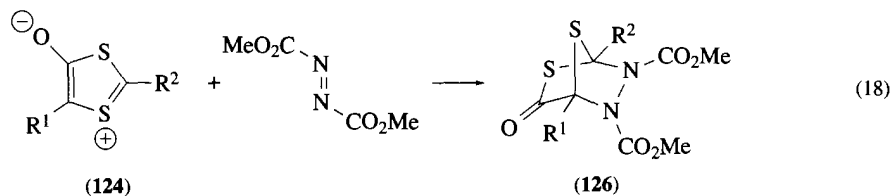
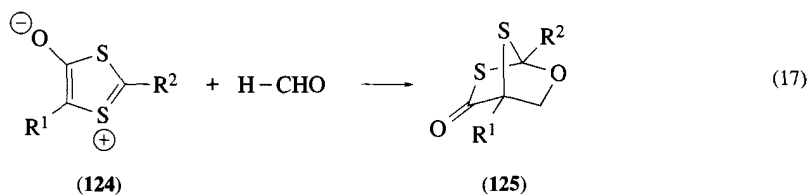


Similar reactions have been reported for acenaphthylenes, cyclopentenones, *p*-benzoquinone, norbornadiene, cyclopentadiene, 1,3-cyclohexadiene, and 1,5-cyclooctadiene <78CB3037>. The reaction of dimethyl-7-oxabicyclo[2.2.1]hepta-2,5-diene-2,3-dicarboxylate (**120**) with the 1,3-dithiolone (**113**) proceeds with the formation of the cycloadduct (**121**) (Scheme 28); pyrolysis or photolysis of this adduct (**121**) resulted in a double fragmentation to give the thiophene (**122**) and the furan (**123**) <75CC840>.

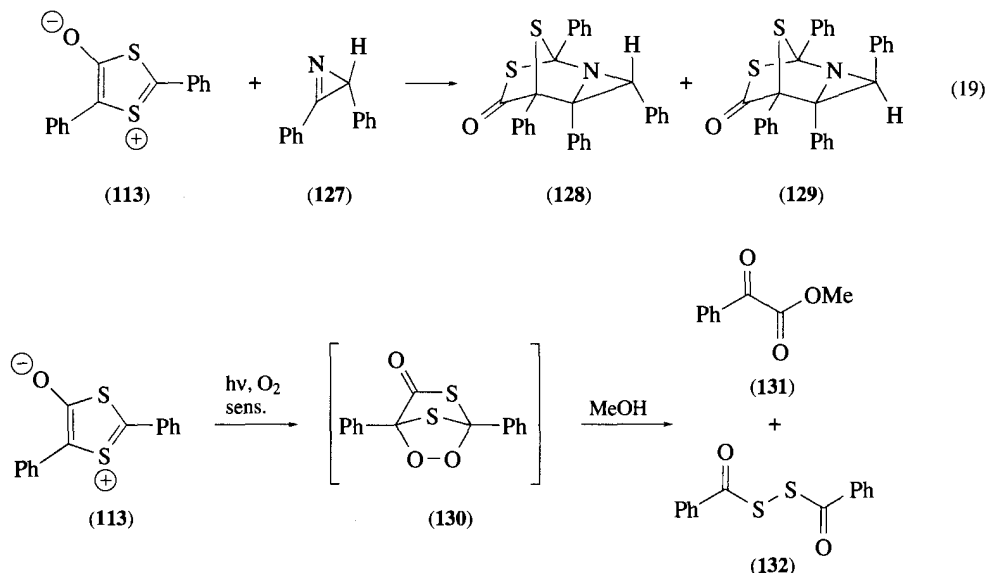


Scheme 28

Further examples including extrusion and ring expansion reactions <75JCS(P1)632> as well as intramolecular [3 + 2] cycloadditions have been reported <81LA347>. In addition, the mesoionic 1,3-dithiolones (**124**) react with formaldehyde regiospecifically in a [3 + 2] cycloaddition reaction with formation of the 2-oxa-6,7-dithiabicyclo[2.2.1]heptanone derivative (**125**) (Equation (17)) <78CB3171>. Furthermore, upon reaction with the N=N bond of dimethyl azodicarboxylate, (**126**) is obtained (Equation (18)) <78CB3171>.

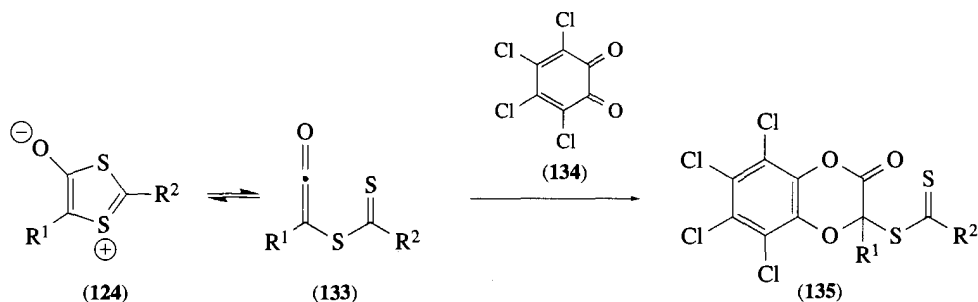


The reaction of 2,3-diphenylazirine (127), however, afforded the two isomeric products (128) and (129) (Equation (19)) <76JOC1724>. Furthermore, photochemically generated singlet oxygen using Bengal Rosa as a triplet sensitizer acts as a dipolarophile and adds in a [3 + 2] cycloaddition reaction with the 1,3-dithiolone (113) (Scheme 29); after fragmentation of the primarily formed cycloadduct (130), methyl phenylglyoxylate (131) and dibenzoyl disulfide (132) are formed <80CL717, 81CB285>.



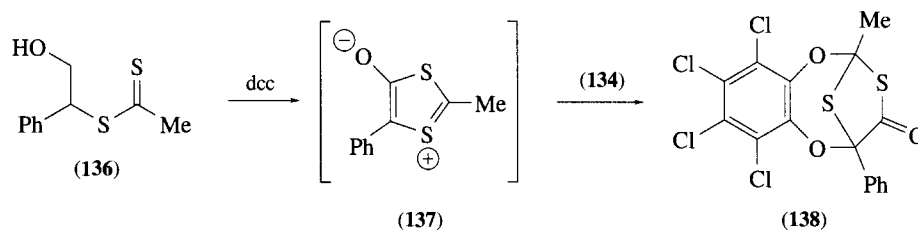
Scheme 29

A [4 + 2] reaction has been postulated as an explanation for the reaction of the mesoionic 1,3-dithiolium-4-ones (124) via their nondetectable tautomeric ketene (133) with *o*-chloranil (134) to afford (135) (Scheme 30) <81ZN(B)609>.



Scheme 30

A [4 + 4] cycloaddition reaction has been used for trapping an *in situ* formed 1,3-dithiolone. Thus, treatment of the thioester (136) with dcc in the presence of *o*-chloranil results in the intermediate formation of the 1,3-dithiolone (137) which is trapped by the *o*-chloranil to form (138) (Scheme (31)) <79CB1650>.

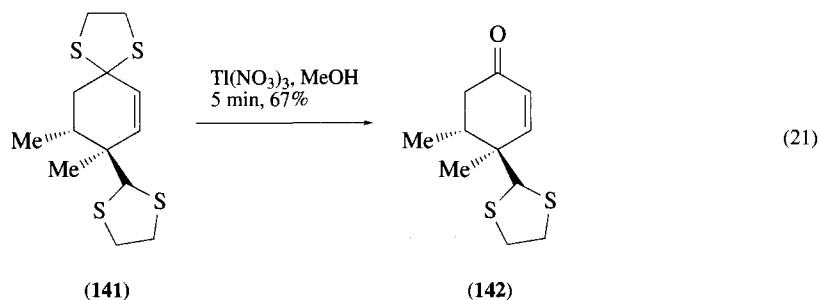
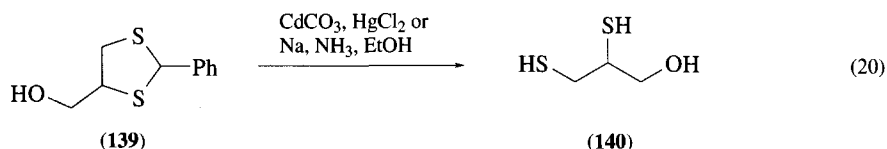


Scheme 31

3.12.5 REACTIONS OF 1,3-DITHIOLANES

3.12.5.1 Cleavage Reactions

1,3-Dithiolanes are quite resistant to both acid and alkaline hydrolysis (pH 1–12), bases, and many nucleophiles and against hydride reduction; the ring can be cleaved, however, by a mixture of mercury(II) chloride/cadmium carbonate quite efficiently (Equation (20)) <53CLY227>. Alternatively sodium and ethanol in liquid ammonia <47JCS592>, or silver(I) oxide in methanol using prolonged reaction times <72CC1323>, *N*-bromosuccinimide in acetone <75TL1353>, or thallium(III) nitrate in methanol can be used. The latter reagent was used to effect selective cleavage of α,β -unsaturated thioketals (141) to afford (142) (Equation (21)) <75TL1353, 89TL15>.

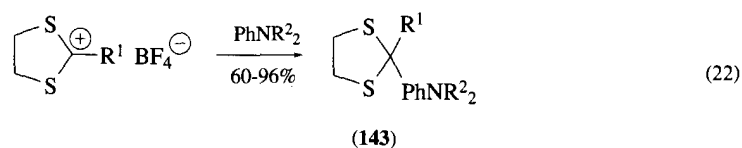


Alternative use <88TL5471> of thallium trifluoroacetate <72CJC3740, 79SC301>, iodine in DMSO <73TL3735>, chloramine T <71TL3449>, *N*-chlorobenzotriazole <71CC750>, trialkylsilyl triflates/*p*-nitrobenzaldehyde <91CC1750>, ddq <93JOC7576>, of oxygen during photolysis <77CL680>, methyl fluorosulfonate <72S561>, sulfur dioxide <72CC382>, methyl iodide in aqueous methanol <72CC382>, triethyloxonium tetrafluoroborate followed by a treatment with a 3% cuprous sulfate solution <72TL1085>, or of trimethylsilyl iodide (or bromide) in DMSO <82S965> has been reported.

3.12.5.2 Nucleophilic Attack at Carbon

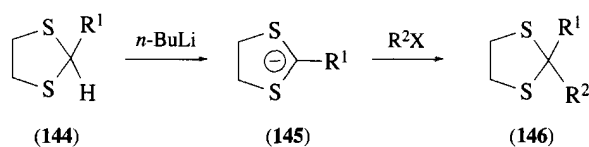
Deprotonation of 1,3-dithiolanes leads to the formation of a cationic *S,S*-acetal carbon which easily reacts with nucleophiles such as hydride reagents <85CB3166>, Grignard reagents <81TL1821>.

and electron-rich arenes such as anilines resulting in the formation of 2-(4-aminophenyl)-1,3-dithiolanes (**143**) (Equation (22)).



3.12.5.3 Electrophilic Attack at Carbon

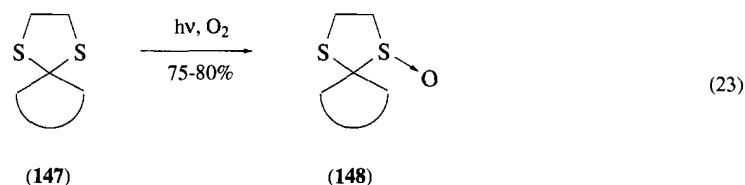
Carbanions can be synthesized quite easily by the reaction of 1,3-dithiolanes (**144**) with equimolar amounts of *n*-butyllithium; these carbanions (**145**) can be trapped by reaction with primary or secondary halogenides to afford (**146**) (Scheme 32) <65AG1134, 65AG1135, 69S17>.



Scheme 32

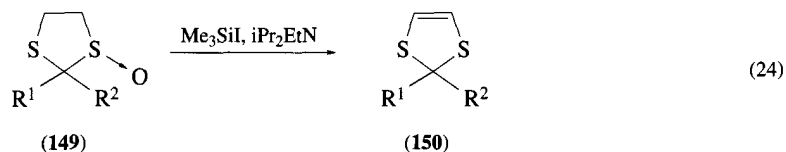
3.12.5.4 Oxidations at Sulfur

Photooxidation of 1,3-dithiolanes (**147**) results in excellent yields of 1,3-dithiolane-1-oxides (**148**) (Equation (23)) <89TL4007> the mass spectra of which have been studied extensively <88OMS(23)841, 90JHC327>. These enantiomers could be separated by chiral stationary phase HPLC <88JC199>.

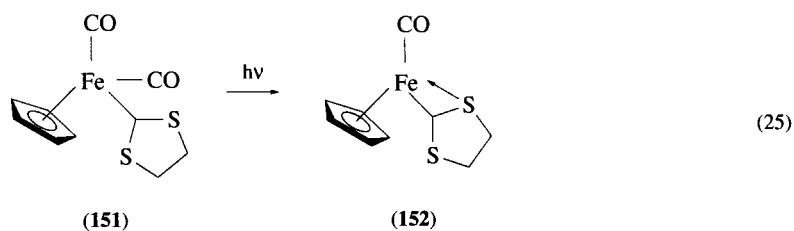


Oxidation under more vigorous conditions leads to the formation of mono- or bisulfones <81S995>.

Treatment of the 1,3-dithiolane *S*-oxide (**149**) with iodotrimethylsilane and ethyldiisopropylamine results in an efficient dehydration and yields the corresponding dithioles (**150**) (Equation (24)) <90S271>, whereas upon reaction with *t*-butyldimethylsilyltriflate and ethyldiisopropylamine cycloreversion takes place to afford the corresponding thioketones <90JHC327>.

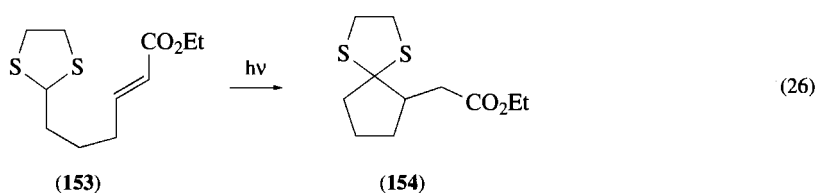


Photochemical elimination of carbon monoxide from the dithiolanyl iron complex (**151**) is accompanied by a change in bonding to give (**152**) (Equation (25)) <91MI 312-02>.



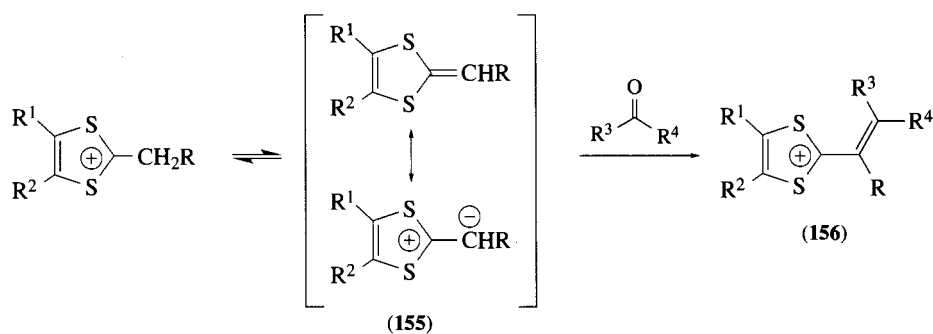
3.12.5.5 Reactions with Radicals

Intramolecular addition of the 1,3-dithiolan-2-yl radical derived from (153) by photolysis gives (154) (Equation (26)) <90TL7035>.

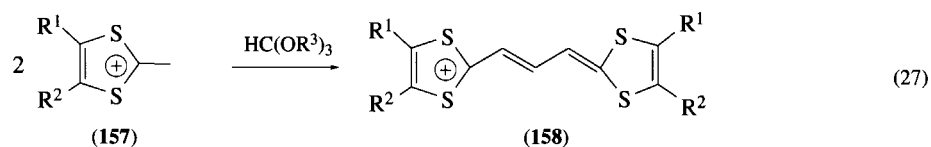


3.12.6 REACTIONS OF SUBSTITUENTS ATTACHED TO RING CARBON ATOMS

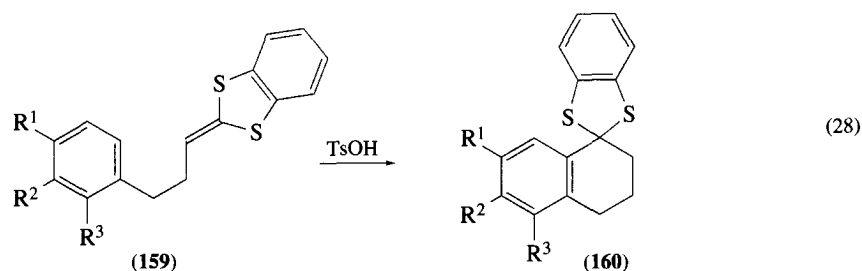
α -Hydrogens of C-linked substituents at position 2 exhibit an acidic character due to the resonance stabilization of the conjugated base (155). Upon reaction with aldehydes in acetic acid the condensation products (156) are obtained (Scheme 33) <66AHC(7)39, 80AHC(27)151>. The reaction with ketones and pyrones makes the addition of a strong base necessary.



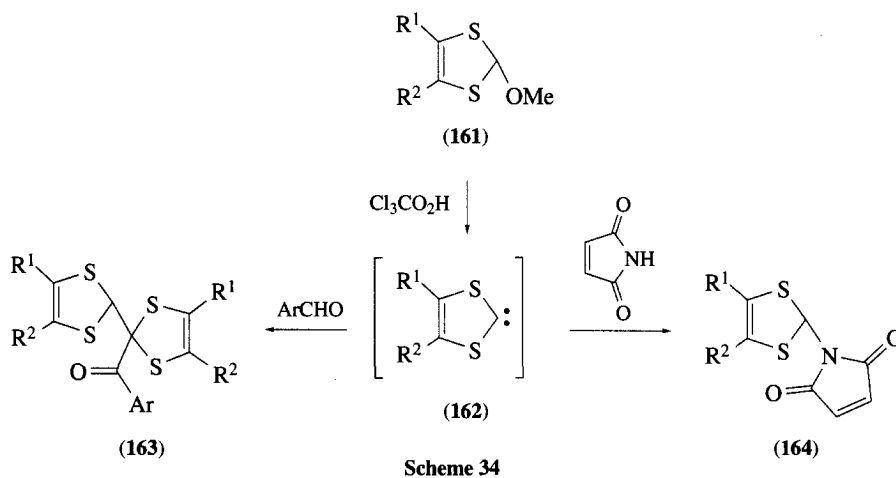
2-Methyl-1,3-dithiolylum ions (157) give, on reaction with orthoformates, compounds of type (158) (Equation (27)) <66AHC(7)39>.



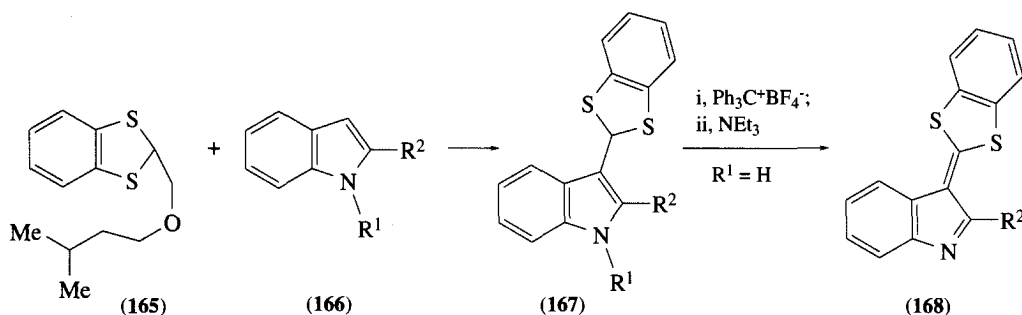
An intramolecular Friedel-Crafts alkylation of the 2-alkylidene branched 1,3-dithiole (159) leads to 1,1-bis(organothio)tetralines (160) (Equation (28)) <78BCJ2674>.



2-Alkoxy-1,3-dithioles can serve as generators of carbenes. Thus, reaction of (161) with trichloroacetic acid produces a carbene (162) which in the presence of aromatic aldehydes forms the 1,3-dithiole derivatives (163) (Scheme 34) <80PJC717>. Quite similarly, from (162) and succinimide the imide (164) is obtained <80PJC145>.



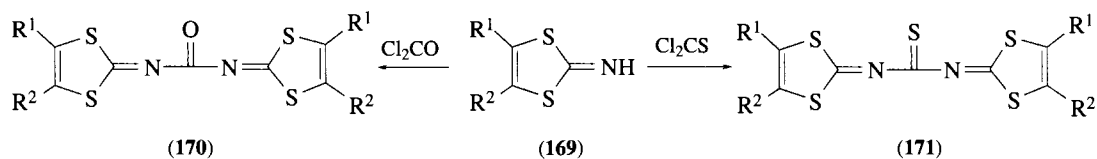
The benzodithiole (165) reacted with the indole derivative (166) in acetic acid to form the substitution products (167) (Scheme 35) <80BCJ1661>. Consecutive treatment of (167; R¹ = H) with triphenylmethyl tetrafluoroborate and triethylamine afforded the dibenzo-1,4-dithia-6-azafulvalene (168) <80BCJ1661>.



These compounds have also been obtained from 2-methylsulfanyl-1,3-dithiolium salts upon reaction with indoles followed by a treatment of the intermediary dithiolium salts with dbu <80BCJ1661>.

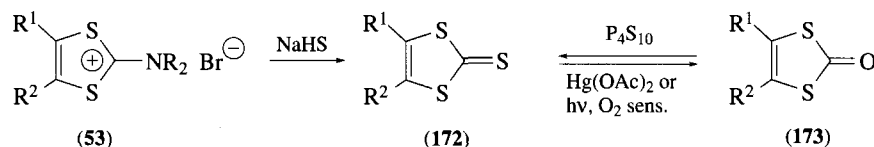
2-Imino-1,3-dithioles are easily converted into acylimines; thus by treatment of (169) with phosgene or thiophosgene in the presence of pyridine the corresponding ureas (170) or thioureas (171) were obtained (Scheme 36) <76JPR127, 79JPR827>.

Reaction of the 2-amino-1,3-dithiolium bromide (53) with sodium hydrogen sulfide in DMF/acetic acid gave 91% of the 1,3-dithiole-2-thione (172) (Scheme 37) <75S277> which can also be



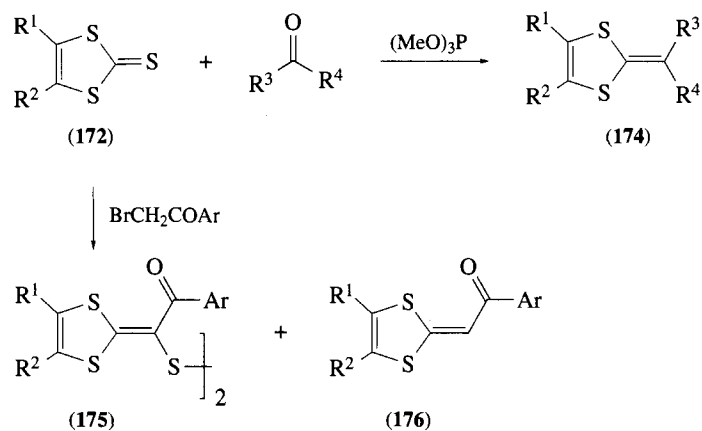
Scheme 36

obtained from 1,3-dithiol-2-one (173) by treatment with tetraphosphorus decasulfide $\langle 76\text{S489} \rangle$; the reconversion can be performed with mercury acetate $\langle 80\text{CB1898} \rangle$ or with singlet oxygen $\langle 77\text{JPR875} \rangle$.



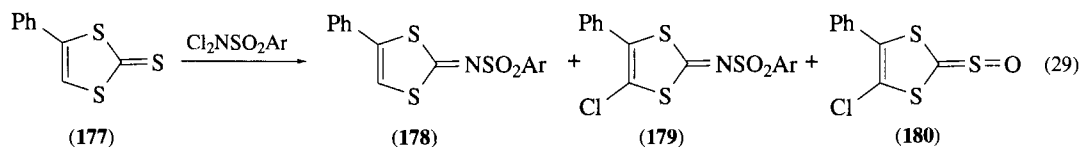
Scheme 37

Beside their ability to form TTF, 1,3-dithiole-2-thiones (172) have been coupled in the presence of trimethyl phosphite with ketones to afford (174) or with phenacylbromide to yield (175) and (176) (Scheme 38) $\langle 77\text{CL287}, 80\text{BCJ2281} \rangle$. The latter reaction is postulated to proceed via an unstable thiocarbonyl ylide and an episulfide intermediate which suffers loss of sulfur or ring opening and hydrogen shift followed by air oxidation to afford the products $\langle 80\text{BCJ2281} \rangle$.

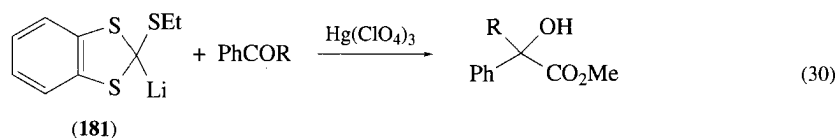


Scheme 38

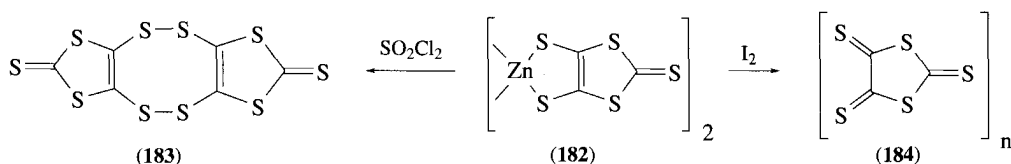
Furthermore, the 1,3-dithiole-2-thione (177) reacts with *N,N*-dichlorosulfonamides to yield the 1,3-dithiole-2-ylidenesulfonamides (178) and (179) as well as the 1,3-dithiole-2-thione oxides (180) via a nucleophilic attack of the exocyclic sulfur substituent on the chlorine of the amide thus producing an ion pair (Equation (29)) $\langle 79\text{LA689} \rangle$.



Finally, the lithiated 2-ethylthio-1,3-benzodithiole (181) can serve as a methoxycarbonyl anion equivalent; upon reaction of (181) with ketones followed by treatment with mercury perchlorate in methanol the corresponding α -hydroxy acids are obtained (Equation (30)) $\langle 81\text{SC209} \rangle$.



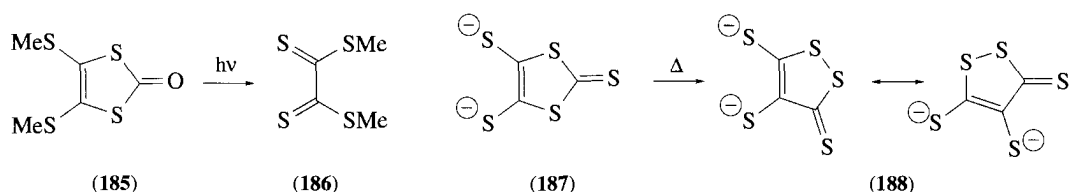
The zinc chelate of 1,3-dithiole-2-thione-4,5-dithiolate (**182**) gave, on reaction with sulfuryl chloride, a dimer (**183**) (Scheme 39) <90CC34>, whereas upon reaction with iodine the polymer (**184**) was obtained <89ZOR658>.



Scheme 39

The latter material was also obtained as a byproduct in several other reactions of similar type <62JA4756, 62JA4772, 91JCS(P1)3341>.

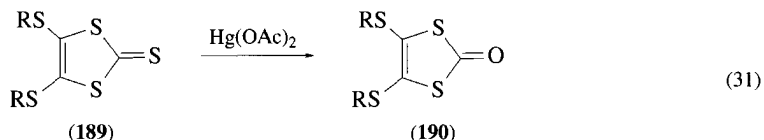
4,5-Bis(methylsulfanyl)-1,3-dithiol-2-ones (**185**) are decarbonylated upon irradiation with a medium pressure mercury lamp giving rise to dialkyl tetrathiooxalates (**186**) (Scheme 40) <80CB1898, 84AP(317)995>, whereas the free alkali metal salts (**187**) are thermally unstable and undergo a clean rearrangement into the corresponding salts of 1,2-dithiole-3-thione-4,5-dithiolates (**188**) <82PS(12)237>. A similar rearrangement of the isostructural mesoionic 2,5-diphenyl-1,3-dithiolylum-4-olate to 4,5-diphenyl-1,2-dithiol-3-one has been reported <82JCS(P1)1885>.



Scheme 40

In addition, 4,5-bis(alkylsulfanyl)-1,2-dithiole-3-thiones were obtained from a photochemically induced rearrangement of 4,5-bis(alkylsulfanyl)-1,3-dithiole-2-thiones <86KGS1568>.

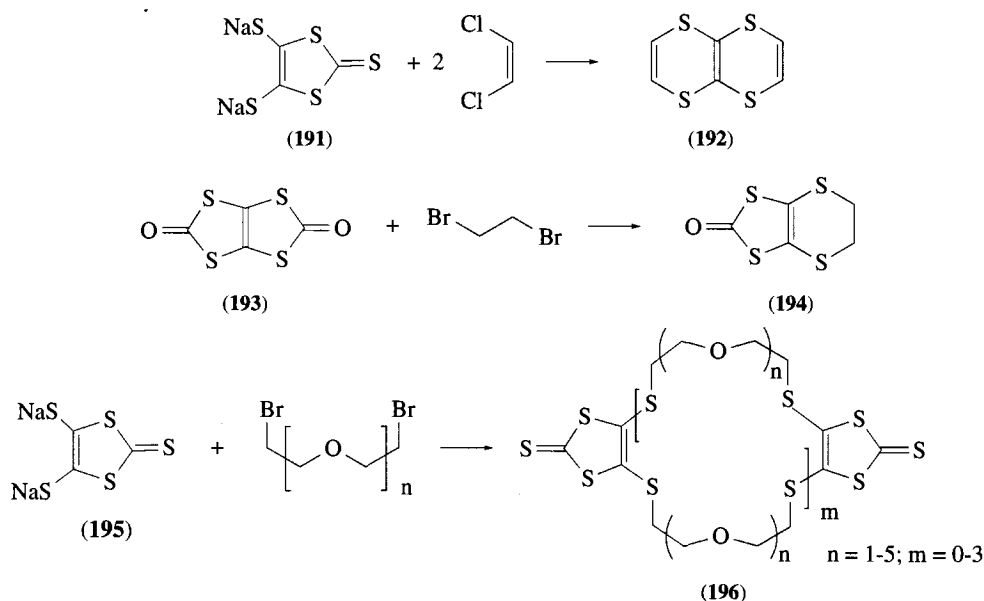
Transchalcogenation of the 1,3-dithiole-2-thiones (**189**) into their more reactive 2-one analogues (**190**) has been performed with mercuric acetate (Equation (31)) <80CB1898, 92ZN(B)898, 94S809>.



The retro reaction was accomplished with boron sulfide <77JA5521> or tetraphosphorus decasulfide <64CB1298>. Several 2-selenones have also been prepared <92ZN(B)898, 94S809>.

The alkylation of 1,3-dithiole-2-thione-4,5-dithiolates proceeds very smoothly under a variety of conditions <75ZC28, 79PS(7)49, 94S809, 95S215>. Upon reaction with 1,*N*-dihaloalkanes the corresponding five-, six-, and seven-membered rings are obtained <91ACS709>. More complex mixtures, however, are obtained upon alkylation with 1,4-dihalobutanes. Even reactions with vinylic halides occur in fair yields. Thus, (**191**) gave, on reaction with 1,2-dichloroethene, the 1,4-dithino[2,3-*d*]-1,4-dithiin (**192**) in 88% yield (Scheme 41) <88JHC783>. Ring opening and alkylating ring closure has been used for the synthesis of 4,5-ethylene-dithio-1,3-dithiol-2-one (**194**) from (**193**) <92ZN(B)718>. Alkylations have been used for the synthesis of crown ether derivatives <85BCJ1343, 90JCS(D)3789>.

90JCS(P1)175, 92CC1550, 92TL3035). Thus, (195) afforded, upon reaction with di-, tri-, tetra-, penta-, or hexaethyleneglycoldibromide, compounds of type (196) (92JOC6403).



Scheme 41

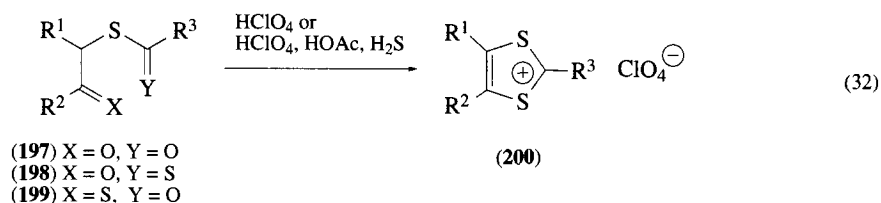
By a similar strategy thia-crowns (92JCS(P1)2907, 92MI 312-04) and aza-crowns (93JOC1359) as well as macrocycles incorporating other ligands such as pyridine (89CC1406) or thiazole rings (95S215) and cryptands (92AM(4)568) have been prepared.

3.12.7 RING SYNTHESSES

3.12.7.1 1,3-Dithiolylum Ions, Mesoionic 1,3-Dithiol-4-ones, and 1,3-Dithioles

3.12.7.1.1 From nonheterocyclic compounds

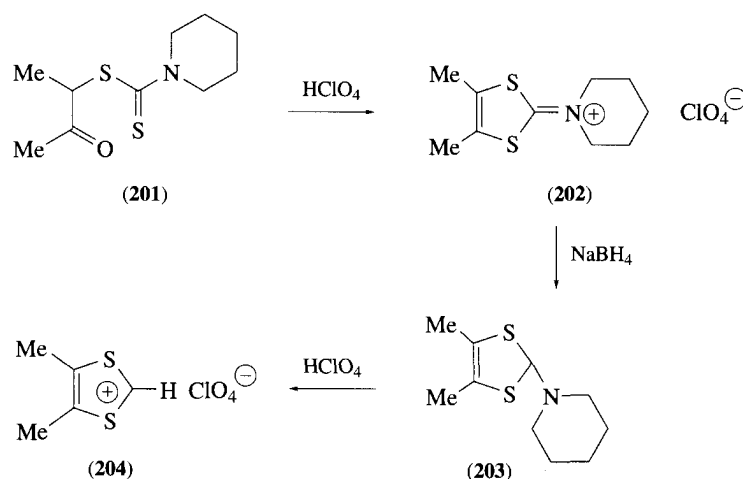
Several methods are known for the preparation of 1,3-dithiolylum salts from acyclic precursors by formation of one bond. Thus, acid-catalyzed cyclization of thioesters (197) or dithioesters (198) or of the thio-analogues (199) using either mixtures of perchloric acid and glacial acetic acid, 70% perchloric acid or concentrated sulfuric acid in the presence of H_2S (66AHC(7)39) or $\text{H}_2\text{S}/\text{BF}_3$ (80AHC(27)151) results in the formation of (200), albeit sometimes in somewhat low yields (Equation (32)) (60PCS252, 62JCS5104, 64JOC1703, 64JOC1708, 64JOC2877, 69CPB1924, 70CJC1991, 77TL2579, 88MI 312-01).



Alternatively, dithiocarbamates as exemplified by (201) afford, upon reaction with perchloric acid, the perchlorates, (202) (Scheme 42). Reduction of (202) with sodium borohydride in ethanol gave (203) which is again treated with perchloric acid to afford (204) (80PJC2379).

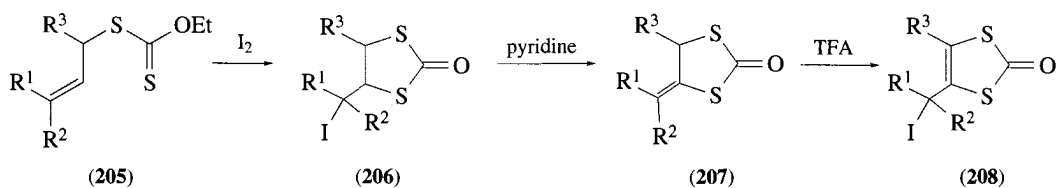
In a similar manner several bis(1,3-dithiolylum) salts (77TL4607, 80AHC(27)151) and *N,N*-disubstituted 2-amino-1,3-dithiolylum salts have been prepared (64JOC1708, 64JOC2877, 69CPB1924, 77CC388, 78JPR404, 78TL239, 80PJC2379, 85IJ279, 86MI 312-02).

The unsaturated dithiocarbonates (205) gave, upon reaction with iodine, the dithiolanone deriva-



Scheme 42

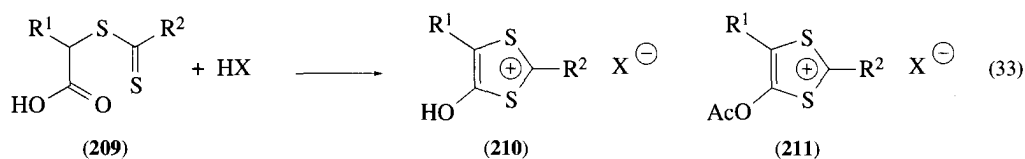
tives (206) (Scheme 43). Elimination of hydrogen iodide gives (207) and subsequent treatment with trifluoroacetic acid results in the formation of 1,3-dithiol-2-ones (208) <80JOC2959>.



$\text{R}^1 = \text{R}^2 = \text{H}, \text{Me}; \text{R}^3 = \text{H}; \text{R}^1 = \text{H}, \text{R}^2, \text{R}^3 = -(\text{CH}_2)_3-$; overall yield 63-97%

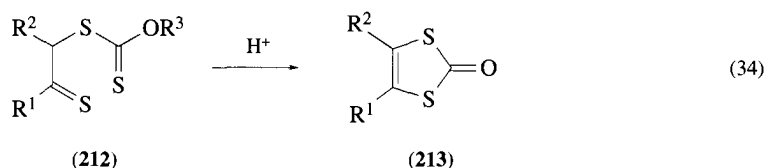
Scheme 43

α -(Thioacylthio)carboxylic acids (209) can be cyclized by strong acids (fluorosulfuric acid, perchloric acid, or conc. sulfuric acid) to afford the corresponding 4-hydroxy-1,3-dithiol-2-yl cations (210) (Equation (33)) <64JOC1708, 78CB3178>. In the presence of acetic anhydride the 4-acetoxy compounds (211) are formed <78CB3178>.

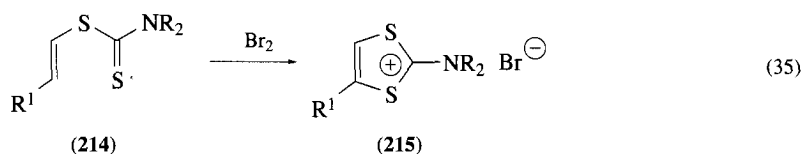


$\text{R}^1 = \text{H}, \text{Ph}; \text{R}^2 = \text{Ph}, \text{NMe}_2, \text{SMe}, \text{SEt}; \text{X}^- = \text{ClO}_4^-, \text{HSO}_4^-, \text{SO}_3\text{F}^-$

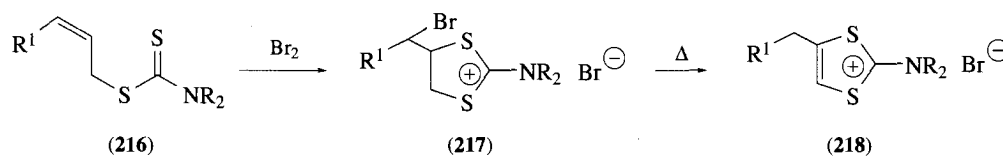
1,3-Dithiol-2-ones (213) are also obtained by acid-catalyzed cyclization of thioxodithiocarbonates (212) (Equation (34)) <76S489>.



By a similar approach *S*-vinyl-*N,N*-dialkyl-dithiocarbamates (214) afford, upon reaction with bromine, the 1,3-dithiol-2-yl bromides (215) (Equation (35)) <73CL867, 75S277>.

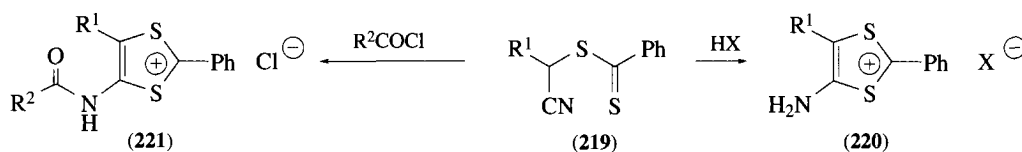


Allyl dithiocarbamates also react with bromine as exemplified by the reaction of **(216)** to afford the dithiolanylium salts **(217)**, which on thermolysis eliminate hydrogen bromide to yield the corresponding 1,3-dithiolium bromides **(218)** (Scheme 44) <74AJC1309, 74CL1041, 76BCJ827, 80AHC(27)151>.



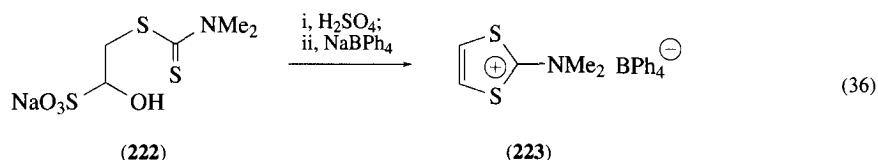
Scheme 44

4-Amino-1,3-dithiolium salts **(220)** can be obtained from cyanoalkyl dithiobenzoates **(219)** (Scheme 45); by cyclization in the presence of acyl chlorides the corresponding *N*-acyl derivatives **(221)** are obtained <65BCJ596, 63BCJ1437>.

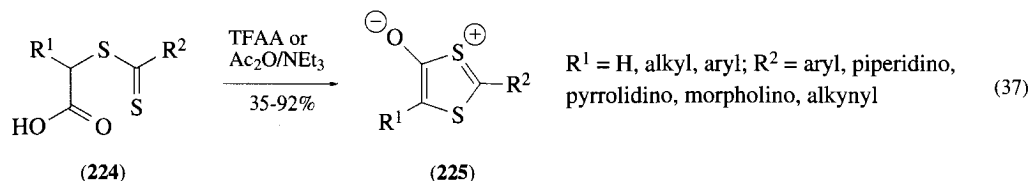


Scheme 45

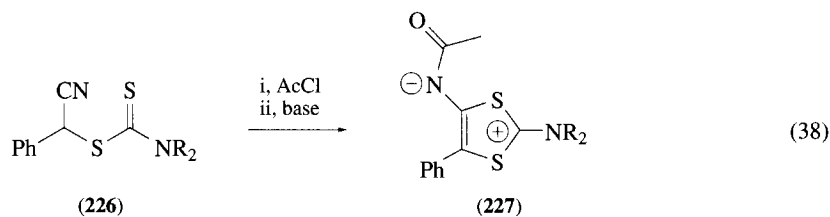
Consecutive reaction of the dithiocarbamate **(222)** with concentrated sulfuric acid and with sodium tetraphenyl borate gave **(223)** in 86% yield (Equation (36)) <80AHC(27)151>.



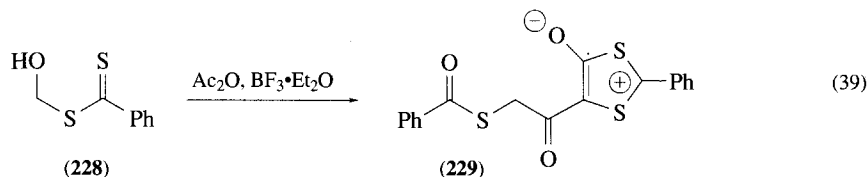
Mesoionic 1,3-dithiolones **(225)** are obtained by the anhydrocyclization of α -(thioacylthio)- or α -(thiocarbonylthio)carboxylic acids **(224)** with acetic anhydride/triethylamine (1 : 1) or trifluoroacetic anhydride (Equation (37)) <68TL4743, 69CC569, 76CB740, 76JOC1724, 77JOC1633, 78CB2021, 81LA347>, whereas upon reaction with perchloric acid, 4-hydroxy-1,3-dithiolium salts are formed <64JOC1708, 78CB3178>.



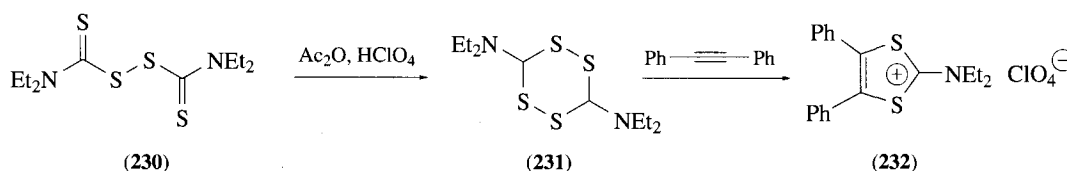
The nitriles **(226)** gave, upon reaction with acetyl chloride followed by treatment with base, the corresponding mesoionic compounds **(227)** (Equation (38)) <63BCJ1437, 65BCJ596, 78CB2021>.



The reaction of thiobenzoylthioglycolic acid (**228**) with acetic anhydride in the presence of boron trifluoride results in the formation of the dithiolone (**229**) (Equation (39)) <76JOC1724>.

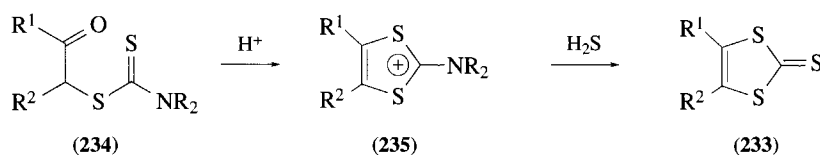


Treatment of bis(diethylaminothiocarbonyl)disulfane (**230**) with acetic anhydride/perchloric acid results in an intermediary tetrathiane (**231**), which upon treatment with diphenylethyne is transformed into 2-diethylamino-4,5-diphenyl-1,3-dithiolylum perchlorate (**232**) (Scheme 46) <83KGS1420>.



Scheme 46

A variety of methods has been described for the synthesis of 1,3-dithiole-2-thiones (**233**), well-known precursors for the generation of 1,3-dithiole derivatives. β -Keto-*N,N*-dialkylthiocarbamates (**234**) are easily cyclized with conc. sulfuric acid or 70% perchloric acid to yield the corresponding 2-amino-1,3-dithiolylum salts (**235**), which upon treatment with hydrogen sulfide in methanol or pyridine, afford the 1,3-dithiole-2-thiones (**233**) in excellent yields (Scheme 47) <64JOC1703, 67ZC58, 77TL2579>.

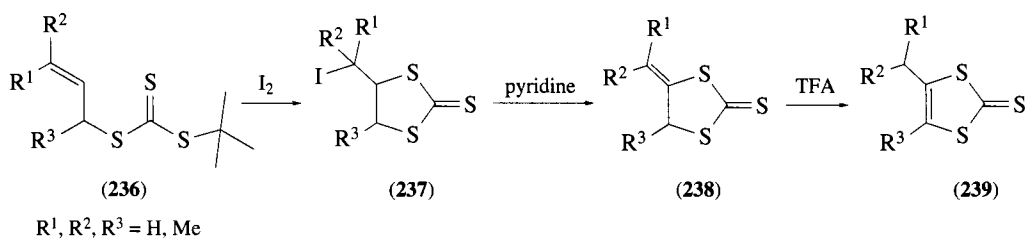


Scheme 47

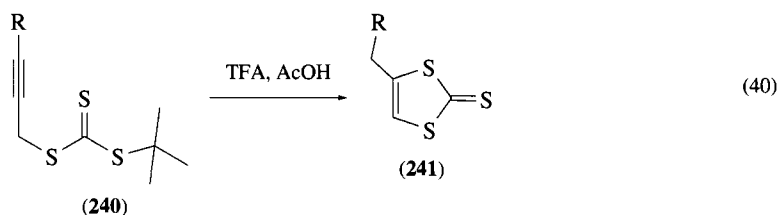
Alternatively, (**234**) can be cyclized directly using a methanolic solution of hydrogen sulfide in the presence of catalytic amounts of dimethylammonium-*N,N*-dimethyldithiocarbamate in fair yields <75JPR123>.

Allyl-*t*-butyltrithiocarbonates (**236**), which are obtained from readily available allyl halides by a multi-step reaction with sodium *t*-butyltrithiocarbonates, can be cyclized with concomitant loss of hydrogen iodide and isobutylene using elemental iodine to afford 1,3-dithiolane-2-thiones (**237**) (Scheme 48); treatment of (**237**) with pyridine again results in a loss of hydrogen iodide and (**238**) is formed. Compound (**238**) can be isomerized using trifluoroacetic acid and (**239**) is obtained <80JOC2959>.

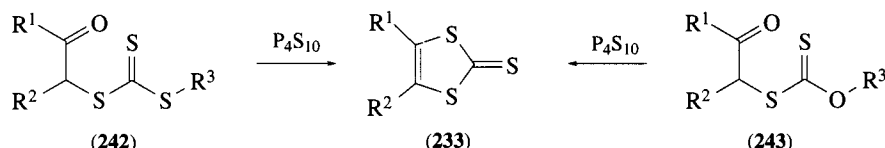
By a similar method, monosubstituted 1,3-dithiole-2-thiones (**241**) are obtained in excellent yields by a ring-closure reaction of propargyl-*t*-butyltrithiocarbonates (**240**) with trifluoroacetic acid/glacial acetic acid (Equation (40)) <78TL5161>.



Scheme 48

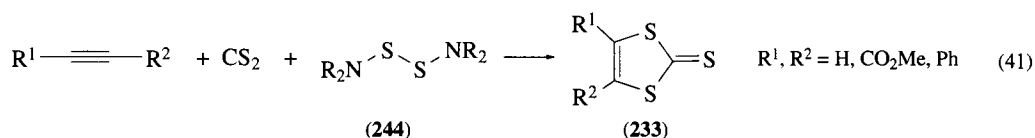


The mixture of trifluoroacetic acid/acetic acid has also been used for the cyclization of β -keto-*S*-*t*-butyltrithiocarbonates with tetraphosphorus decasulfide to afford (**233**) <80JOC175>. Alternatively, (**233**) is obtained from (**242**) or β -keto-*O*-alkyldithiocarbonates (**243**), by treatment with tetraphosphorus decasulfide in boiling decaline (Scheme 49) <62JCS5104, 69RZC1089, 76S489, 78JA3769>.

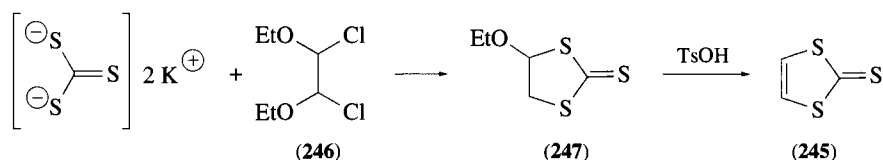


Scheme 49

Reaction of carbon disulfide with alkynes in the presence of bis(amino)disulfides (**244**) at $140^\circ C$ in a steel autoclave afforded the 1,3-dithiole-2-thiones (**233**) (Equation (41)) <70JOC2002, 78JOC2917, 83CC405>.



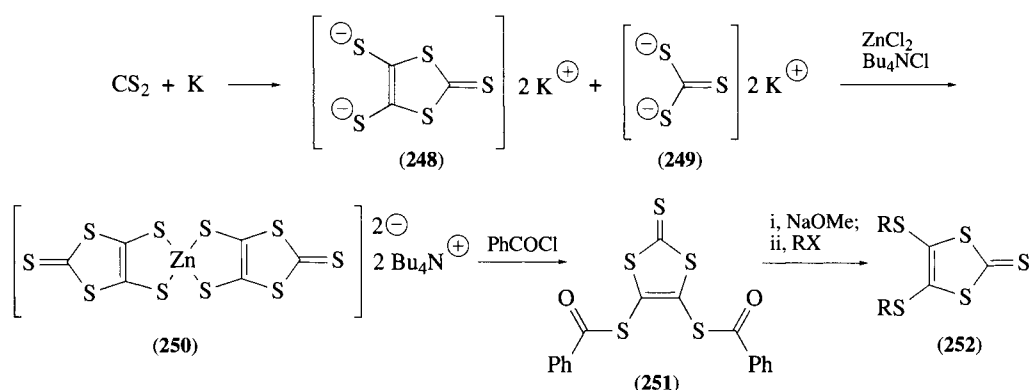
The unsubstituted 1,3-dithiole-2-thione (**245**) can be accessed, however, by the reaction of dimethyl acetylenedicarboxylate with 1,3-dithiolane-2-thione (Scheme 50) <74JOC2456>, from the reaction of sodium acetylide with carbon disulfide and elemental sulfur <64CB1298>, or by a two-step synthesis from the 1,2-dichloroethyl ethylether (**246**) and potassium trithiocarbonate. The intermediary 4-ethoxy-1,3-dithiolone-2-thione (**247**) affords, upon reaction with *p*-toluene sulfonic acid with concomitant loss of ethanol, the unsubstituted derivative (**245**) <76CC920>.



Scheme 50

Reduction of carbon disulfide also provides a starting point for the synthesis of these compounds. For small scale preparation the electrochemical reduction of CS_2 in DMF on a platinum or mercury electrode offers a way for the preparation of 4,5-dithio-1,3-dithiole-2-thione dianion (**248**) (together with significant amounts of potassium trithiocarbonate (**249**)), which upon alkylation gives access to 4,5-bis(alkylsulfanyl)-1,3-dithiole-2-thiones (**252**) (Scheme 51) <74JA945, 74JOC511, 81JOC775>. How-

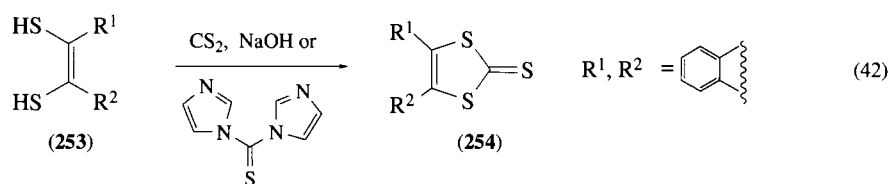
ever, for the synthesis on a preparative scale CS_2 is reduced with elemental potassium in DMF $\langle 80\text{CB}1898 \rangle$. This chemical reduction affords significant amounts of the trithiocarbonate **(249)**, also the 4,5-dithio-1,3-dithiole-2-thione dianion **(248)** can be converted (and thus be separated from undesired **(249)**) into the tetra-*n*-butylammonium zinc chelate **(250)** by treatment with tetra-*n*-butylammonium chloride/zinc chloride $\langle 75\text{ZC}28, 79\text{PS}(7)49 \rangle$. Since the use of potassium in this reaction can lead to explosions, only the use of sodium can be considered safe for large-scale preparations $\langle 95\text{S}215 \rangle$. Benzoylation of **(250)** affords the 4,5-bis(benzoylthio)-1,3-dithiole-2-thione **(251)**. Deacylation with sodium methoxide followed by alkylation yields the corresponding 4,5-bis(alkylsulfanyl)-1,3-dithiole-2-thiones **(252)** $\langle 83\text{JPR}957 \rangle$, which are also accessible by the direct alkylation of the mixture of **(248)**/**(249)** albeit in a somewhat lower yield $\langle 80\text{CB}1898 \rangle$.



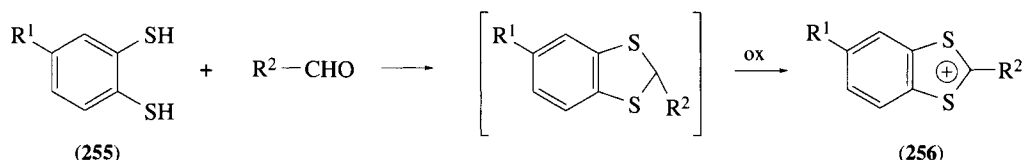
Scheme 51

Not for general application is the reaction of enamines with tetramethylthiuram disulfide/triethylamine/hydrogen sulfide since the enamines of aliphatic aldehydes do not react at all and the ketimines of acyclic dialkylketones give only moderate yields (10–35%), whereas the enamines of cyclic or of aryl substituted ketones give the corresponding 1,3-dithiole-2-thiones in fair to good yields (35–90%) $\langle 75\text{JPR}123 \rangle$.

Benzo-anellated 1,3-dithiole-2-thiones **(254)** are also obtained by the reaction of the dithiols **(253)** with thiocarbonyldiimidazole in glacial acetic acid or with carbon disulfide in alkaline solution (Equation (42)) $\langle 76\text{JOC}145, 83\text{JOC}4713, 83\text{MI} 312-05, 85\text{MCLC}295 \rangle$.

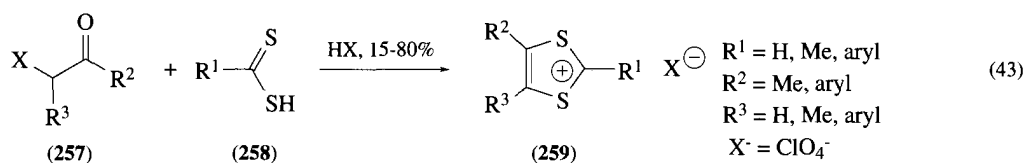


Alternatively, 1,2-dithiobenzenes **(255)** have been allowed to react consecutively with aldehydes and an oxidizing agent (bromine, H_2O_2 , quinones) to afford the corresponding 1,3-benzodithiolylium salts **(256)** (Scheme 52) $\langle 26\text{JCS}1821, 26\text{JCS}2263, 27\text{JCS}534, 59\text{HCA}1779 \rangle$.

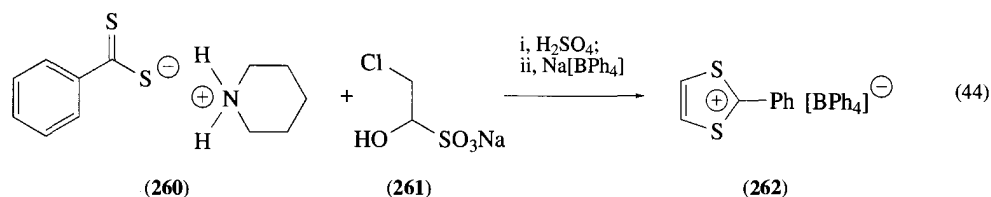


Scheme 52

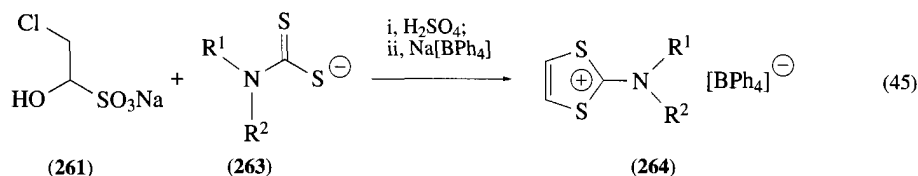
The reaction of α -haloketones **(257)** with an excess of dithio carboxylic acids **(258)** at 60–80°C in the presence of strong mineral acids affords 1,3-dithiolylium salts **(259)** (Equation (43)) $\langle 71\text{JPR}722 \rangle$.



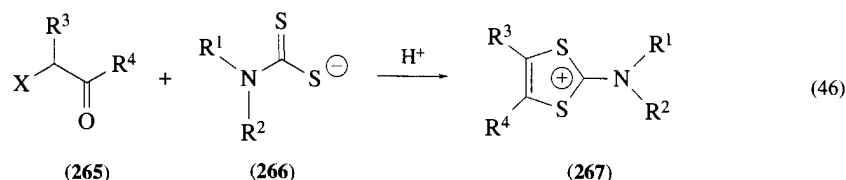
Reaction of the piperidinium salt of the dithiobenzoic acid (**260**) with equimolar amounts of chloroacetaldehyde as its sodium hydrogensulfite adduct (**261**) followed by an acid-catalyzed cyclization gives access to 2-phenyl-1,3-dithiolylum tetraphenylborate (**262**) (Equation (44)) <75S277>.



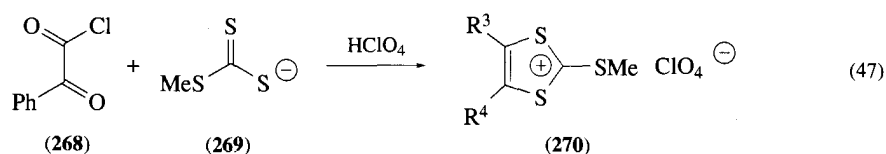
The 2-dialkyldithiolylum tetraphenylborates (**264**) were obtained from (**261**) and sodium *N,N*-dialkyldithiocarbamides (**263**) (Equation (45)) in a similar way <75S277, 76JAP7610076>.



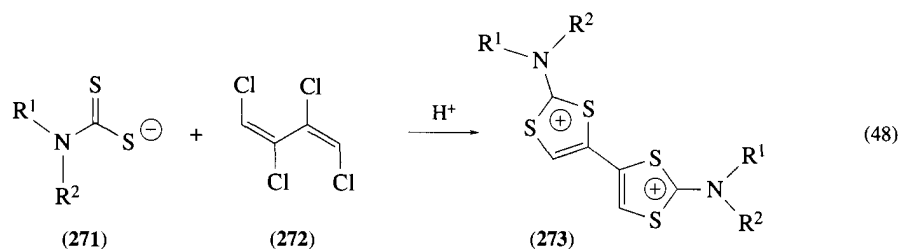
The reaction of α -halogenated ketones (**265**) with sodium *N,N*-dialkyldithiocarbamides (**266**) in the presence of strong acids, affords the corresponding 2-alkylamino-1,3-dithiolylum compounds (**267**) (Equation (46)) <69CPB1924, 75CL603, 77CC388, 77JAP7783599, 77TL2223, 78CB2028, 78JPR404, 78TL239>.



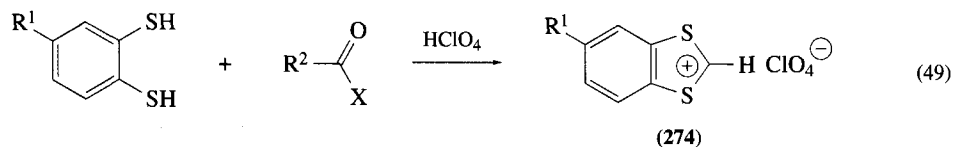
The reaction of 2-chloro-1,2-diphenylethanone (**268**) with sodium methyltrithiocarbonate (**269**) and perchloric acid gave a 35% yield of 4,5-diphenyl-2-methylsulfanyl-1,3-dithiolylum perchlorate (**270**) (Equation (47)) <65JOC732>.



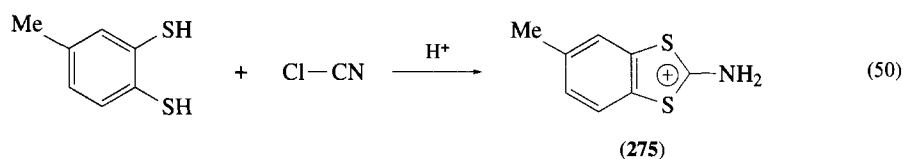
Compounds possessing two dithiolylum units, for example (**273**), can be synthesized by the reaction of *N,N*-dialkyldithiocarbamides (**271**) and 1,2,3,4-tetrachloro-1,3-butadiene (**272**), followed by treatment with strong mineral acid (Equation (48)) <76JAP7652172, 77JAP7783561>.



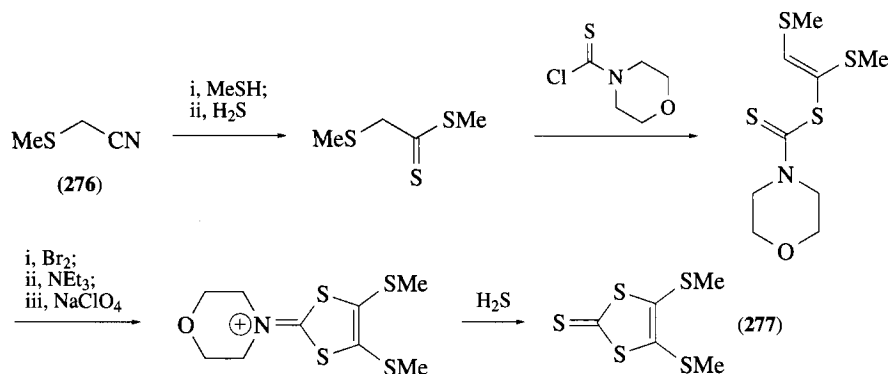
1,3-Benzodithiolylum salts (**274**) are easily prepared by the condensation of carboxylic acids (Equation (49)) <58C79, 59HCA1779, 73LA310, 74JHC507, 74LA403> with <59HCA1779, 73LA310, 74JHC507, 74LA403> or without the addition of phosphorus oxychloride, or of carboxylic acid chlorides <59HCA1733, 63HCA2167, 74BSF510>, or of carboxylic esters <77S263> with dithio-benzenes <64JOC2877, 69RZC1089>.



2-Amino-1,3-dithiolylum salts (**275**) were prepared by the acid or base catalyzed reaction between chlorocyan and 1,2-dithiobenzene (Equation (50)) <64JOC738>.

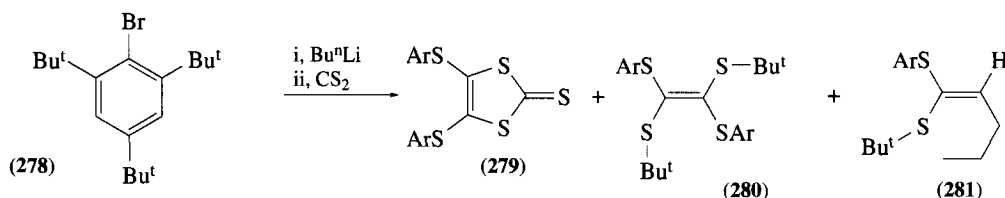


4,5-Bis(methylsulfanyl)-1,3-dithiole-2-thione (**277**) was prepared from 2-methylsulfanyl-acetonitrile (**276**) by classical heterocyclic ring chemistry (Scheme 53) <80CB1898>.



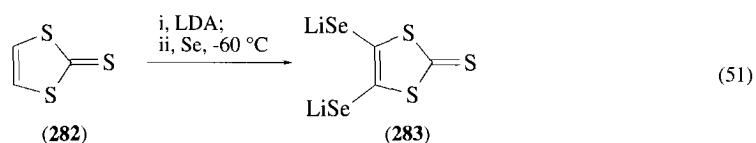
Scheme 53

1-Bromo-2,4,6-tri-*t*-butylbenzene (**278**) gave, upon treatment with *n*-butyllithium, a halogen metal exchange reaction to afford 2,4,6-tri-*t*-butylphenyllithium, which reacts with carbon disulfide at -78°C to give a mixture of three compounds (**279**) (3.6% yield), (**280**) (41% yield), and (**281**) (19% yield) (Scheme 54) <88JPO75>.

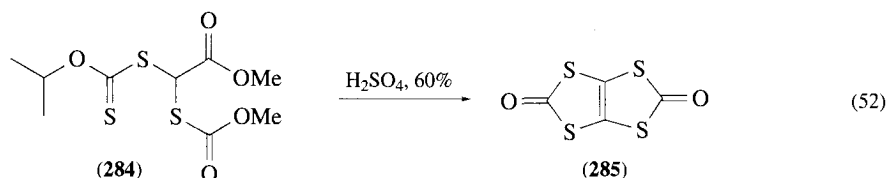


Scheme 54

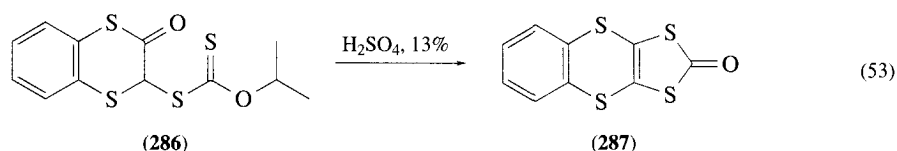
4,5-Chalcogenation of 1,3-dithiole-2-thiones (**282**) and analogues by *in situ* chalcogen insertion into the C—Li bond produces 4,5-dichalcogenolato-1,3-dithiole-2-thiones (**283**) (Equation (51)) <86MI 312-01, 90ZAAC(581)59>. Unfortunately, scrambling of the heteroatom has been shown to happen <90MCLC171>.



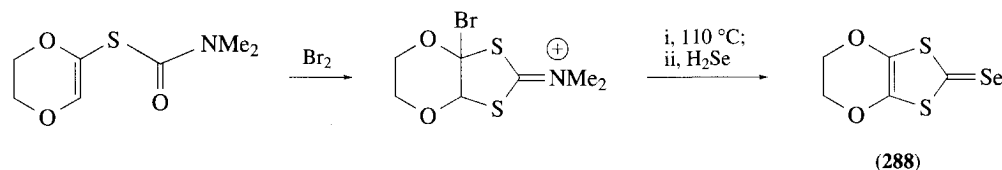
1,3-Dithiolo[4,5-*d*]-1,3-dithiole-2,5-dione (**285**) can be prepared by cyclization of methyl 2,2-bis(*O*-isopropylthioxanthyl)acetate (**284**) with concentrated sulfuric acid (Equation (52)) <84JOC564>.



By a similar method, 4,5-phenylenedithio-1,3-dithio-2-one (**287**) was prepared from the precursor (**286**), albeit in a somewhat low yield (Equation (53)) <92ZN(B)718>.



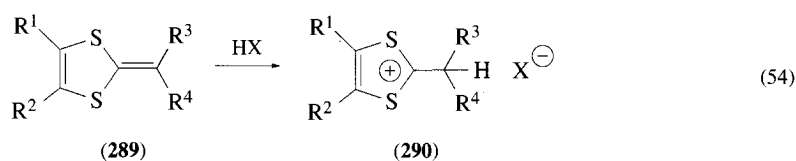
4,5-Dihydroxy substituted 1,3-dithioles (**288**) have been accessed via a rather lengthy synthetic scheme (Scheme 55) <89JA3108, 92CC1410>.



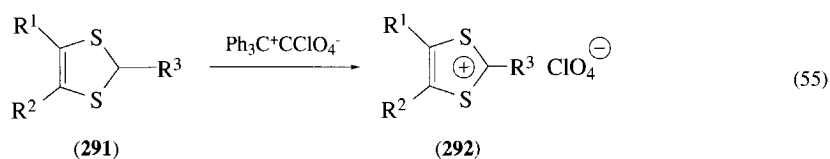
Scheme 55

3.12.7.1.2 From heterocyclic compounds

1,3-Dithiolylium salts (**290**) have been obtained from 1,3-dithiols (**289**) by protonation (Equation (54)) <58LA(614)4, 64JOC1711, 65JOC732>.

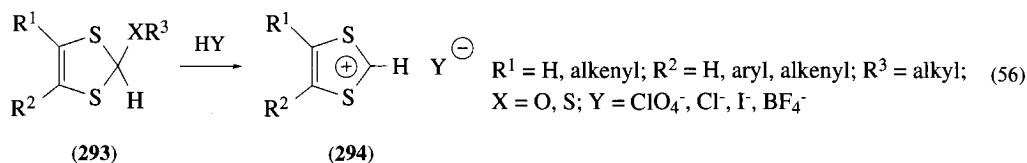


Compounds (**292**) were prepared from 2*H*-1,3-dithiols (**291**) by reaction with triphenylmethyl perchlorate (Equation (55)) <71T4003, 75CL1099, 76JCS(P1)1886, 76S759, 81TL1821>.

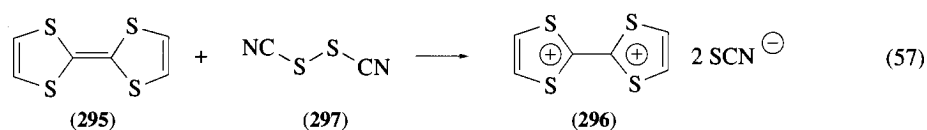


Elimination of thiolate or alcoholate from 2-alkylsulfanyl or 2-alkoxy-1,3-dithiols (**293**) using triphenylmethyl tetrafluoroborate <77CL127, 82BCJ2289>, tetrafluoroboric acid in acetic anhydride <74JOC3608, 75CL1099, 76BCJ3567, 76S471, 78JCS(P1)468, 82BCJ2289>, strong acids <76BCJ3567, 84PJC775>, or

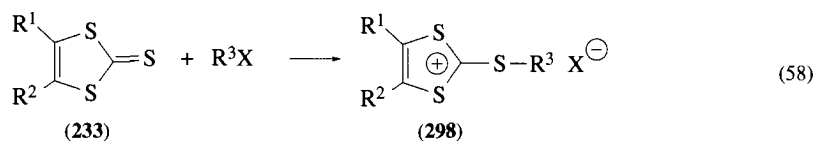
bromine <82MI 312-01> resulted in the formation of 1,3-dithiolylum salts (**294**) being unsubstituted at position two (Equation (56)).



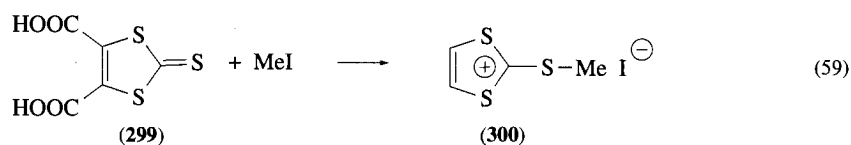
Similarly, the 4-aryl-1,3-dithiolylum salts were obtained from 2-amino-4-aryl-1,3-dithiols <69CPB1924, 78JPR404>. Compounds possessing two dithiolylum moieties, for example (**296**), have been prepared from TTF (eg., (**295**)) either by reaction with dicyanodisulfane (**297**) (Equation (57)) <77CR(C)463>, chlorine <70CC1453>, bromine <78JPR404>, iodine <78JPR404>, and other oxidants <76S489, 87SR155>, or electrochemically <71JA2258, 73LA310>.



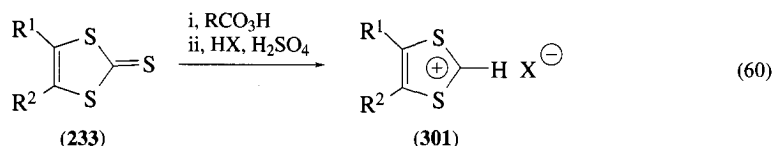
1,3-Dithiole-2-thiones are excellent starting materials for the synthesis of 1,3-dithiolylum salts via halogenation, alkylation, or oxidation. Thus, 2-alkylsulfanyl-1,3-dithiolylum salts (**298**) were obtained from the 1,3-dithiole-2-thiones (**233**) by alkylation (Equation (58)) <53JCS292, 59HCA1733, 63HCA2167, 64CB1298, 64JA5290, 65CB1365, 65USP3187009, 68CB1428, 72S29, 74JA945, 74LA403, 75TL1259, 77MI 312-01, 78JOC678, 81CC920, 81ZOR1055, 83JOC4713, 84KGS705>.



Treatment of the 2-thione (**299**) with methyl iodide leads to the formation of 2-methylsulfanyl-1,3-dithiolylum iodide (**300**) with concomitant decarboxylation (Equation (59)) <65USP3187009>.

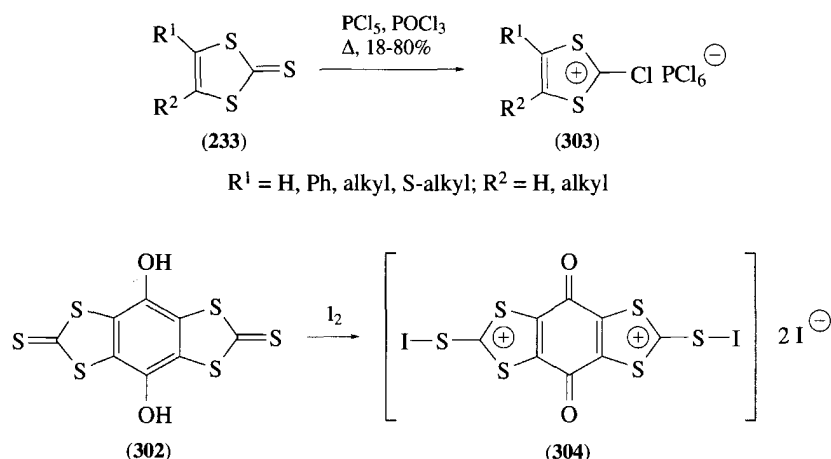


Reaction of 1,3-dithiole-2-thiones (**233**) with peracids results in the formation of 1,3-dithiolylum salts (**301**) (Equation (60)) <62JA3410, 62JCS5104, 64JA5290, 64USP3155682, 74JOC2456, 76JOC730, 77JAP7795695, 78JA3769, 84KGS180>.

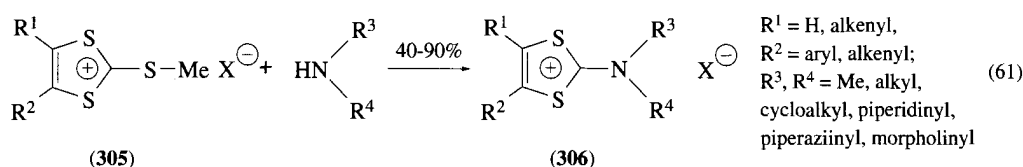


Reactions between 1,3-dithiole-2-thiones (**233**) or (**302**) with iodine <77JAP7795695>, phosphorus pentachloride <84S319>, thiophosgene <79LA689>, or other halogenating agents <84S319> lead to the corresponding dithiolylum salts (**303**) and (**304**), respectively (Scheme 56).

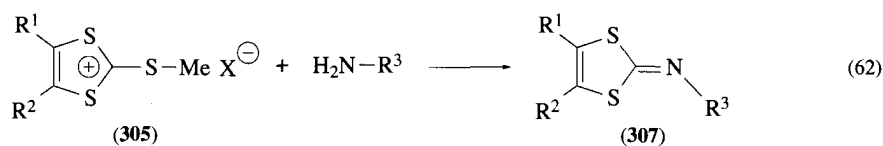
The reaction of 2-methylsulfanyl-1,3-dithiolylum salts (**305**) with secondary amines results in the formation of the corresponding 2-amino-dithiolylum salts (**306**) (Equation (61)) <64JOC2877>.



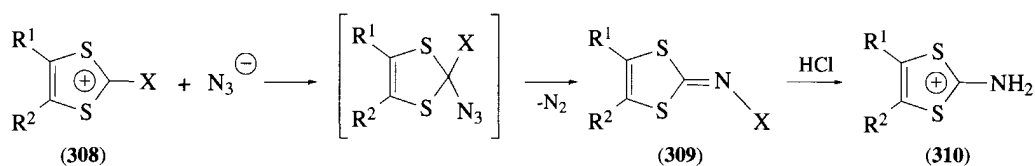
Scheme 56



The reaction of (305) with primary amines, however, affords the corresponding imino-derivatives (307) (Equation (62)) <65JOC1677, 71LA(754)46>.

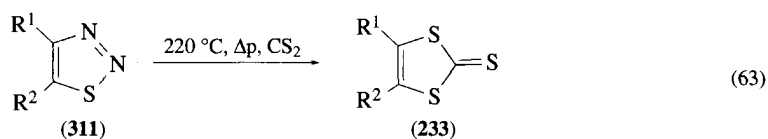


2-Amino-1,3-dithiolium chlorides (310) are also available by the reaction of 2-halogenated 1,3-dithiolium salts (308) with azide followed by a treatment of the intermediate 2-iminodithioles (309) with acid (Scheme 57) <83S50>.

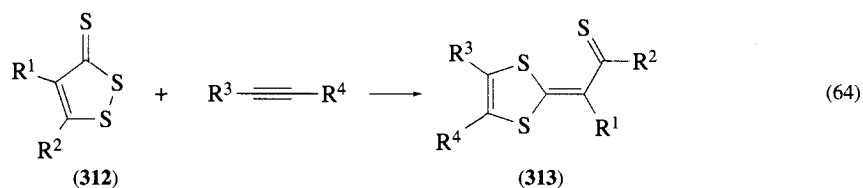


Scheme 57

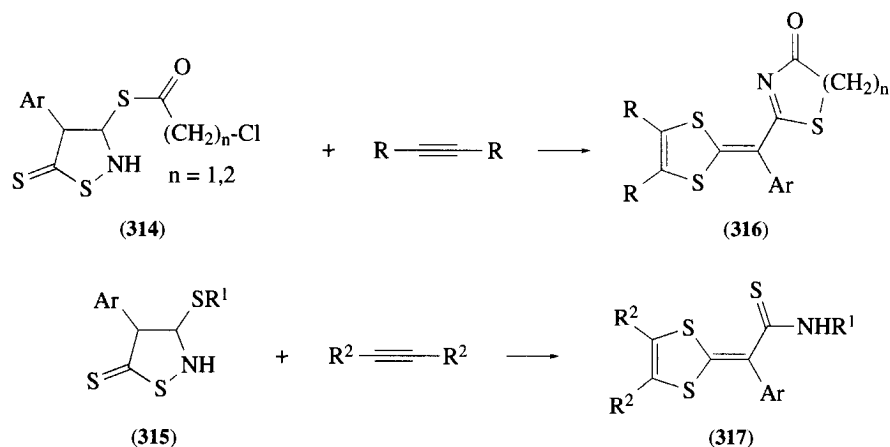
Thermolysis of 1,2,3-thiadiazoles (311) in carbon disulfide under forced conditions provides a synthetic route to trimethylene- and tetramethylene-1,3-dithiole-2-thiones and benzo-1,3-dithiole-2-thiones (233) (Equation (63)) <61E566, 76JOC730>. Alternatively, a photochemical path has been devised <61E566>.



1,2-Dithiole-3-thione derivatives can be used as starting materials for the synthesis of 1,3-dithioles. Thus, 1,2-dithiole-3-thiones (312) react with alkynes or even benzyne to afford (313) (Equation (64)) <68CB1428, 80ZOR883>.

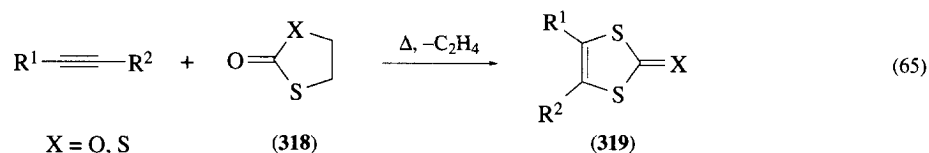


Reaction of 3-chloroacetylthio-3-isothiazoline-5-thiones (314) or of 3-thio(or 3-acylthio)-3-isothiazoline-5-thiones (315) with reactive alkynic compounds furnishes the 1,3-dithioles (316) and (317), respectively (Scheme 58) <80H(14)785, 80JCS(P1)2693, 81H(16)595>.



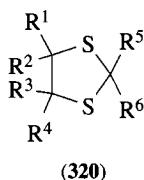
Scheme 58

Alkynes with electron-withdrawing substituents react with *O,S*-ethylene dithiocarbonate (318; X = O) or ethylene trithiocarbonate (318; X = S) to afford ethylene and 1,3-dithiol-2-ones (319; X = O), or 1,3-dithiole-2-thiones (319; X = S), respectively (Equation (65)) <70JOC2002, 72JCS(P1)41, 74JOC2456>.



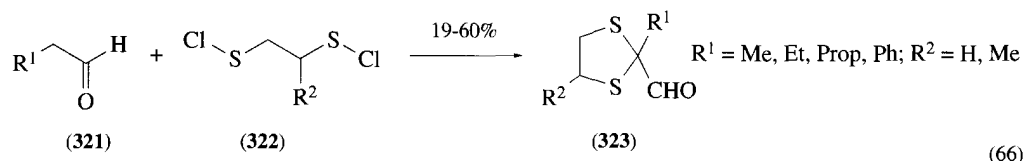
3.12.7.2 1,3-Dithiolanes

1,3-Dithiolanes are characterized by a general formula (320) with R¹–R⁶ being alkyl or aryl substituents. They can be regarded as *S,S*-acetals and are very attractive protecting groups for carbonyls as well as acyl or formyl anions in umpolung reactions <77S357>.

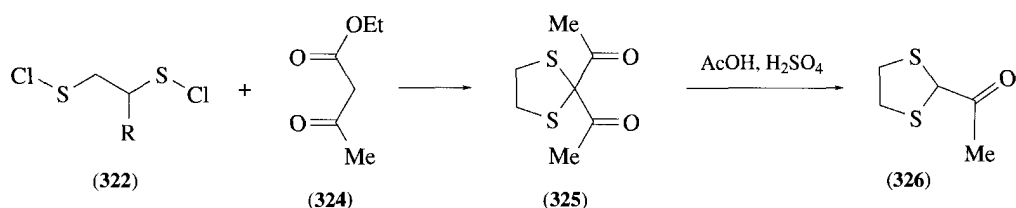


3.12.7.2.1 From nonheterocyclic compounds

Carbonyl compounds (321) possessing an α -methylene moiety react with 1,2-bis(chloro-sulfenyl)alkanes (322) to give 1,3-dithiolanes (323) (Equation (66)) <72JOC887>; similarly, 2-alkylidene 1,3-dithiolanes are accessible <91S301>.

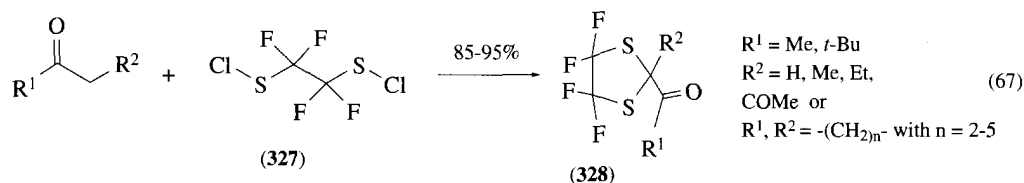


Use of ethyl 3-oxobutanoate (**324**) allows a convenient synthesis of 2-acetyl-2-ethoxycarbonyl-1,3-dithiolanes (**325**) (Scheme 59); these compounds are easily decarboxylated to form 2-acetyl-1,3-dithiolanes (**326**) <72JOC887>.

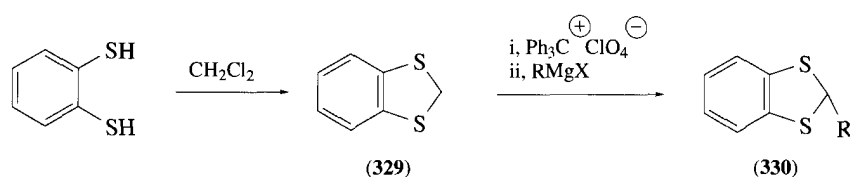


Scheme 59

Use of 1,2-bis(chlorosulfonyl)tetrafluoroethane (**327**) even allows the synthesis of 4,4,5,5-tetrafluoro-substituted compounds (**328**) (Equation (67)) <86CZ417, 86RRC935, 87ZAAC(545)143>.



The reaction of suitable substituted geminal di-halogenated alkanes with 1,2-dithiols in the presence of potassium carbonate leads to the formation of 1,3-dithioles only in the presence of a suitable phase-transfer catalyst <82LA1589, 87S56>. Treatment of the 1,2-benzenedithiol (**329**) with triphenylmethyl perchlorate and Grignard compounds gave the 2-substituted analogues (**330**) in good yields (Scheme 60) <81TL1821>.



Scheme 60

There have been alternatives to the geminal dihalogenides, *O,O*-acetals (**331**), or *N,N*-acetals used for transacetalization reactions to afford compounds (**332**) (Equation (68)) <66CR(268)1718, 73BSF3499, 79MI 312-02, 81LA1899>. However, the broadest applicability shows the reaction of aldehydes or ketones with suitable substituted 1,2-dithiols in the presence of a catalyst, for example, hydrochloric acid, zinc chloride, borontrifluoride diethyl ether complex <87JOC827>, aluminium trichloride, titanium(IV) chloride <83TL1289>, Nafion H <81S282>, ion exchange resins <89SC2383>, sulfur dioxide <82S831>, chlorotrimethylsilane, tetrachlorosilane, samarium triiodide <93OPP365>, and many other acidic catalysts <91TL2259>. Thus, the reaction of aldehydes (**333**) with 2,3-dithiosuccinic acid dimethyl ester (**334**) in the presence of dry hydrochloric acid gave the 4,5-dimethoxycarbonyl substituted 1,3-dithiolanes (**335**) in good yields (80–87%) (Equation (69)) <85TL5265>.



corresponding 4,7-dithiospiro[2.4]heptanes (337) (Equation (70)) $\langle 87S393 \rangle$.



1,2-dithiol selectively at their keto group leading to 2-formyl-1,3-dithiolanes (**342**) <71JHC469>.



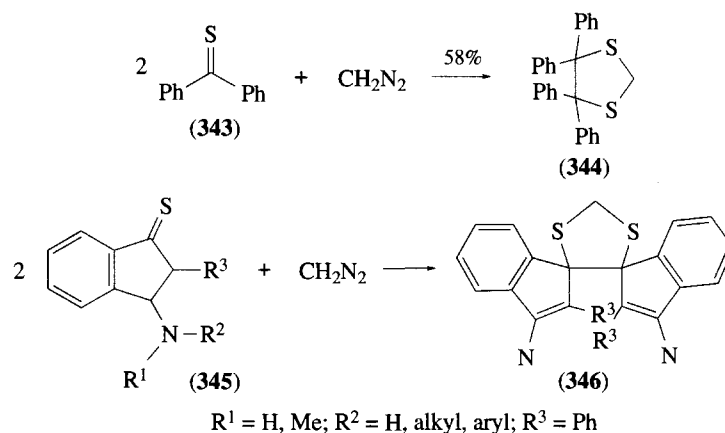
Scheme 61

Chlorotrimethylsilane has been used quite successfully as a catalyst for the dithio-acetalization of ketones (Equation (71)) ^[84JOC5198] as tetrachlorosilane has been used for aldehydes ^[89SC433].



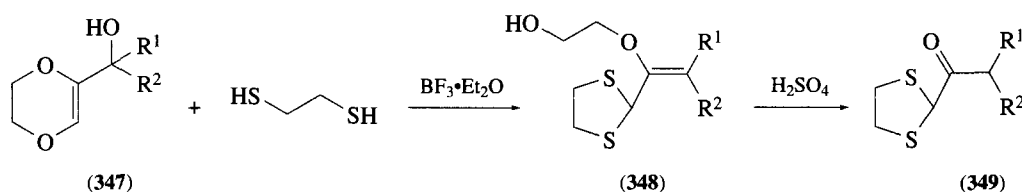
Other catalysts have been used for this transformation, for example Mg or Zn trifluoromethanesulfonate <75TL3841, 83TL169>, polyphosphoric acid trimethylsilylester <87S164>, thionyl chloride on silica gel <86JOC1427>, Montmorillonit <89SC31, 92CC1192>, H-Y-zeolite <92TL825>, boron trifluoride/water <92MI 312-03>, and tellurium tetrachloride <92PS(67)261>. Reaction of thiobenzophenone (**343**) with diazomethane gave access to 4,4,5,5-tetraphenyl-1,3-dithiolane (**344**) (Sch-

eme 62) <30CB2575, 31CB2577, 67CB767, 81JA7032>. Similarly, 3-amino-1-thionoindenes (**345**) gave, upon reaction with diazomethane, the corresponding 3-amino anellated ring systems (**346**) <78KGS36>.



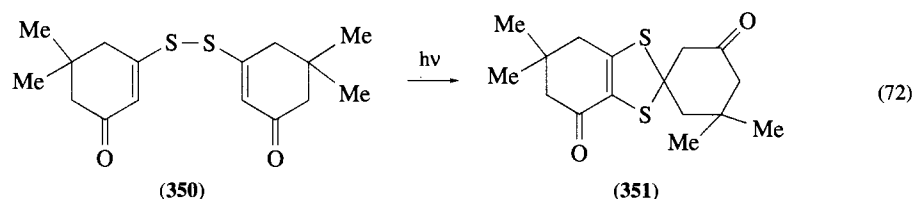
Scheme 62

Enolethers, as exemplified by the substituted 2-(1-hydroxyalkyl)-5,6-dihydro-1,4-dioxines (**347**), afford, upon reaction with 1,2-ethanedithiol in the presence of catalytic amounts of boron trifluoride diethyl ether complex, the corresponding 2-(1-alkoxy-1-alkenyl)-1,3-dithiolanes (**348**), which upon hydrolysis give 2-acyl-1,3-dithiolanes (**349**) (Scheme 63) <80TL3919>.

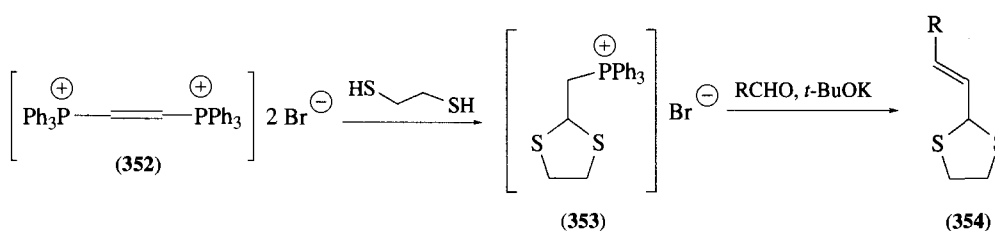


Scheme 63

Similarly bis(5,5-dimethyl-3-oxa-1-cyclohexenyl)disulfane (**350**) gave upon photolysis the spiro-anellated compound (**351**) (Equation (72)) <73TL4319>.

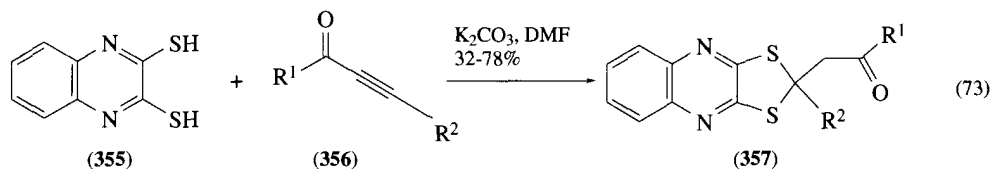


1,2-Bis(triphenylphosphonium)ethane dibromides (**352**) react with 1,2-ethanedithiol in the presence of base almost quantitatively to give 2-(triphenylphosphoniomethyl)-1,3-dithiolanes (**353**) which upon addition of an aldehyde afford the corresponding 2-(1-alkenyl)-1,3-dithiolanes (**354**) (Scheme 64) <78S826>.

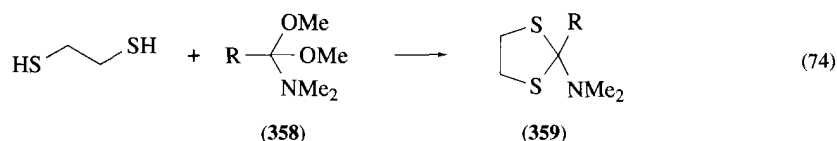


Scheme 64

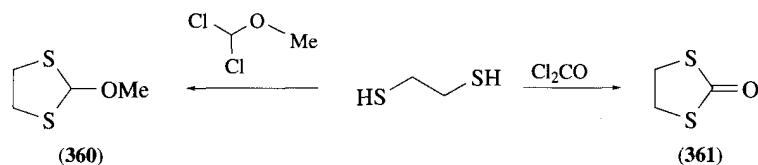
Also alkynes have been used for the synthesis of dithiolanes. Thus, 2,3-dithioquinoxaline (**355**) gave, by vinylogous addition onto 3-oxo-1-alkynes (**356**) 2-(2-oxoalkyl)-1,3-dithiolo[4,5-*b*]quinoxalines (**357**) (Equation (73)) <82KGS1489>.



The synthesis of 1,3-dithiolanes (**359**) which contain a 2-dimethylamino group results from the reaction of ethanedithiol with an amide acetal (**358**) (Equation (74)) <69BSF332>.

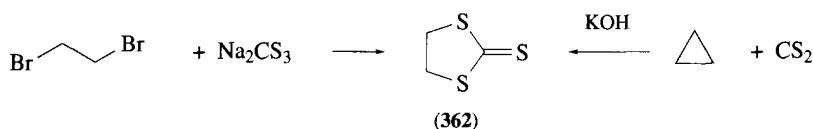


Reaction of 1,2-ethanedithiol with dichloromethyl methylether in the presence of sodium results in the formation of the 2-methoxy-1,3-dithiolane (**360**) (Scheme 65) <72HCA75>, whereas its reaction with phosgene yielded the 1,3-dithiolan-2-one (**361**) <41RTC453>.



Scheme 65

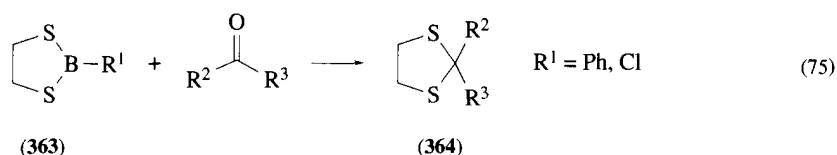
The 1,3-dithiolane-2-thione (**362**) can be accessed either by the reaction of ethylenedibromide with sodium trithiocarbonate (Scheme 66) <1862LA(123)83> or by the reaction of ethylene oxide with potassium hydroxide and carbon disulfide <46JCS1050>.



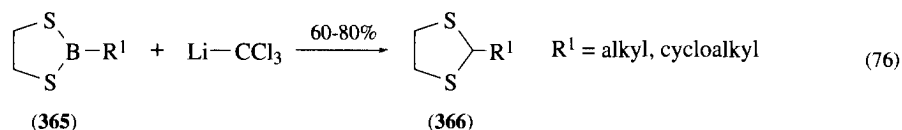
Scheme 66

3.12.7.2.2 From heterocyclic compounds

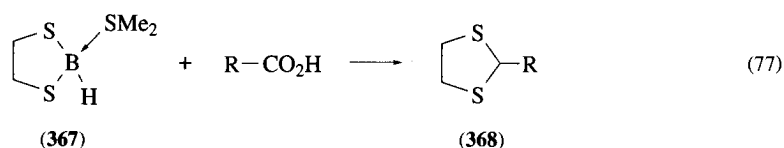
Almost neutral conditions allow the transformation of complex and rather sensitive carbonyl compounds by using 2-phenyl- (or 2-halogeno-) 1,3,2-dithiaborolane (**363**) into 1,3-dithiolanes (**364**) (Equation (75)) <79JOC656>.



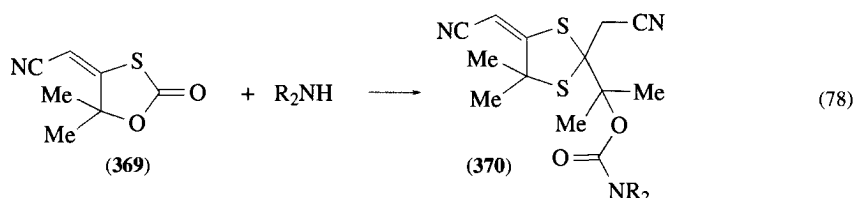
2-Alkyl-1,3,2-dithiaborolane (**365**) reacts with trichloromethylithium to yield the corresponding 2-alkyl-1,3-dithiolanes (**366**) (Equation (76)) <84JOC892>.



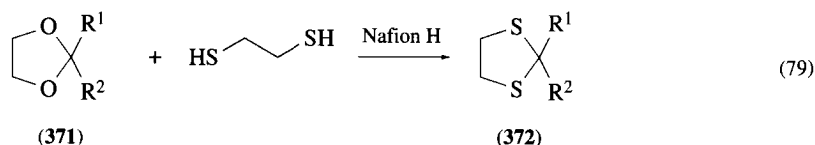
Reaction of 1,2-ethanedithiol with boron trifluoride dimethylsulfide complex gives (367) which is a useful reagent for the one-step conversion of carboxylic acids RCO_2H into 1,3-dithiolanes (368) (Equation (77)) <89MI 312-01>.



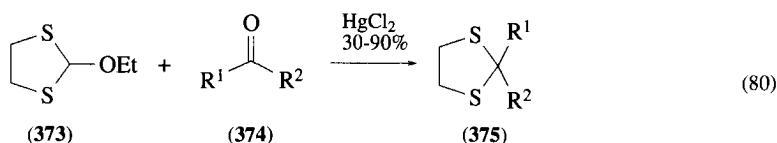
The oxathiolone (369) afforded, upon reaction with secondary amines, the 1,3-dithiolane (370) (Equation (78)) <89KGS855, 92KGS335>.



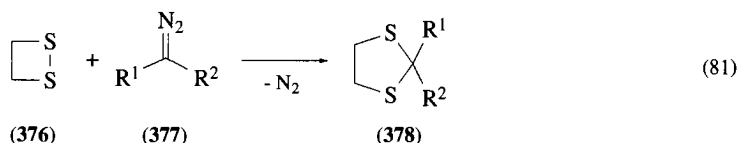
The direct conversion of 1,3-dioxolanes (371) to 1,3-dithiolanes (372) with 1,2-ethanedithiol is catalyzed by Nafion-H (Equation (79)) <91MI 312-01>.



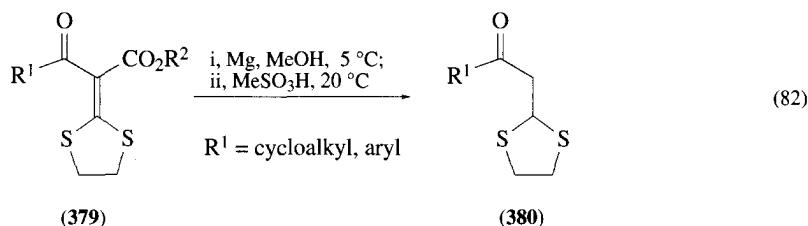
Carbonyl compounds (374) sensitive to acids can also be transformed into the corresponding 1,3-dithiolanes (375) by reaction with 2-ethoxy-1,3-dithiolane (373) in the presence of mercury(II) chloride or other Lewis acids (Equation (80)) <81BCJ1434>.



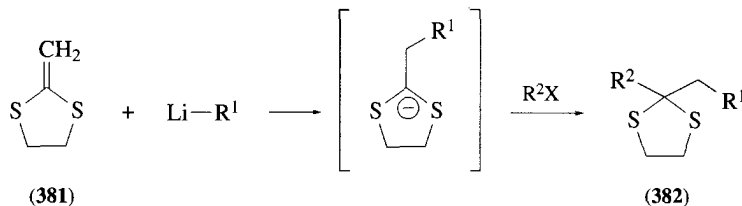
Cyclic disulfanes (376) react with diazoalkanes (377) via their corresponding carbenes under insertion to yield (378) (Equation (81)); Cu(I)Cl or dimeric rhodium acetate is used in these reactions as a catalyst <85TL5187, 88T3159>.



The reduction of cyclic ketene *S,S*-acetals (379) is used quite often for the synthesis of 1,3-dithiolanes (380) (Equation (82)). Thus, hydrogen and a catalyst <75S385>, lithium aluminum hydride or sodium borohydride <77TL3623, 80JA3095>, as well as trifluoroacetic acid/triethylsilane <79TL3525> or trifluoroacetic acid/trimethylsilane <83JCS(P1)1299> have been applied. In addition, magnesium in methanol has been shown to be an excellent reducing agent for these transformations <88S792>.

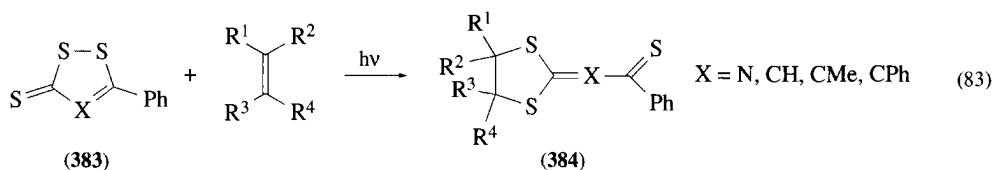


Alkylolithium compounds add to ketene *S,S*-acetals (**381**) and the resulting carbenoids can be trapped by electrophiles resulting in the formation of *S,S*-acetals (**382**) (Scheme 67) <88S792>.



Scheme 67

Photocycloaddition reactions have been used for the transformation of 1,2,4-dithiazole-3-thiones and 1,2-dithiole-3-thiones (**383**) in the presence of alkenes to afford the corresponding 1,3-dithiolanes (**384**) (Equation (83)) <75JCS(P1)270, 80ZOR443>.



3.12.8 SYNTHESSES OF A PARTICULAR CLASS OF COMPOUNDS—TETRATHIAFULVALENES

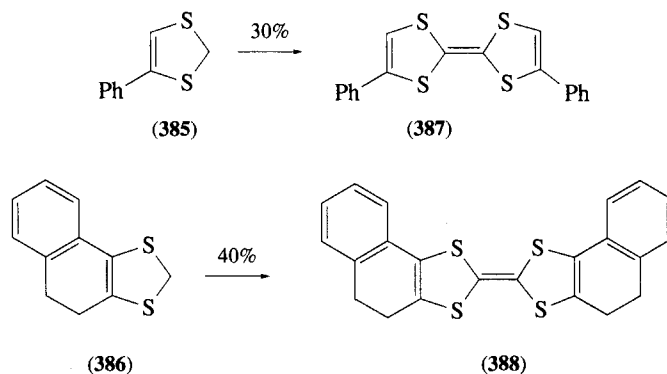
Tetrathiafulvalenes (TTF) are electron donors which easily form charge-transfer complexes with electron acceptors, such as radical salts, some of which possess a segregated stack structure ("organic metals") <74ACR232, 77AG534, 79ACR79, 83UK1301, 84ACR227, 85ACR261, 85MI 312-01, 86T1209, 87SR155, 93SR245>. The discovery of the exceptional electric conductivity of TTF has encouraged research into their synthesis. In addition to the original methods for the synthesis of TTF <70CC1453, 74JOC2456, 74JOC3608, 80CC38> there also exists the preparation of analogues where all the hydrogens are substituted by alkyl <73TL2253, 80CC38>, aryl <26JCS2263, 74LA403, 75JOC746, 75S168, 78ANY(313)467, 80CC38, 84TL991, 84TL995>, cycloalkyl <71AG(E)509, 78ANY(313)467, 80CC38>, or alkylsulfanyl <74JA945, 83MI 312-01> groups as well as those possessing electron-withdrawing groups <73JA4379, 74CC751, 75JOC3577, 80CC38, 81JOC446>.

In addition, the synthesis of unsymmetrically substituted analogues of TTF <74JOC2456, 76CC966, 77TL4033, 78JOC369, 82TL1813, 83MI 312-02, 84JOC390, 84TL2403> and those derivatives with the TTF system being part or attached to a polymeric system <75CL603, 76JOC1412, 76MM360> have been described. Synthetic methodology allows the selective synthesis of compounds unsymmetrical about the carbon-carbon bond <78JOC369, 82TL1813, 84TL991, 84TL995> thus avoiding tedious separation of isomeric mixtures which was always obtained using classical approaches <65AG(E)435, 77TL4033, 78JOC416, 82TL1813, 83MI 312-02>.

3.12.8.1 Formation of the Tetrahetero-substituted Bond in the Final Step

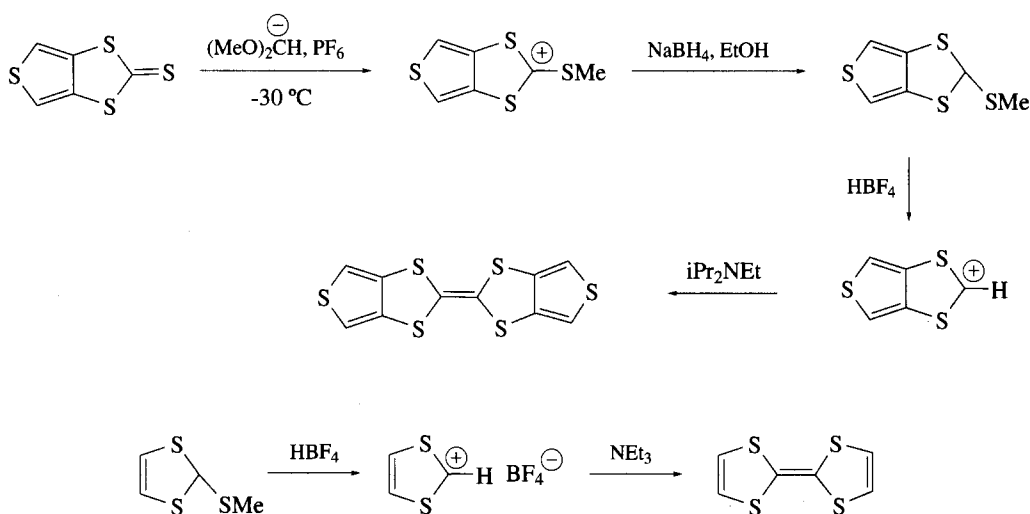
For these syntheses the π -bond is formed via an elimination reaction involving either two protons (electrochemical oxidation), or one proton and one or two heteroatoms. In addition, the σ - and π -bonds can be forced simultaneously by a coupling reaction of two carbenes.

Thus, the synthesis of TTF by pyridine-assisted electrochemical oxidation of dihydrotetra-thiafulvalenes has only been described for 1,3-dithioles with an aryl substituent in the 4-position, as exemplified by the transformation of (385) and (386) to afford (387) and (388) in 30% and 40% yield, respectively (Scheme 68) <84TL2403>.

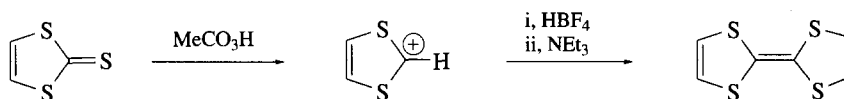


Scheme 68

The synthesis of TTF via an elimination of a proton in 1,3-dithiolylum salts in the final synthetic step involves the reaction of a carbene or of a phosphorous ylide on a 1,3-dithiolylum salt possessing a hydrogen at C(2). These educts can be accessed either by an alkylation of suitable 2-thioxo-1,3-dithiolylum salts (Scheme 69) <70CC1453, 74JOC3608, 75TL1259, 77JOC768, 77TL4033, 78ANY(313)467, 81CC920, 81ZOR1055, 82TL1813, 83JOC4713> or by oxidation of a 2-thioxo-1,3-dithiol by peracid <62JA3410, 64JA5290, 73TL2253, 74JOC2456, 75CL603, 76JOC730, 77TL2223, 78ANY(313)467> or hydrogen peroxide in acetic acid (Scheme 70) <62JCS5104>.



Scheme 69

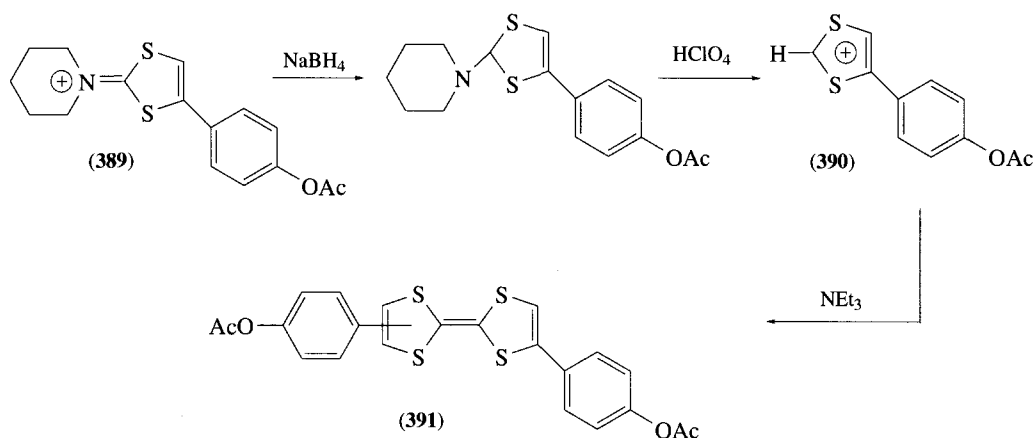


Scheme 70

Although the presence of alkyl groups in positions 4 and/or 5 does not seem to interfere with the course of the reaction <75CL603>, the presence of electron-withdrawing groups in these positions renders the reaction difficult <64JA5290> or will even totally inhibit the reaction.

Alternatively, the 1,3-dithiolylum salts (390) can be obtained from 2-*N,N*-dialkylamino- or 2-alkylsulfanyl-1,3-dithiolylum salts (389) <69CPB1924, 74JOC3608, 77TL2579> by their reduction with

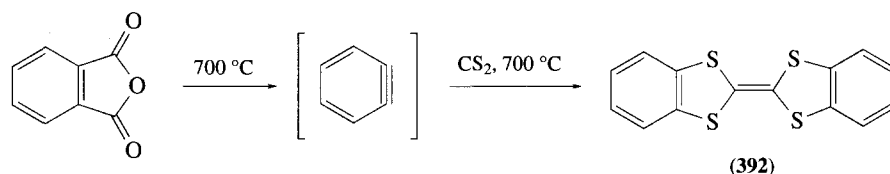
sodium borohydride followed by a reaction with strong acid. Deprotonation of (390) affords the corresponding TTF (391) (Scheme 71) <74JA945, 76JOC2855, 76S489>.



Scheme 71

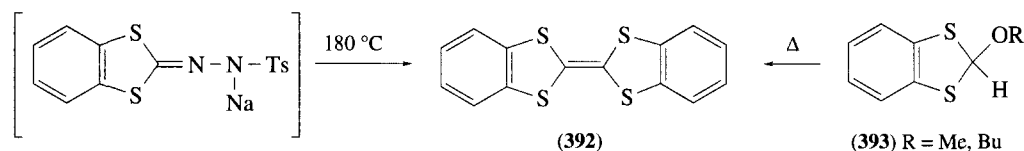
As seen from these examples, the treatment of 1,3-dithiolium salts with an excess of a tertiary amine leads directly to TTF <65AG(E)435, 70CC1453, 74JOC3608, 75CL603, 76JOC730, 77TL4033, 78ANY(313)467, 81CC920, 82TL1813, 83JOC4713>. A mixture of *cis* and *trans* stereoisomers is obtained if the dithiolium salt is unsymmetrical <65AG(E)435, 75CL603, 75CR(C)1037, 77TL2579>.

Benzo- or naphtho-anellated 1,3-dithiolium salts were obtained by the reaction of 1,2-thio compounds with formic acid <59HCA1733, 70RZC2319, 73LA310, 74LA403> or by that of 2-amino-carboxylic acids with isopentyl nitrite in the presence of carbon disulfide and treatment of the obtained 2-isopentyl-1,3-dithioles with acid <78JCS(P1)468>. Naphtho-anellated or heterocycle substituted 1,3-dithiolium salts were accessible by the alkylation of 1,3-dithiole-2-thiones followed by a reduction (e.g., with sodium borohydride) and treatment with acid <79JPR675, 83JOC4713>. In addition, dibenzo-TTF (392) has been obtained by a gas phase reaction starting from phthalic anhydride and carbon disulfide at 700°C (Scheme 72) <70TL629>.



Scheme 72

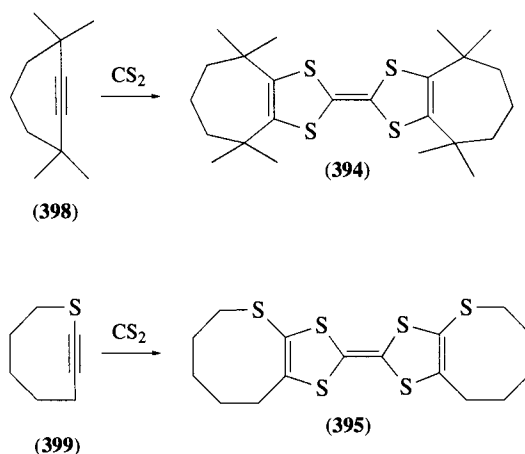
Alternatively, dibenzotetrathiafulvalene (392) has been obtained in 51% yield by the pyrolysis of either 2-imino-1,3-benzodithiol in the presence of one equivalent of sodium methoxide in diglyme at 180°C <74LA403> or by pyrolysis of suitable 2-alkoxy-1,3-benzothioles (393) at 190 – 200°C (Scheme 73) <75S168>.



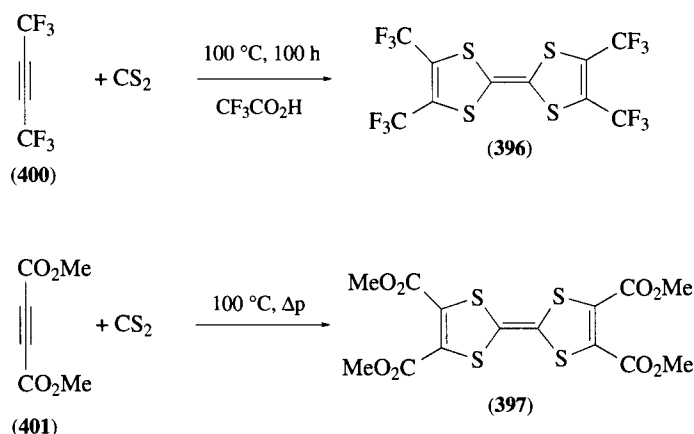
Scheme 73

Furthermore, TTF (394)–(397) are accessible by the reaction of carbon disulfide with strained (398) or (399) (Scheme 74) <74JA945, 89LA435> or of electrophilic acetylene derivatives (400) or (401) (Scheme 75) in the presence of an acid <70JA1412, 73JA4379> or under high pressure <81JOC446>, thus

allowing TTF to be obtained, substituted by electron-withdrawing groups <76KGS338, 81JOC446, 84BCJ2035, 85JOC2788>.

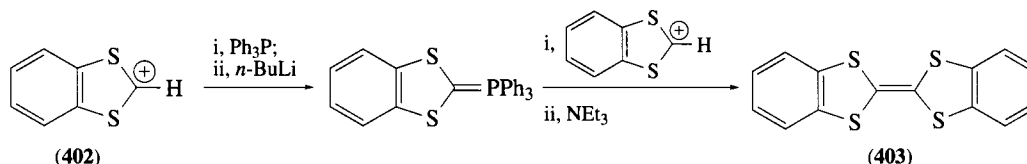


Scheme 74



Scheme 75

TTF can also be prepared by the elimination of a proton and of triphenylphosphine in the final step. Thus, 1,3-dithiolium salts (402) react with 2-triphenylphosphino-1,3-dithioles to afford intermediates which give TTF (403) upon treatment with base at low temperatures (Scheme 76). This method also permits the selective preparation of unsymmetrical TTF <78JOC369, 82TL1813, 83MI 312-02>. The phosphorus ylides used in these reactions are easily accessible by the reaction at -78°C between *n*-butyllithium and the corresponding phosphonium salt which is obtained by the reaction of triphenylphosphane with 1,3-dithiolium salts <78JOC369>.

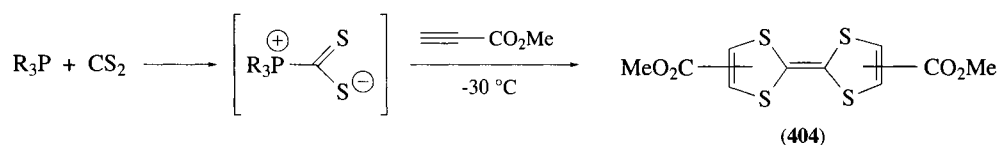


Scheme 76

Similarly, TTF (404) was obtained from trialkylphosphanes and alkynes in the presence of carbon disulfide (Scheme 77) <29JCS33, 71JA4961, 74JOC2456>.

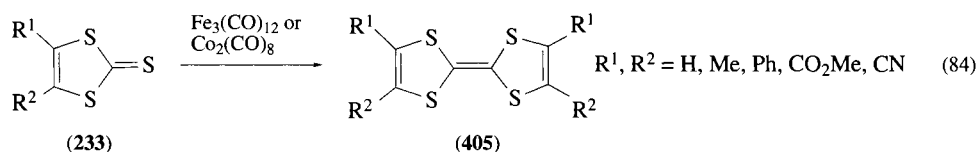
3.12.8.2 TTF by Elimination of Two Heterosubstituted Entities in the Final Step

TTF may be obtained by dethiooxygenation of 2-thioxo-1,3-dithioles by transition metal complexes. Thus, the reaction of 2-thioxo-1,3-dithioles (233), (un)substituted in the 3- and/or

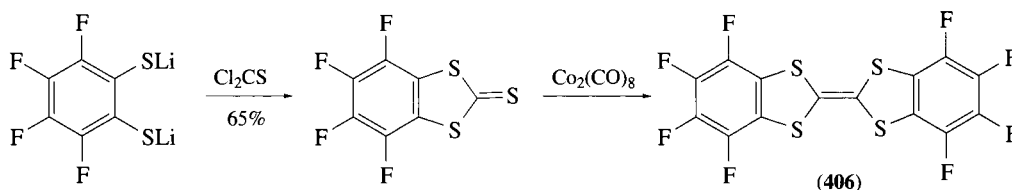


Scheme 77

4-positions, with iron carbonyl $Fe_3(CO)_{12}$ $\langle 75JOC3577 \rangle$, or more efficiently with dicobaltoctacarbonyl $\langle 80CC38, 91JCS(P2)963 \rangle$ led to syntheses of unsubstituted or alkyl-, aryl-, or electron-withdrawing group substituted TTF (**405**) in moderate yields (25–42%) (Equation (84)).

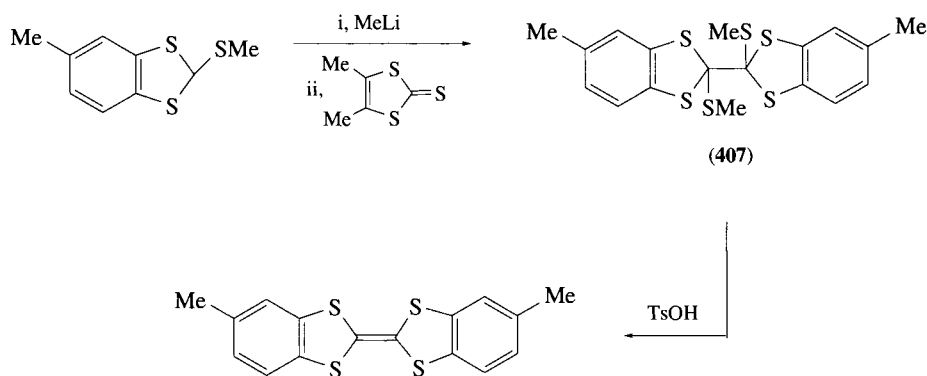


The synthesis of various halogenated TTF has been reported $\langle 89S207, 91S263 \rangle$. For the synthesis of octafluorodibenzo TTF (**406**), the first TTF derivative with fluorine directly bound to the π -system, again $Co_2(CO)_8$ has been used in the key step to afford the desired TTF as a dark red solid in 62% yield (Scheme 78) $\langle 94S460 \rangle$.



Scheme 78

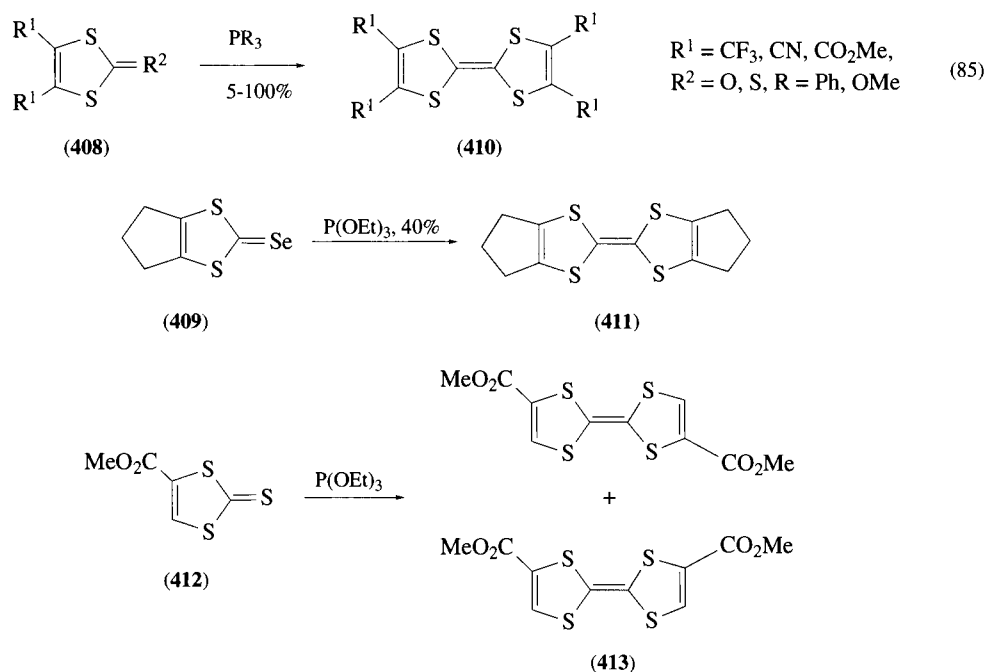
The halogenated TTF compounds are accessed by β -elimination reactions of two alkylsulfanyl groups from hexathioorthoxalates. Thus, the solvent dependent thermal decomposition of hexathioorthoxalates (**407**) $\langle 26JCS2263, 74JA945, 79JOC1476, 84TL995 \rangle$ can be applied not only to symmetrical hexathioorthoxalates but also to those possessing two differently substituted heterocycles (Scheme 79) $\langle 84TL991, 84TL995 \rangle$.



Scheme 79

Alternatively, 2-oxo- $\langle 74CC751, 75JOC2577, 77JA5521, 80CC497, 80JA6651, 83MI\ 312-01 \rangle$, 2-thioxo- $\langle 70JA1412, 73JA4379, 73LA310, 74CC751, 75JOC3577, 76CC966, 76JOC2855, 84JOC1117, 84TL833 \rangle$ (**408**) (Equation (85)) and 2-selenoxo- (Scheme 80) $\langle 76CC966, 76JOC879, 78ANY(313)467, 78OMS(13)121, 80CC28, 83JOC4713 \rangle$ 1,3-dithioles (**409**) or (**412**) react with trivalent phosphorus compounds to form the corresponding TTF (**410**), (**411**), or (**413**) bearing unsubstituted rings or rings substituted with electron donating groups. Among the groups formed are cycloalkyls $\langle 77MI\ 312-01, 78OMS(13)121 \rangle$, alkylsulfanyls $\langle 77JA5909 \rangle$; electron-withdrawing groups such as esters $\langle 76JOC879, 76JOC2855 \rangle$, trifluoromethyl

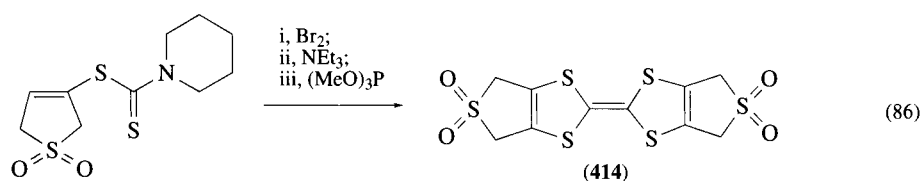
<70JA1412, 73JA4379>; nitriles <74CC751, 75JOC3577>; or bearing aromatics <73LA310, 76CC966, 78OMS(13)121, 80CC28, 80CC497, 83MI 312-05>.



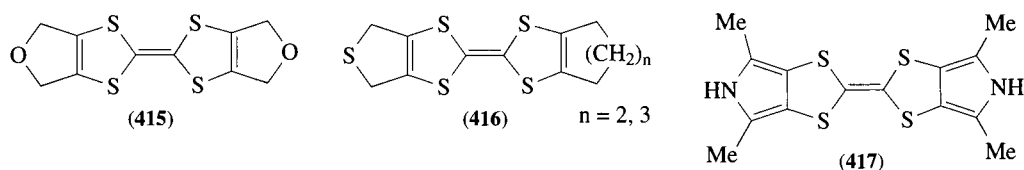
Scheme 80

Desulfurization with $(\text{MeO})_3\text{P}$ has also been performed at high pressure <90JCS(P1)3358>. The use of *p*-acetoxybenzyl as a sulfur-protecting group during triethylphosphite mediated coupling reactions allowed improved access to TTF tetrathiolate <92TL3923>. Treatment of 1,3-dithiole-2-selenones with triphenylphosphane also gave TTF derivatives in good yield <91KGS1278>. Unsymmetrical derivatives (412) react with phosphines or phosphites to give mixtures of the two possible diastereomers (413) <76JOC2855>, whereas the phosphines react with mixtures of 1,3-dithiolthiones <76JOC879, 76JOC1412, 76MM360> to give mixtures of all possible TTF.

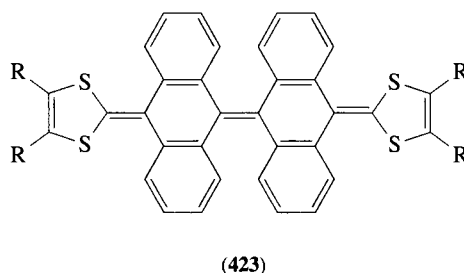
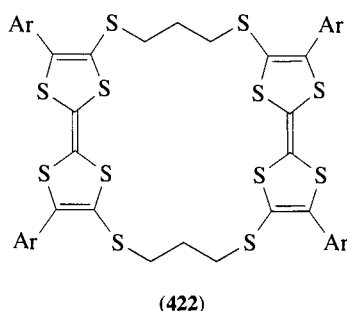
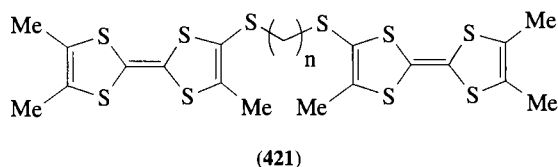
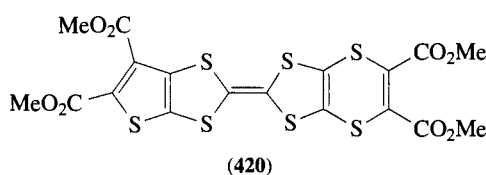
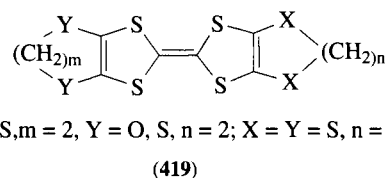
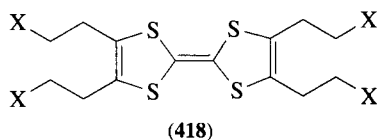
TTF were also obtained by treatment of 2-alkyl (or 2-aryl) 1,3-dithiolylium salts with triethylphosphite or triphenylphosphane. By use of 2-alkylseleno-1,3-dithiolylium salts the highest yields were obtained <84JPR479>. The synthesis of new electron donors such as (414) has been described (Equation (86)) <88TL3467>.



In this context it is of interest to note that the synthesis of examples bearing long chain alkyl groups <88CC1391, 89SM379, 90CC816> as well as of alkylated <88SMB9> and tetrabromo, and of mono and dibromo (or chloro) derivatives <89S207, 91CC92, 91S263> have been reported. Analogues (415) <88SMB651>, (416) <88CS365>, and (417) <88JA7903> have been synthesized and their electrochemical properties have been studied.



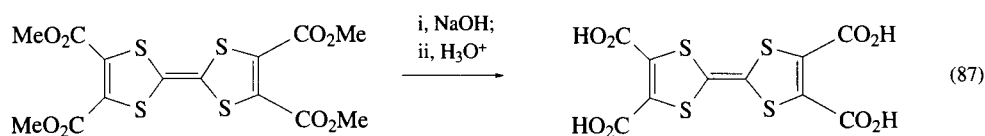
Novel dimeric TTF derivatives include **(418)** <91CC843, 91JOC5684, 91SM2561> but also bis-anellated TTF **(419)** <91CC952, 91KGS848, 91SM2381, 91TL479>, unsymmetrical derivatives **(420)** <90CL2129, 91TL2737, 91TL2741> and extended analogues, such as **(421)**, **(422)**, and **(423)** <90S1149, 90TL7307, 90TL7311, 91CC320, 91CC1132, 91JCS(P1)157, 91KGS1278, 91S26, 91SM2323, 91SM2327, 91TL2897, 91TL4897, 92TL3923> have been reported.

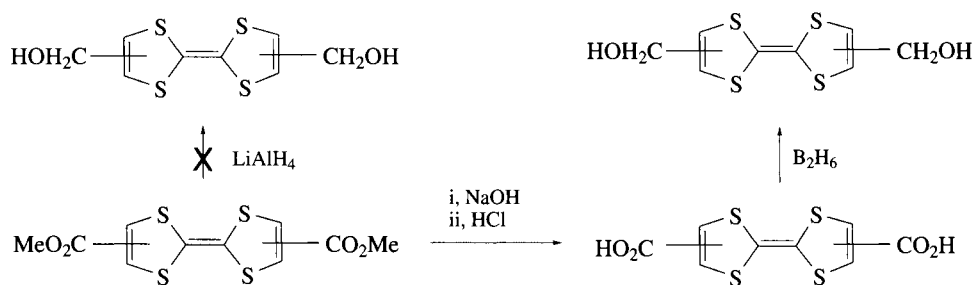


3.12.8.3 TTF Starting From the General TTF Structure

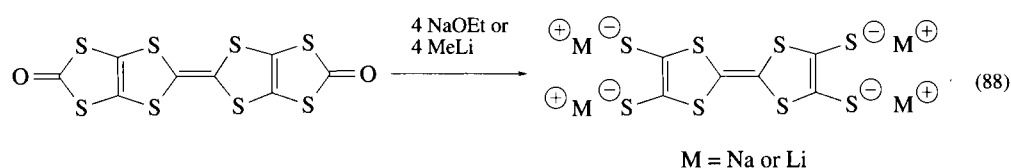
The significance of functionalized electroactive molecules is now well recognized. Thus, the synthesis of new functionalized TTF derivatives has been central to the development of highly conducting Langmuir–Blodgett films <87SR155> and “molecular shuttles” <86T1209>. A number of TTF derivatives containing either formyl <83CC405, 89CC1520, 91SM2575, 92T3081, 92TL2685> or other oxygen based functional groups, such as esters, ketones, and alcohols <74ACR232, 83UK1301, 84ACR227, 85ACR261, 85MI 312-01> as well as amines <77AG534, 79ACR79> have been synthesized.

Several “trivial” functional group modifications have been performed, among them the decarboxylation, hydrolysis (Equation (87)) or reduction (Scheme 81) of ester groups, <75CC383, 75CL603, 76JOC882, 76JOC2855>, the formation of amides <76JOC2855, 76MM360, 76S489>, esters <76MM360, 76S489>, and anhydrides <76JOC2855>, as well as the hydrolysis of the 2-thione-1,3-dithioles (Equation (88)) <77JA5521>.



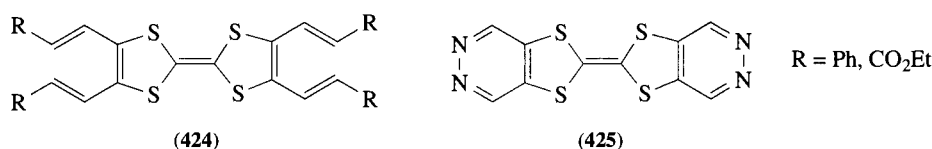


Scheme 81

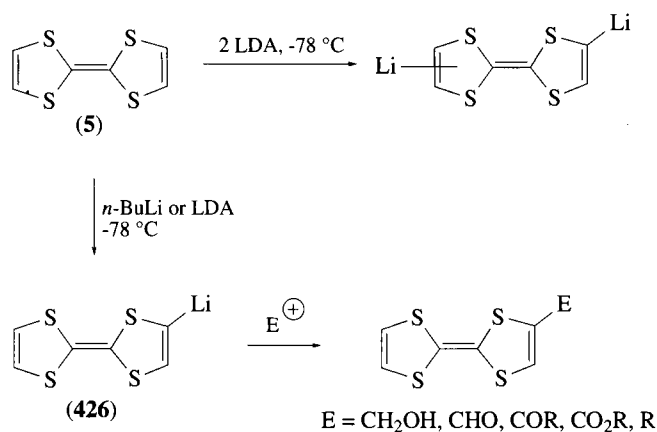


M = Na or Li

Palladium catalyzed coupling of trialkylstannyl-TTF with aryl bromides or iodides allows the convenient preparation of aryl-TTF <92CC158>. The preparation of tetraformyl-TTF has allowed access to several new systems including (424) and (425) <92TL3081>.

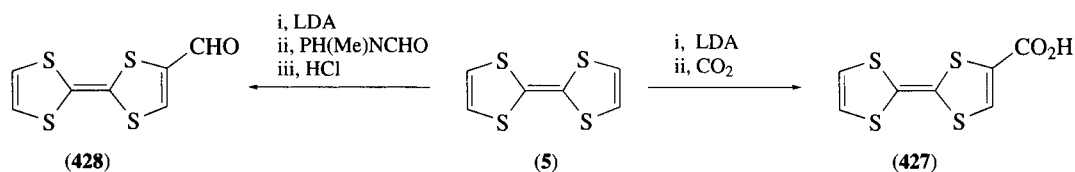


Metallation of TTF (5) has been accomplished at -78°C by either lithium diisopropylamide or by *n*-butyllithium (Scheme 82) <77CC161, 79JOC1476>. It has been found that strict temperature control is essential for the success of these reactions, since at -20°C a redistribution of product formation is observed <79JOC1476>. 1-Lithio-TTF (426) reacts at -70°C with a series of electrophiles to afford the corresponding alcohols, aldehydes, ketones, carboxylic acids, and esters as well as monoalkylated TTF <77CC161, 79JOC1476>. Improvement of this procedure allowed the synthesis of carboxy-TTF (427), formyl-TTF (428), and hydroxymethyl-TTF in 80–92% yield (Scheme 83) <94S489>.

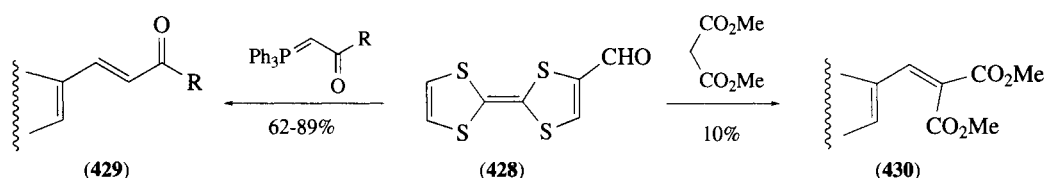


Scheme 82

The high yield preparation of these compounds makes them attractive building blocks for redox systems <78CC832, 92SM201, 92T3983>. Wittig alkenation of formyl-TTF (428) with resonance stabilized ylides afforded chain elongated alkenes (429) in high yields (62–89%), whereas Knoevenagel-type condensation gave the corresponding 1,1-bis(carboxymethoxy)ethene derivative (430) in only 10% yield (Scheme 84) <94S489>.



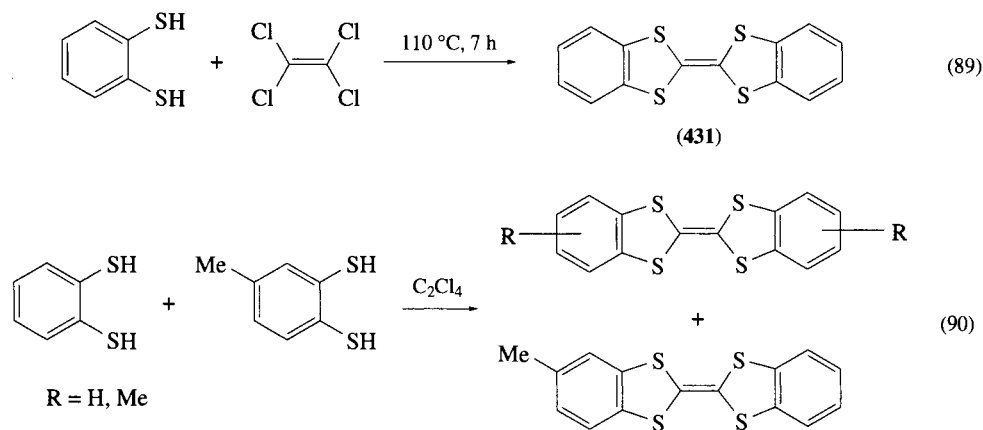
Scheme 83



Scheme 84

3.12.8.4 TTF from Tetrachloroethylene

Tetrachloroethylene has been used as the central building block both for the synthesis of TTF, symmetrical and unsymmetrical with respect to the sulfur substituted carbon-carbon bond. As early as 1926 it was found that tetrachloroethylene reacts with 1,2-benzene-dithiolate to yield dibenzotetrathiafulvalene (**431**) in 16% yield (Equation (89)) <26JCS2263, 71JA2258>. A great advantage of this reaction is that it does not require the preliminary synthesis of heterocycles <76JOC145>. An extension of this method by using tetrachloroethylene and two variously substituted 1,2-benzene-dithiols allows the synthesis of TTF unsymmetrical with respect to the heterosubstituted carbon-carbon bond <76JOC145>. This synthesis, however, is not selective and leads to mixtures of different benzo-tetrathiafulvalenes (Equation (90)) <76JOC145>.



In the search for a synthetic approach to monobenzo-TTF, it has been shown <78JOC416> that it is possible to prepare geminal dichloro derivatives by reaction of sodium *cis* ethene dithiolate or 1,2-benzene-dithiol with an excess of tetrachloroethylene. However, these derivatives cannot be used to obtain TTF (**5**) by substitution of the two remaining halogens by sodium *cis* ethenedithiolate or sodium *cis* dicyanoethene dithiolate; neither monobenzo-TTF (**432**) can be obtained by this approach (Scheme 85) <78JOC416>.

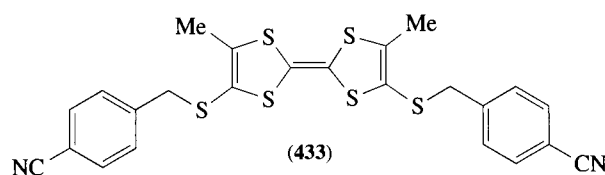
Due to transdithiolation reactions it was possible to obtain dibenzo-TTF (**431**) from ammonium benzene dithiolate and 2-chloromethylene-1,3-dithiol in ca. 30% yield <78JOC416>.

3.12.8.5 Miscellaneous Methods and Compounds

A photochemical method for the synthesis of TTF in modest yields (5–25%) is the irradiation of 1,3-dithiole-2-thiones with UV light <79ZC192, 85CC1803>. The irradiation of 1,3-dithiole-2-thiones

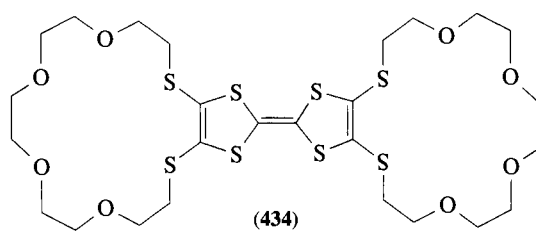


Improved syntheses allowed excellent access to TTF and methylated derivatives (92BSBI37), to mono carboxylic acids and esters (92BSB741) to dialkylaminomethyl-TTF (91TL6407, 92TL3923), bis(hexadecylthio)-TTF (92MI 312-02), symmetrical, (92TL4321, 92PS(67)305), unsymmetrical (92CCI408, 91TL6033, 92TL973), and vinylogous analogues (95TL1645). In addition, several oligomeric TTF (91CCI370, 92JOC4859, 95S521) and the first TTF covalently linked to two acceptors, such as (433), have been prepared (92BSF205).



3.12.9 IMPORTANT COMPOUNDS AND APPLICATIONS

The practical use of 1,3-dithiols as synthons in organic synthesis is small whereas 1,3-dithiolanes are quite often used as protecting groups for aldehydes and ketones $\langle 92\text{HOU}(\text{E14a/3})403 \rangle$. TTF and



other tetrachalcogenafulvalenes are electron donors which easily form charge-transfer complexes with electron acceptors thus forming radical salts. Among them, of special interest are those which possess a segregated structure and can be regarded as organic metals; their structure and properties such as superconductivity and critical temperature have been the focus of scientific interest since the mid-1970s and have been reviewed several times <66AHC(7)39, 70QRS275, 74ACR232, 76S489, 77AG534, 79ACR79, 80AHC(27)151, 83UK1301, 84ACR227, 85MI 312-01, 86T1209, 87SR155, 92HOU(E14a/3)403, 93SR245, 93HOU(E8a)630, 95S215>.

3.13

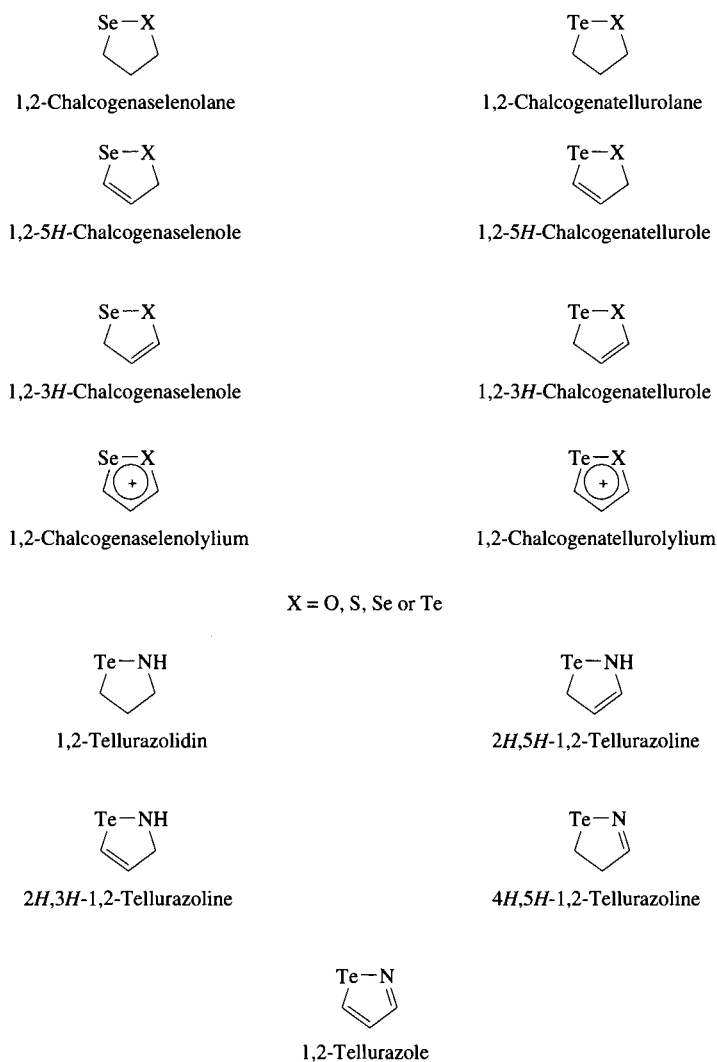
Two Adjacent Heteroatoms with at least One Selenium or Tellurium

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3.13.1 INTRODUCTION

Five-membered monocyclic rings containing one selenium or one tellurium atom and another adjacent heteroatom (oxygen, sulfur, selenium, tellurium, or nitrogen) form different ring systems, including the less saturated systems summarized in Scheme 1.



Scheme 1

Many of these systems still remain unknown. For the systems which are known, many of the parent systems, as well as derivatives including benzo-fused analogues, have been prepared.

Whereas the 1,2-dithiole system has been known for a long time and a detailed literature exists for this system (82AHC(31)63, 84CHEC-I(6)1049, 93HOU(E8a)470, 95SR173), the literature is far less detailed for the 1,2-diselenolane first reported in 1890 (1890CB1090) and the 1,2-ditellurolane reported in 1977 (77JA255), the literature of the mixed systems being even less. A number of studies have focused mostly on organic conductors and hypervalent compounds. A systematic classification scheme which includes a concise description of such type of hypervalent bonding has been devised (80JA7753).

1,2-Ditelluroles and 1,2-tellurazoles as well as 1,2-oxatellurolane derivatives have been reviewed (86SR15, 93AHC(58)48). A review on 1,2-ditelluroles has been published (91KGS291) as well as a review on synthetic methods (90HOU(E12b)775). The subject of this chapter was treated in the first edition of *Comprehensive Heterocyclic Chemistry* (CHEC-I) together with the isomeric 1,3-compounds (84CHEC-I(6)947).

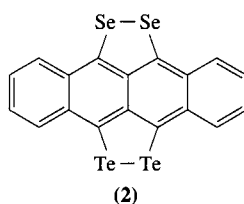
3.13.2 MOLECULAR STRUCTURE

3.13.2.1 X-ray Diffraction

The x-ray structure of the ditellurolane compound (1) has been reported. The small dihedral angle (8.5°) found in (1) results in a considerable overlap of the two tellurium lone-pair p orbitals which gives rise to the doubly occupied π and π^* orbitals <93JA885>.

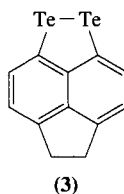


The structure of 5,6-diseleno-11,12-ditellurotetracene, DSeDTeT (2) has been determined for the bromine salt (DSeDTeT)₂Br <86MI 313-01>.

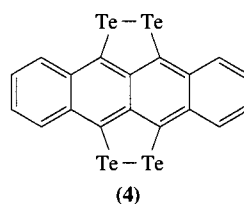


The DSeDTe units form a uniform column along the c axis. The normal of the molecular plane largely tilts from the c axis (48.2°).

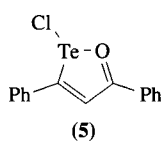
Analogous studies have been carried out on dichalcogen-bridged acenaphthenes (3). The crystal structure was determined for the complex with TCNQ. Both acceptor and donor were found to take planar conformations. They form unusual modified, mixed stacking columns along the [1.1.1] direction. A pair of donors and a pair of acceptors make an alternately stacking column <88BCJ2013>.



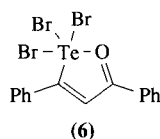
The structure of the 5,6:11,12-bis(ditelluro)tetracene (4) was reported. The structure shows rather short interstack Te—Te contacts of 37.01 nm <82MCLC(86)79, 82OM739>.



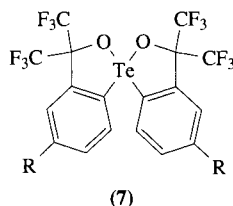
The structure of the oxatellurole compound (5) has been reported <83JA875>. Compound (5) shows a nearly linear (170°) arrangement of Cl—Te—O; a three-center-four-electron bond is proposed for this arrangement. The structure determination of benzocondensed compounds has also been reported <90ZOB2764>.



Bromine compounds like (6) were described. In this case three-center-four-electron bonds were also proposed <86JOC1692>.

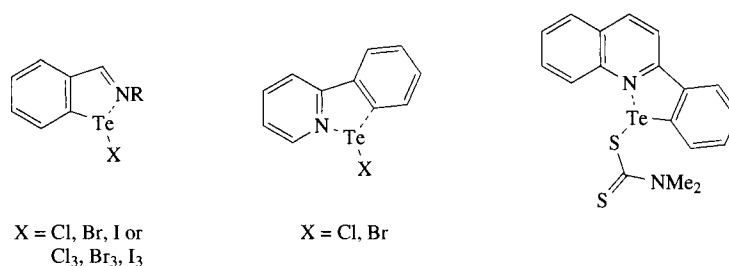


Pertelluranes like (7) were prepared and the structure given.



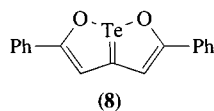
The intermolecular Te—O distances (35.59–35.86 nm) are very close to the sum of the van der Waals' radii for Te and O <84JA7529>.

No structures of simple 1,2-tellurazoles are reported; however, structures of hypervalent compounds which can be considered either as hypervalent tellurazoles or compounds with an extraordinary strong Te—N co-ordination resulting in a short tellurium–nitrogen distance have been reported. Such compounds are derived from azomethinimines <88ZOB1176, 90JOM(390)29, 91JOM(402)331, 93JCS(D)619>, from pyridines <91JOM(420)327>, or from quinolines (Scheme 2) <88JOM(356)159>.

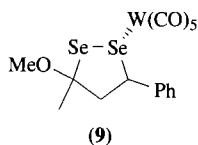


Scheme 2

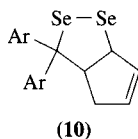
The structure of 2,5-diphenyl-1,6-dioxo-6aλ⁴-tellurapentalene (8) has been recorded <83JOC5149>. The bicyclic system is planar as reported for the corresponding trithiapentalene case and the dioxathiapentalene <77ACS(31)711, 79JCS(P2)1521, 81JST(75)327>.



Structure determination of selenium compounds is much more abundant. The structure of penta-carbonyltungsten-coordinated 1,2-diselenolanes (9) has been reported <92CC1050>.



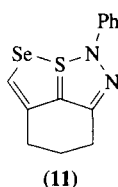
The structure of condensed compounds like 4,4'-diphenyl-2,3-diselenabicyclo[3.3.0]oct-7-ene (**10**) has been established <94JCS(P1)2151>.



1,5,9,13-Tetraselenacyclohexadecane (16Se_4) forms a dication $[16\text{Se}_4]^{2+}([\text{SO}_3\text{CF}_3]^-)_2$. The structure of this dication has been determined and displays a linear Se—Se—Se arrangement with nearly equal Se—Se distances 26.69 and 25.92 nm comparable to reported distances in 1,6,6a λ^4 -triselenapentalene 25.48–25.83 nm suggesting a weak bonding between the selenium atoms <90JA3706>.

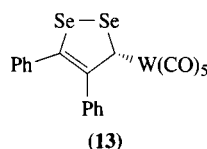
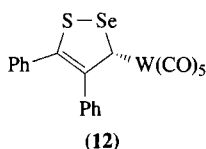
Structures of derivatives of 1-oxa-6,6a λ^4 -diselena-2-azapentalene, 1-thia-6,6a λ^4 -diselena-3-azapentalene and 1,6-dithia-6a λ^4 -selena-3-azapentalene have been reported. The three chalcogen atom arrangement in all three cases forms an angle of approximately 170° <87CC967>.

The structure of the trithiapentalene analogue 6,7-dihydro-2-phenyl-5H-2a λ^4 -thia-2-selena-1,2-diazacyclopent[cd]indene (**11**) was reported. The tricyclic frame of the molecule is almost planar <91AX(C)759>.

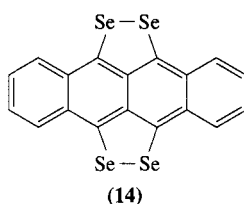


The x-ray structure determination of 7-nitro-2,1-benzothiaselenol-3-one has been carried out <89AX(C)489>. The structure of the analogous 7-nitro-2,1-benzoxaselenol-3-one was reported too <88AX(C)340>. The structure of benzo-1,2-thiaselenol-3-thione was reported <82H(19)657>.

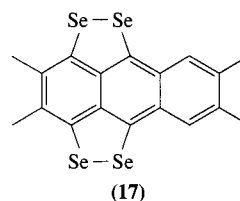
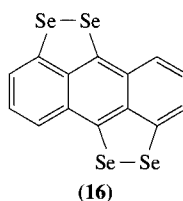
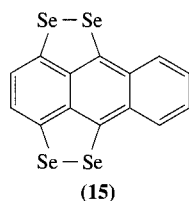
The Fischer carbene complex $(\text{W}(\text{CO})_5\text{COEtPh})$ reacts with PhCCSeLi and Se_8 to give (**12**) and (**13**), the structure of both is reported <88OM1853>.



The observation that peri-dichalcogen-bridged polyacenes are superior electron donors for constructing organic conductors has resulted in several papers dealing with the structure of this class of compounds. A survey of structural aspects of one-dimensional conductors based on tetrathiatetracene is found in <82MI 313-02>. In connection with the telluro compounds, the mixed seleno and telluro compound (**2**) has already been mentioned. Other seleno-bridged tetracenes like (**14**) have been studied <82MCLC79, 82OM739>.



Anthracene bridged derivatives like (**15**) and (**16**) have been studied too. Dimethyl and tetramethyl derivatives like (**17**) were further included in the studies. <82AX(B)2855, 91BCJ2091>.



3.13.3 EXPERIMENTAL STRUCTURAL METHODS

3.13.3.1 Mass Spectrometry

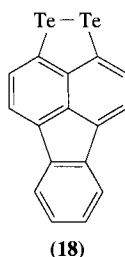
Mass spectra have been used intensively for structure elucidations and for characterization of many of the compounds dealt with in this chapter. However, if no systematic treatment was made of the mass spectrometric data, they will not be mentioned separately in this section.

The intensities of peaks with an abundance of more than 2% of the molecular ion clusters of (3) have been observed and compared to calculated intensities <80TL4565>.

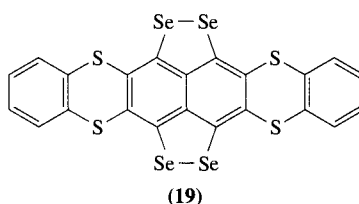
3.13.3.2 Ultraviolet-Visible Spectroscopy

In the same way as in Section 3.13.3.1, only papers dealing with more systematic discussion of UV-VIS spectra will be mentioned here.

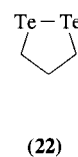
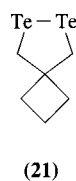
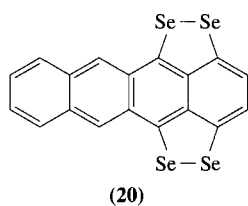
The UV-VIS spectrum of fluorantheno[3,4-*cd*]-1,2-ditellurole (18) and its diselena analogue have been recorded. In contrast to fluoranthene itself which has no absorption above 800 nm, compound (18) shows a strong absorption at 503 nm (log ϵ 4.54) <86TL2011, 87SM(19)595>.



The UV-VIS spectrum of (19) itself together with the iodine-doped compound has been recorded <91MI 313-01>.



The electronic spectrum of (14) and its isomer (20) which both form highly conductive complexes with TCNQ and analogous acceptors have been reported <90BCJ2441>. The solvatochromic behavior of the ditellurides (1), (21), and (22) has also been discussed <93JA885>.

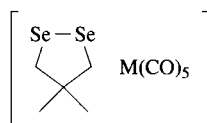


3.13.3.3 Nuclear Magnetic Resonance Spectroscopy

The isotopes ^{77}Se and ^{125}Te , which give rise to NMR signals, both have a natural abundance of ca. 7% which opens the possibility to obtain NMR spectra of both nuclei in natural abundance. Enriched mixtures of both elements are also available for synthesis of enriched compounds.

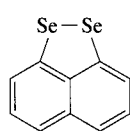
3.13.3.3.1 Proton NMR spectroscopy

Dynamic nuclear magnetic resonance studies were carried out on mononuclear complexes of type (23). Detailed variable temperature NMR studies established the existence of pyramidal inversion about the coordinated selenium ligand atom and an intramolecular 1,2-metal shift between adjacent chalcogen ligand atoms $\langle 85\text{JCS(D)}1569 \rangle$.

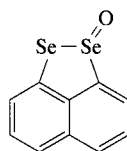


(23) M = Cr, Mo or W

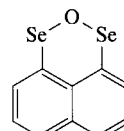
Based on a detailed discussion of the ^1H NMR spectra from the oxidation products of (24), it was concluded that the oxidation products consisted of 60% of (25) and 40% of (26) $\langle 88\text{JOC}2435 \rangle$.



(24)



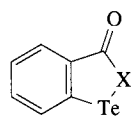
(25)



(26)

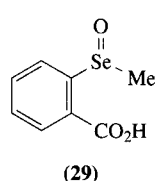
3.13.3.3.2 Carbon-13 NMR spectroscopy

Carbon-13 NMR spectra of compounds of type (27) were reported. It was observed that the chemical shift of the four C-atoms, which were not part of the heterocyclic ring, was only a little dependent on the nature of X $\langle 86\text{SA(A)}57 \rangle$.

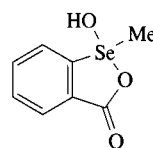


(27) X = Se or S

Based on $^1J(^{77}\text{Se}-^{13}\text{C})$ values, it is concluded that the equilibrium in Equation (1) is on the right side in solution favoring the cyclic selenurane structure (28) whereas the sodium salt has the acyclic structure (29). The values of the coupling constants are in the range of 61–65 Hz for selenuranes and 77–81 Hz for selenoxides. The observed 65.1 Hz for (29) and 81.4 Hz for (28) are in the typical regions for a selenurane and selenoxide, respectively $\langle 81\text{CL}1353, 82\text{OMR}(20)117 \rangle$.



(29)



(28)

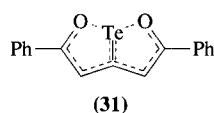
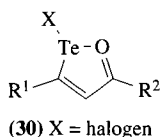
(1)

The structure of the tellurane (5) and the pertelluranes of structure (6) were discussed based on ^{13}C NMR spectra compared to model substances $\langle 86\text{JOC}1692 \rangle$.

3.13.3.3 Selenium-77 and Tellurium-125 NMR spectroscopy

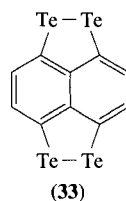
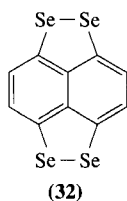
The ^{77}Se — ^{13}C coupling constants are used in the discussion of selenoxide–selenurane equilibrium in Equation (1) <81CL1353, 82OMR(20)117>.

The presence of a three-center–four-electron bonding in compounds like (5) and (8) is discussed based on a comparison of the ^{125}Te NMR chemical shifts and the $\text{Te}(3d_{5/2})$ binding energies obtained by x-ray photon spectroscopy. It is suggested that the net bonding interaction for the two groups of compounds may be represented by (30) and (31). It is concluded that ^{125}Te NMR spectra are a valuable tool for such studies, as the chemical shifts are sensitive to geometry, oxidation state of tellurium, and the electronic environment of tellurium <89OM866>.



3.13.3.4 Photoelectron Spectroscopy

The photoelectron spectra of (4), (14), (24), (32), and (33) were discussed and compared with the corresponding sulfur compounds. It was observed that the energies of the HOMOs, determining the π -donor properties of dichalcogeno- and tetrachalcogenonaphthalenes as well as tetrachalcogenonaphthalenes, are practically independent of the nature of the heteroatoms (S, Se or Te) <90ZOB421>.



3.13.4 THERMODYNAMIC ASPECTS

3.13.4.1 Electrochemistry and Conductivity

Being candidates for donors in organic conductors, the electrochemistry of peridichalcogen-bridged polyacenes has, in particular, attracted interest. A survey of the electrochemistry and conductivity of cation-radical salts based on tetraselenotetracene and tetrathiotetracene is found in Scheme 3 <82MI 313-01>.

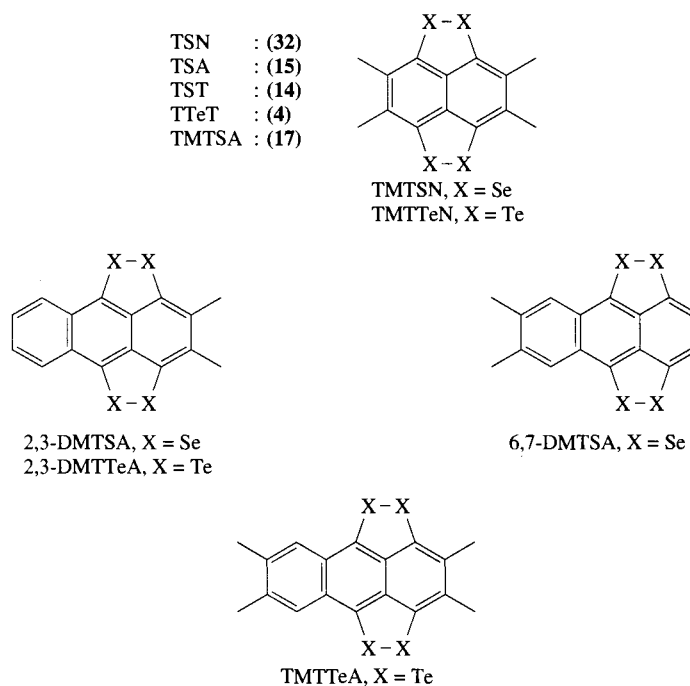
Cyclic voltammograms of tetrachalcogenoanthracenes of type (15) all show two reversible one-electron redox waves. Introduction of methyl groups lowers the oxidation potentials. Substitution of tellurium for selenium results in a considerable lowering of both the first and second oxidation potential. The electrochemistry of complexes with TCNQ and analogues of TCNQ is also included <90CL567, 91BCJ2091>. See Tables 1 and 2 for physical constants of donors and complexes with various acceptors.

Similar results were obtained for the tetracene derivatives (14) and (20) with the tendency that the tetracene derivatives have stronger donating abilities than the anthracene counterparts <90BCJ2441, 91SM2389>. The tetratelluro analogue of (14) has been studied and shows a similar behaviour <82OM739>.

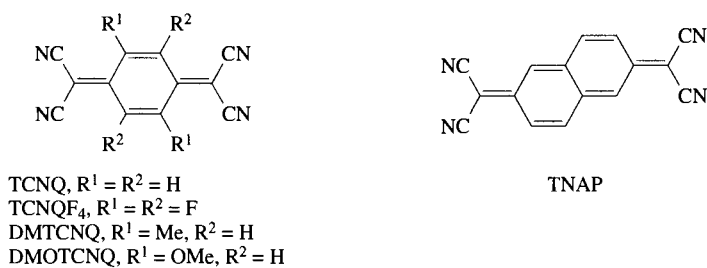
Electrochemistry and ESR spectra of (20) and its tetratelluro analogue have been reported <83MI 313-01>.

Tetraseleno- and tetratelluronaphthalenes (32) and (33) exhibited two reversible oxidation waves. The donor character is strengthened by introduction of tellurium <87CL315>. Analogous results were obtained from compounds of type (34) <88SMB509>.

Donors



Acceptors



Scheme 3

Table 1 Half-wave oxidation potentials of peri-chalcogen donors <91BCJ2091>.

Compound ^a	$E_{1/2}(1)/V$	$E_{1/2}(2)/V$	$\Delta E/V$
TSA	0.35	0.71	0.36
2,3-DMTSA	0.31	0.72	0.41
2,3-DMTTeA	0.20	0.63	0.43
6,7-DMTSA	0.30	0.68	0.38
TMTSA	0.26	0.68	0.42
TMTTeA	0.16	0.55	0.39

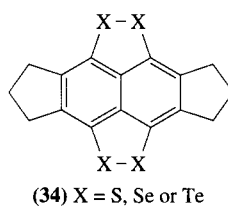
^aFor the acronyms used cf. Scheme 3.

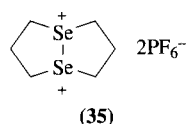
Table 2 Charge transfer complexes of peri-dichalcogenide anthracens <91BCJ2091>.

Complex ^a	D : A	CT band $\times 10^3 \text{ cm}^{-1}$	$\Delta E_{\text{redox}}^{\text{s}}$ V	σ S cm^{-1}
2,3-DMTSA · TCNQ	1 : 2	2.8, 9.9, 11.4	0.12	1.2
2,3-DMTTeA · TCNQ	1 : 1	10.2	0.01	5.3×10^{-6}
6,7-DMTSA · TCNQ	1 : 1	3.2, 11.5	0.11	2.0
TMTSA · TCNQ	1 : 2	6.1, 10.0, 11.5	0.07	2.7×10^{-1}
TMTTeA · TCNQ	1 : 1	10.0	-0.03	1.8×10^{-6}
2,3-DMTSA · TCNQF ₄	1 : 1	11.2	-0.29	5.4×10^{-6}
2,3-DMTTeA · TCNQF ₄	1 : 1	10.5	-0.40	1.8×10^{-7}
6,7-DMTSA · TCNQF ₄	1 : 1	11.0	-0.30	8.8×10^{-5}
TMTSA · TCNQF ₄	1 : 1	11.1	-0.34	5.2×10^{-7}
2,3-DMTSA · DMTCNQ	2 : 1	4.6, 11.3, 12.6	0.19	5.3×10^{-1}
2,3-DMTTeA · DMTCNQ	2 : 1	10.2	0.08	1.2×10^{-3}
6,7-DMTCNQ · DMTCNQ	2 : 1	5.4, 11.6	0.18	2.7×10^{-8}
TMTSA · DMTCNQ	2 : 1	11.5	0.14	1.2×10^{-5}
TMTTeA · DMTCNQ	2 : 1	10.2	0.04	4.6×10^{-2}
2,3-DMTSA · DMOTCNQ	1 : 1	6.9	0.32	5.0×10^{-7}
2,3-DMTTeA · DMOTCNQ	1 : 1	10.3	0.19	3.2×10^{-2}
6,7-DMTSA · DMOTCNQ	2 : 1	non	0.29	1.9×10^{-9}
TMTSA · DMOTCNQ	2 : 1	non	0.25	1.0×10^{-8}
TMTTeA · DMOTCNQ	2 : 1	non	0.15	1.1×10^{-7}
2,3-DMTSA · TNAP	1 : 1	3.5, 8.9	0.10	2.6×10^{-2}
2,3-DMTTeA · TNAP	1 : 1	8.5, 10.2	-0.01	4.9×10^{-2}
TMTSA · TNAP	1 : 1	8.8, 10.0	0.05	9.2×10^{-3}
TMTTeA · TNAP	1 : 1	8.8, 10.3	-0.05	6.0×10^{-1}

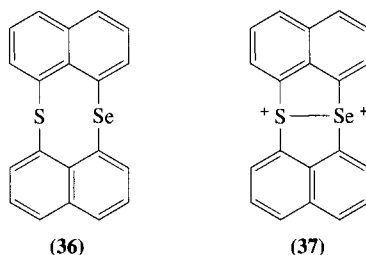
^aFor the acronyms used cf. Scheme 3. ^s $\Delta E_{\text{redox}} = E_{1/2}(\text{D}) - E_{1/2}(\text{A})$.

The cyclic voltammogram of fluorantheno[3,4-cd]-1,2-ditellurole (**18**), as well as its diseleno analogue, exhibited one reversible oxidation wave, the donor character being most pronounced for the tellurium compound <86TL2011, 87SM(19)595>.

The electrochemistry of σ -bonded heteroatom dications (**35**) has been studied by cyclic voltammetry in acetonitrile. Only a one-reversible reduction peak was observed at +0.11 V <90TL6375>.



The electrochemical oxidation of (**36**) suggests the intermediate formation of dication (**37**), which is also observed from the chemical oxidation <91TL4345>.

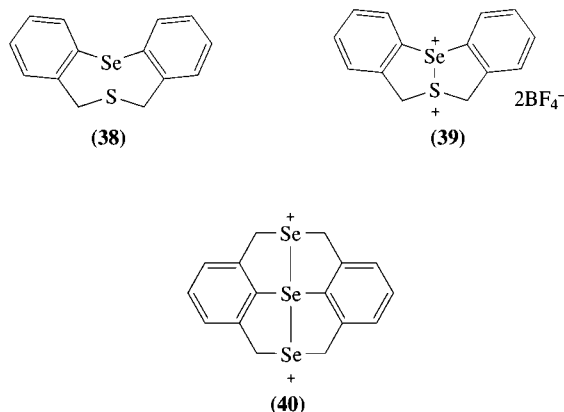


Cyclic voltammograms were obtained from (**38**) to study the formation of dication (**39**) which can also be obtained by oxidation with 2 equivalents of the one-electron oxidizing agent NO^+PF_6^- <90TL2307>.

It is observed that the selenurane (**40**) undergoes facile electrochemical reduction in acetonitrile at -0.10 V <92JA3117>.

3.13.5 REACTIVITY

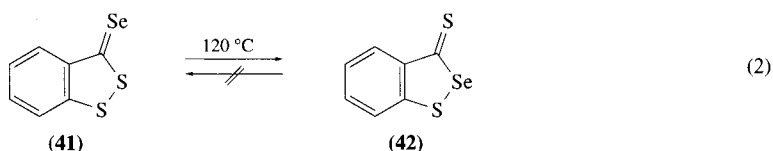
Generally speaking, the chemical reactivity of the known systems has not been studied much, the physico-chemical properties being more intensively investigated.



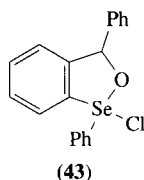
3.13.5.1 Thermal and Photochemical Reactions Involving No Other Species

3.13.5.1.1 Thermolysis

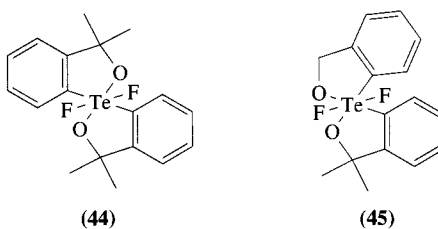
It is observed that (41) isomerizes to (42) in 68% yield at 120°C whereas the reverse isomerization does not take place (Equation (2)) <82H(19)657>. The analogous thermal scrambling of sulfur in 1,2-dithiole-3-thione has been studied by mass spectrometry using ^{34}S labeled compounds <91JCR(S)226>.



The selenurane (43) was transformed into 2-(phenylseleno)benzophenone upon heating at 195°C for 10 minutes <90CPB874>.



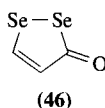
It is observed that the pertellurane (44) upon heating at 60°C in 3 days isomerizes to (45). The kinetics of the isomerization was studied <84JA7529>.



3.13.5.2 Reactions with Electrophiles

3.13.5.2.1 Reactions involving protons or Lewis acids

The 1,2-diselenol-3-one (46) is easily protonated in trifluoroacetic acid, which results in a shift of the protons to lower field in the ^1H NMR spectrum <87KGS855>.

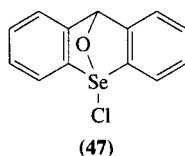


The ditelluroles (1) and (21) react with triflic acid in methylene chloride to give (1:1) salts <93JA885>.

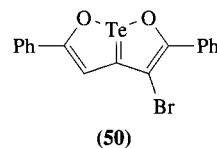
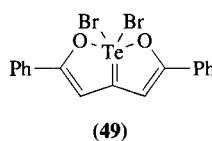
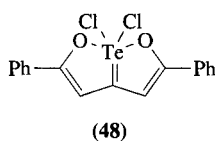
3*H*-1,2-Benzothiaselenol-3-one reacts as a selenium-transferring reagent for the conversion of nucleoside *H*-phosphonates and nucleoside *H*-phosphonothioate diesters into the corresponding seleno analogues <92TL7255>.

Oxidation of naphtho[1,8-*cd*]-1,2-diselenole with *m*-chloroperbenzoic acid results in the formation of (25) and (26) <88JOC2435>.

10-Chloro-10,9-epoxy-9-phenylselenoxanthene (47) derives from the reaction of 9-phenylselenoxanthene-9-ol with *N*-chlorosuccinimide <84H(22)1473, 90CPB874>.



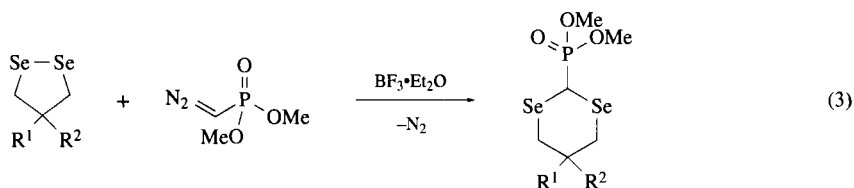
2,5-Diphenyl-1,6-dioxo-6aλ⁴-tellurapentalene (8) is oxidized at low temperature by chlorine or bromine to pertelluranes (48) and (49), which are reduced by hydrazine to give the dioxatellurapentalene (50) <83JOC5149>.



1,2-Oxatellurolylium and 1,2-oxaselenolylium salts are oxidized by bromine and chlorine to trihalogenopertelluranes of the same type as (69) <82USP4329284, 85EUP138220>.

3.13.5.2.2 Reactions involving carbenes

1,3-Diselenanes are formed from 1,2-diselenolanes and dimethyl diazomethanephosphonate according to Equation (3) <91TL4189>.



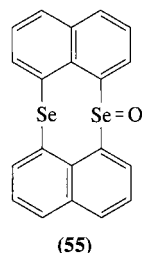
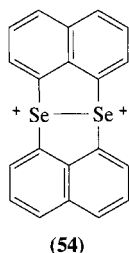
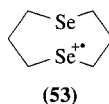
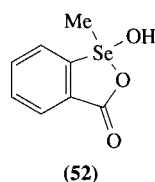
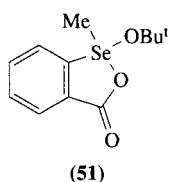
3.13.5.3 Reactions with Nucleophiles

3.13.5.3.1 Reaction with bases

Compound (51) is extremely water sensitive and loses the *t*-butyl group to give (52) <81TL4241, 82JOC2275>.

The dication (35) is reduced to the cation radical (53) in the reaction with fluorenyllithium, the same was observed with ferrocene <90TL6375>, which indicates that the fluorenyl carbanion acts as a one-electron donor.

The dication (54) reacts with water to give the selenoxide (55) <91TL4345>.



3.13.5.3.2 Reaction with aromatics

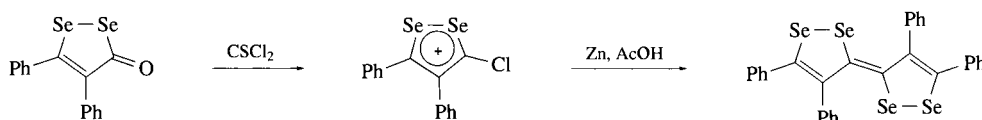
Dication (35) reacted with aniline and *N,N*-dimethylaniline according to Scheme 4. Aliphatic amines like diisopropylamine did not react. Thiophenol was oxidized by (35) to diphenyl disulfide; the difference is probably due to difference in oxidation potentials <90CL393>.



Scheme 4

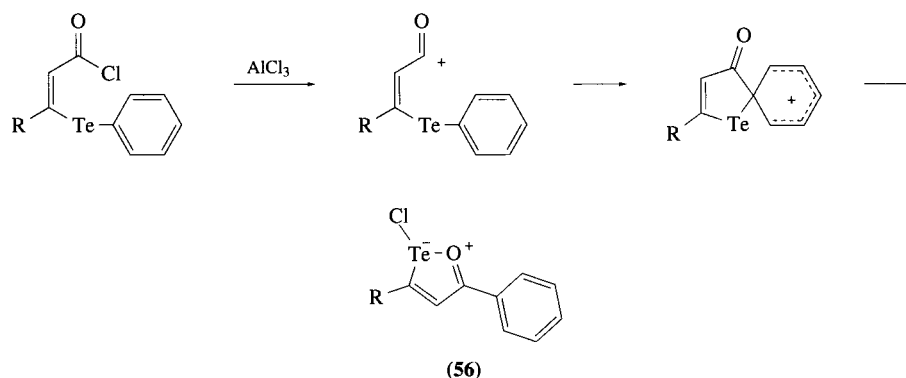
3.13.6 REACTIVITY OF SUBSTITUENTS ATTACHED TO RING CARBON ATOMS

4,5-Diphenyl-1,2-diselenol-3-one and thiophosgene reacted with the formation of 3-chloro-4,5-diphenyl-1,2-diselenolylium chloride which was further reduced by Zn to 3,3'-bis(4,5-diphenyl-1,2-diselenol-ylidene), (1,2-TSeF) according to Scheme 5 <88BSF101>, 1,2-TSeF is one of the few known TSeFs <93SR245>.



Scheme 5

3-Methyl-5-aryl-1,2-oxatellurolylium chlorides (56) react with acid chlorides in the presence of an amine base or pyridine to give 1,6-dioxo-6aλ⁴-tellurapentalenes like compound (48) (Scheme 6) <87OM1597>.



Scheme 6

3.13.7 SYNTHESIS

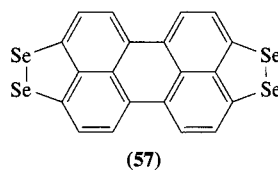
The synthesis of five-membered heterocycles containing one selenium or tellurium atom and another heteroatom adjacent can be classified in three groups, according to the number of building blocks required in a one-step reaction: (i) *one-component synthesis*, in which the starting molecule is cyclized by joining two heteroatoms or by joining one heteroatom and one carbon atom; (ii) [2 + 3] *two-component synthesis*, in which a two-atom unit is joined with a three-atom unit; (iii) *multicomponent synthesis*, in which the heterocyclic ring is formed from nonisolated intermediates formed in a reaction of more than two building blocks.

3.13.7.1 One Component Synthesis

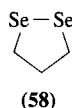
Naphtho[1,8-*b,c*]-1,2-diselenole (**24**) is formed by the oxidation of 1,8-bis(methylseleno)naphthalene with benzoyl peroxide <92CL1437>.

2-Oxa-6,7-ditelluraspiro[3,4]octane (**1**) and 6,7-ditelluraspiro[3,4]octane (**21**) were both prepared from the corresponding bistellurocyanatomethyl compounds by heating <93JA885>.

The tetraselenaperylene derivative (**57**) was prepared by reacting (**24**) with AlCl_3 in nitrobenzene <84EUP107392>.



1,2-Diselenolane (**58**) has been prepared from 1,3-bis(selenocyanato)propane and KOH <93TI605>.

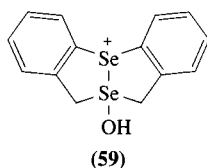


A series of hypervalent diselenide and ditelluride dications of the same type as (**35**) have been described <B-93MI 313-01>.

1,5-Diselenoniabicyclo[3.3.0]octane hexafluorophosphates were prepared by reaction of 1,5-diselenacyclooctane with nitronium hexafluorophosphate <89CC1789, 90TL6375>. 2,2,8,8-Tetra-deuterated salts have also been synthesized <93TI605>.

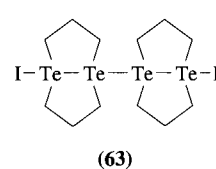
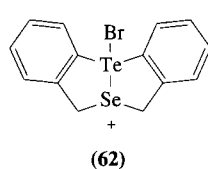
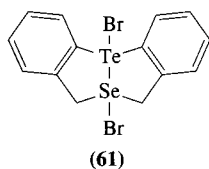
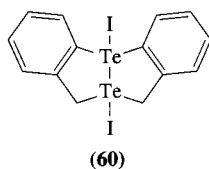
1,5-Ditelluroniabicyclo[3.3.0]octane hexafluorophosphate could be prepared in an analogous way <91TL4537>.

Benzocondensed systems like **(59)** have been described formed by the reaction of 5*H*,7*H*-dibenzo[*b,g*]-1,5-diselenocine Se-oxide with silyl triflate <92JCS(P1)2247>.

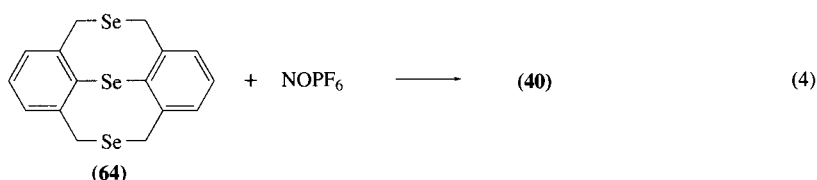


The transient existence of dication **(54)** formed from dinaphtho[1,8-*b,c*]-1,5-diselenocine has been reported <91TL4345>.

Telluro analogues of **(59)** were prepared from the corresponding dibenzo[*b,g*]-1,5-ditellurocin by reaction with iodine which gave the hypervalent diiodo compound **(60)**. Mixed Se and Te compounds like **(61)** and **(62)** were also described <93CL263>. If 1,5-ditelluracyclooctane was reacted with two equivalents of iodine, the dimer **(63)** could be isolated in quantitatively yield <92JCS(P1)2583>. The mixed Se—Te system is also formed as a dication by reaction of 5*H*,7*H*-dibenzo[*b,g*]-1,5-tellurathiocine with nitronium hexafluorophosphate <92CL151>.



1,1-(Methanoselenomethano)-5*H*,7*H*-dibenzo[*b,g*]-1,5-diselenocine **(64)** is oxidized by concentrated sulfuric acid or 2 equivalents of nitronium hexafluorophosphate to the hypervalent seleneurane **(40)** (Equation (4)) <92JA3117>.

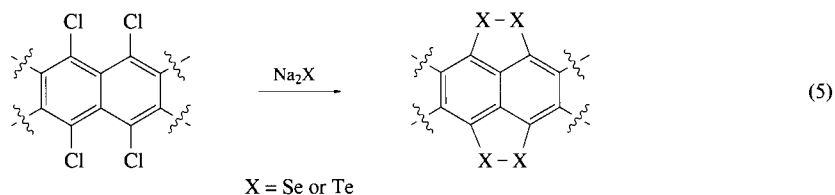


1,2-Oxatellurolylium compounds are formed by isomerization of 2-chlorocarbonyl-ethen-1-yl aryl tellurium derivatives in dichloromethane in the presence of Lewis acids such as aluminum chloride according to Scheme 6 <83JA875, 83JA883, 88OM2188>. The analogous 1,2-oxaselenolylium compounds could be prepared in the same way from 2-chlorocarbonyl-ethen-1-yl aryl selenium derivatives <83JA883>.

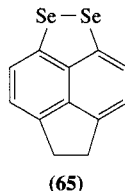
1-Bromo-1-butyl-3*H*-2,1-benzoxatellurole has been prepared from *o*-(dibromobutyltelluro)benzyl alcohol and triethylamine <90ZOB471>.

3.13.7.2 [2 + 3] Two Component Synthesis

The method of synthesis, which is depicted generally in Equation 5, has been utilised for the synthesis of a great number of peridichalcogen-bridged polyacenes which are used as the donor part in organic conductors.



5,6-Dihydroacenaphtho[5,6-*cd*]-1,2-diselenole (**65**) was prepared from 5,6-dibromoacenaphthene via the dilithio derivative <80TL4565, 88BCJ2013>. The ditelluro compound (**3**), however, could not be prepared by this method but was synthesized by reaction of sodium ditelluride with 5,6-dichloroacenaphthene in HMPA <88BCJ2013>.



The tetramethyl derivatives of (**32**) and (**33**) were prepared from the corresponding tetrachloro compounds <87CL315, 88SMB509, 92EUP503113>.

Naphthaceno[1,12-*c,d*:4,5-*c',d'*]bis[1,2]diselenole (**20**) was prepared both from 1,4,5,12-tetrachloronaphthacene and from 1,4,5,5,12,12-hexachloronaphthacene <90BCJ2441, 92JAP(K)0449274>.

The synthesis of naphthaceno[5,6-*c,d*:11,12-*c',d'*]bis[1,2]diselenole (**14**) has been described <87GEP(O)3635124>. Derivatives have also been prepared from 5,12-diacetoxynaphthacene and selenium <89EUP344111>.

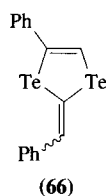
Naphthaceno[5,6-*c,d*:11,12-*c',d'*]bis[1,2]ditellurole, the tellurium analogue of (**14**), was prepared by the reaction of the corresponding tetrachlorotetracene with a new sodium telluride reagent formed directly from the elements in a 1:1 atomic ratio <82OM739>. The synthesis of derivatives with functional groups has been described <85GEP(O)3510090, 88MIP664154>.

Anthra[1,9-*c,d*:4,10-*c',d'*]bis[1,2]diselenole (**15**) was synthesized from 1,4,9,10-tetrachloroanthracene and sodium and selenium in DMF in 20% yield <82CL1841, 83MI 313-01>. Dimethyl and tetramethyl derivatives of (**15**) were prepared from appropriate tetrachloro compounds. The analogue tetratellura compounds were also synthesized <90CL567, 91BCJ2091>.

Fluorantheno[3,4-*c,d*]-1,2-ditellurole (**18**) and the analogue fluorantheno[3,4-*c,d*]-1,2-diselenole were prepared from the corresponding dichloro compound and Na₂Te₂ and Na₂Se₂ respectively <86TL2011, 87SM(19)595>.

The parent 1,2-diselenolane and 4,4-dimethyl-1,2-diselenolane were prepared from the corresponding dibromo compounds and lithium diselenide in THF <88T6119>. 1,2-Diselenolan-4-ol was synthesized from 1,3-dibromopropan-2-ol and sodium hydroselenide <83AJC815>.

It has been reported that the reaction of phenylethyne with elementary tellurium at 60–100°C gave rise to the formation of 3-benzylidene-4-phenyl-1,2-ditellurole <85SUL13, 86ZOR220>. It has, however, since been proved that the product from this reaction is a 1:1 mixture of *cis* and *trans*-2-benzylidene-5-phenyl-2*H*-1,3-ditellurole (**66**) <89TL441>.

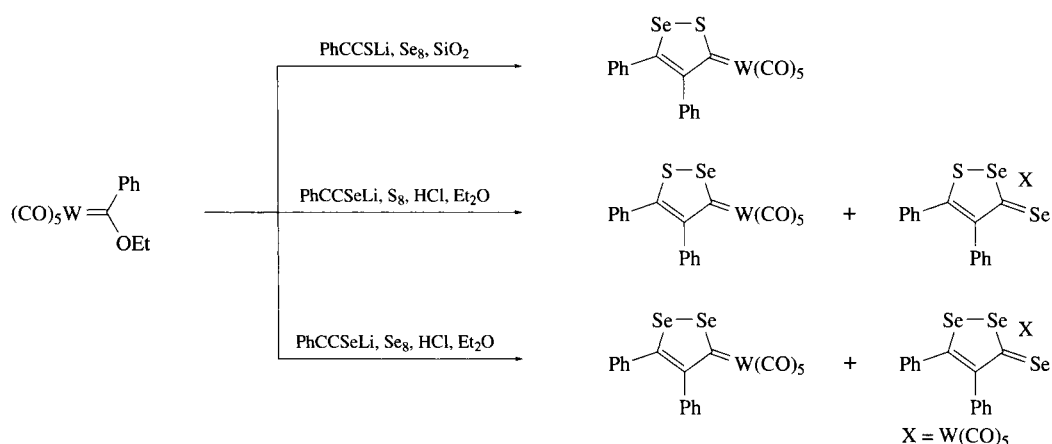


1,2-Diseleno[3,4-*b*]quinolines were prepared from 2-chloro-3-vinylquinolines and sodium hydroselenide in ethanol <81JIC174>.

3.13.7.3 Multicomponent Synthesis

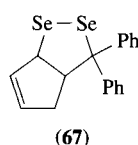
From the Fischer carbene complex (W(CO)₅COEtPh) derivatives of 1,2-selenathiole, 1,2-diselenole, and 1,2-dithiole have been prepared as complexes with W(CO)₅ according to Scheme 7 <84CC634, 88OM1853>.

The gas-phase reaction of dimethylselenide with propargyl alcohol at 450°C gave 1,2-diselenol-3-one (**46**) <87KGS855>. Compound (**46**) was also formed from diphenyldiselenide and propargyl alcohol at 450–600°C. But, 1,2-ditelluro-3-one was not formed from diphenylditelluride and propargyl alcohol under the same conditions <90MI 313-01>.

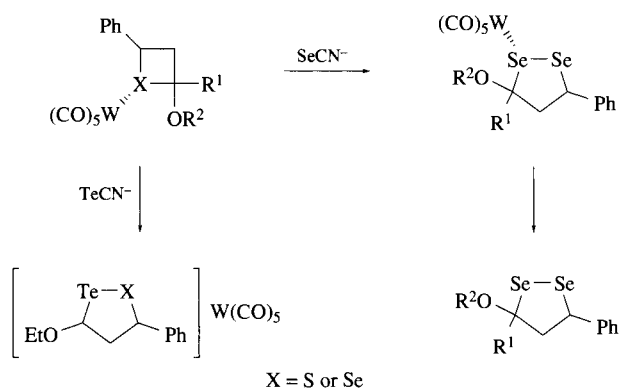


Scheme 7

Treatment of diphenylmethyltriphenylphosphonium bromide with butyllithium and elemental selenium followed by cyclopentadiene gave (**67**). The reaction could also be carried out with other substituted phosphonium salts <90H(31)2107, 94JCS(P1)2151>.



Pentacarbonyltungsten coordinated selenitanes react with seleno- and tellurocyanates by insertion of the chalcogen atom in the Se—C bond of the selenitane to give 1,2-diselenolanes and 1,2-selenatellurolane, respectively, according to Scheme 8. The analogous reaction with the corresponding thietane gave 1,2-thiatellurolane <92CC1050>.



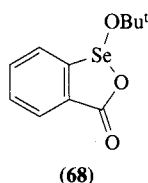
Scheme 8

If 1,3-ditelluroles, with at least one hydrogen present on the ring, are treated in MeCN with triphenylcarbenium tetrafluoroborate, the ^1H NMR spectra of the solution show the formation of 1,3-ditellurolylium ions. The spectrum, however, quickly changes showing the formation of 1,2-ditellurolylium ions instead <82TL1531>.

3,5-Dialkylamino-substituted 1,2-diselenolylium cations have been prepared from 1,3-bis(dialkylamino)-1,3-dichloropropenyl cation by treatment with sodium hydrogen selenide and subsequent oxidation with hydrogen peroxide or *m*-chloroperbenzoic acid <87BCJ2686>. These salts were also prepared by reaction with sodium diselenide in ethanol <86MCLC333>.

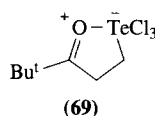
If 2-methylseleno-3-nitrobenzoic acid is reacted with bromine in dichloromethane containing pyridine, 7-nitro-2,1-benzoxaselenol-3-one is formed in 75% yield. If this product is refluxed in thionyl chloride, 7-nitro-2,1-benzothiaselenol-3-one is formed in 92% yield <91T9053>.

The reaction of 2-methylselenobenzoic acid with 1,1'-carbonyldiimidazole followed by addition of *t*-butyl hydroperoxide gave the cyclic selenurane (**68**) <81TL4241, 82JOC2275>.



S-Methyl-1,2-benzodithiolylium iodide reacted with sodium hydroselenide to give 1,2-benzothiaselenole-3-thione (**42**) <82H(19)657>.

The reaction of a silyloxycyclopropane with tellurium(IV)chloride resulted in formation of (**69**) in high yield <91TL229>.

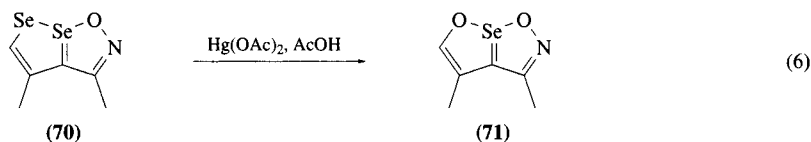


Compounds like (**56**) were also prepared in a multistep reaction starting from tellurochroman-4-one <90ZOB2764>.

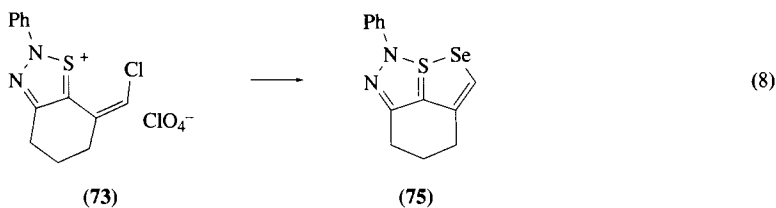
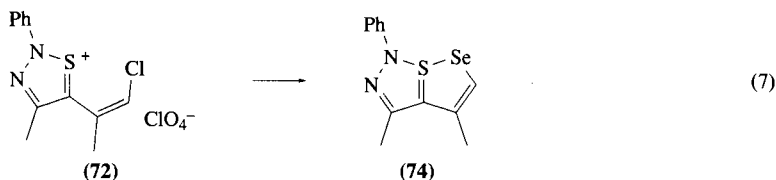
Simple 1,2-tellurazoles are a class of compounds relatively sparsely described. They may be formed in low yields, often not exceeding 10%, from complex reaction mixtures consisting of α -alkynic ketones, hydroxylamine *O*-sulfonic acid, sodium acetate, and potassium telluride <83S824, 87H(26)1587>.

A series of compounds which can be considered hypervalent 1,2-tellurazoles have been prepared and the structures have been given (see Section 3.13.2.1) (Scheme 2). Such compounds have also been reported without structure determinations <85JCS(D)821, 85SR11043, 86EUP192466, 88KGS1426, 88MI 313-01, 88ZOB1684, 89MI 313-01, 89MI 313-02, 90JOM(391)179, 90JOM(397)153>.

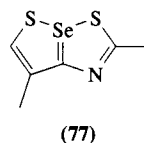
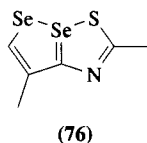
3,4-Dimethyl-1,6-dioxo-6a λ^4 -seleno-2-azapentalene (**71**) was formed in high yield when the diseleno compound (**70**) reacted with mercury(II)acetate in boiling acetic acid (Equation (6)) <81JCS(P1)1596>.



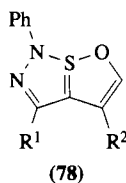
The salts (**72**) and (**73**) in DMF gave, on treatment with aqueous potassium selenosulfate, the thiaselenadiazapentalenes (**74**) and (**75**), respectively (Equations (7) and (8)) <83JCS(P1)777>.



Thiadiselenazapentalenes (76) and (77) are formed when 3,4-dimethyl-1-oxa-6,6a λ^4 -diselena-2-azapentalene reacts with phosphorus pentasulfide <87CC967>.



Compounds of the same type as (74) and (75) were formed from (78) by the reaction with phenylselenophosphonic dichloride and triethylamine. If oxadithiapentalenes reacted with phenylselenophosphonic dichloride, selenadithiapentalenes were formed <88CC1494>.



3.13.8 APPLICATIONS

Peridi- or tetrachalcogen-bridged polyacenes have been claimed in the patent literature for the preparation of electrical conducting materials <88EUP285564, 93EUP521826>. They have also been claimed as copolymers for the preparation of radiation sensitive polymers <90EUP362143>.

1,6-Dioxa-6a λ^4 -seleno(telluro) pentalenes have been claimed for use as sensitizers in electrophotogenic compounds <84USP4450217>.

4,4-Disubstituted-1,2-diselenoles and telluroles have been proposed as fog inhibitors for silver halide photographic materials <89USP4861703>.

3.14

Two Nonadjacent Heteroatoms with at least One Selenium or Tellurium

JAN BECHER, CARL TH. PEDERSEN and PERNILLE MØRK
Odense University, Denmark

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3.14.11 SYNTHESIS OF A PARTICULAR CLASS OF COMPOUNDS AND A CRITICAL COMPARISON OF THE VARIOUS ROUTES AVAILABLE

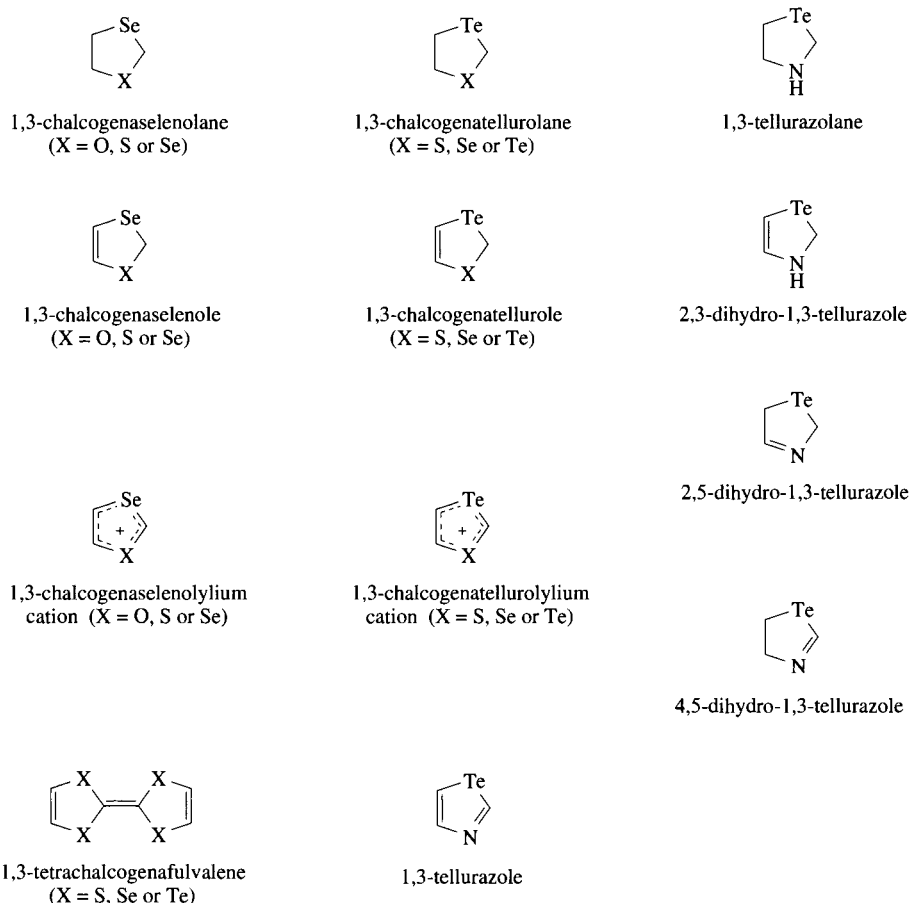
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3.14.12 IMPORTANT COMPOUNDS AND APPLICATIONS

707

3.14.1 INTRODUCTION

The various types of parent five-membered monocyclic rings containing two nonadjacent heteroatoms, and at least one selenium or tellurium atom are shown in Scheme 1.



Scheme 1

The 1,3-diselenole and 1,3-thiaselenole ring systems as well as their benzo-fused analogues are well known and, due to their use as precursors for symmetrical and asymmetrical selenium and tellurium analogues of the tetrathiafulvalenes, there is much interest in these heterocycles mainly related to their properties as conductors.

Selenium and tellurium are more electropositive elements than sulfur and, in general, the chemistry of organic selenium and tellurium compounds is more complicated and difficult than that of the sulfur analogues, not forgetting the toxicity of selenium and the noxiousness of low molecular organic selenium and tellurium compounds.

In spite of these difficulties, a number of tetraselenafulvalenes and mixed sulfur- and selenafulvalenes have been prepared, including a few tellurium analogues. A number of reviews on 1,3-dithiole systems therefore also include the corresponding selenium-containing systems. The most important reviews covering the period 1983–1994 are the following. Two large and comprehensive reviews on tetrachalcogenafulvalenes and their precursors have appeared ^[87SR155, 93SR245], as well as a review on the synthesis of tetrachalcogenafulvalenes ^[86T1209]. A comprehensive and up-to-date review, mainly dealing with the electronic and conducting properties as well as charge transfer

salts of tetrathiafulvalenes and related chalcogenafulvalenes, has also appeared <91CSR355>, along with a related discussion of these properties <89PS(43)187>.

There is also considerable interest in metal complexes of 1,3-dithiole-2-thione-4,5-dithiolates (DMIT) and in their chalcogene analogues such as 1,3-diselenole-2-selone-4,5-diselenate (DSIT) due to their use as starting materials for organic conductors <91CCR115, 91MI 314-01, 91RHA171, 92CCR99>.

The literature on the related tellurium-containing heterocycles is less extensive; however, comprehensive reviews on tellurium-containing heterocycles are found <B-86MI 314-01, 86SR15, 93AHC(58)47> as is a review dealing with synthetic methods for five-membered tellurium containing heterocycles <90HOU(E12b)795>. A review covering syntheses, reactions, and structures of 1,3-diteluroles and tetratellurafulvalenes has also appeared <91KGS291> as well as one covering the syntheses of conductors containing selenium and tellurium <B-87MI 314-01>.

1,3-Selenazoles are covered in Chapter 3.08, whereas the 1,3-tellurazoles are covered in the present chapter.

The heterocycles which are the subject of this chapter were treated in the first edition of *Comprehensive Heterocyclic Chemistry* (CHEC-I) <84CHEC-I(6)947>; five-membered selenium–nitrogen heterocycles are found in <84CHEC-I(6)333>, whereas the tellurazoles were not included.

3.14.2 THEORETICAL METHODS

The ^1H NMR chemical shifts of the 1,3-dichalcogenolylium ions are in agreement with a diamagnetic ring current, and consequently these compounds are 6π heteroaromatic systems <84CHEC-I(6)947>.

CNDO/2 calculations on some fused 1,3-diselenole systems are reported <84CS236>; for a CLOPPA–IPP analysis of ^2J (Se–Se) couplings, see <90JMR(87)209>.

3.14.3 EXPERIMENTAL STRUCTURAL METHODS

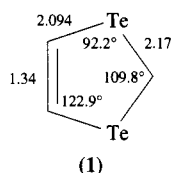
3.14.3.1 X-ray Diffraction

As a result of the continuing interest in sulfur and in the present case selenium- and tellurium-containing conductors based on 1,3-dichalcogenoles, a number of crystal structures have been reported since the publication of CHEC-I in 1984. A search in the Cambridge Structural Database revealed 122 structures (in 1994) for selenium- or tellurium-containing 1,3-dichalcogenoles in combination with, or without, sulfur. The majority of these structures are radical cation salts of tetrachalcogenafulvalenes. An example of a charge transfer complex is shown in <92CB1919>.

The x-ray crystallographic structure of 4-acetyltetraselenafulvalene revealed a significant deviation from planarity in the TSF system <93S465>.

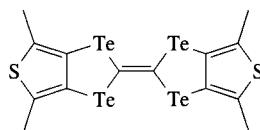
In the tellurazole series, the structure of 2-phenylbenzotellurazole has been reported <89KGS1690>. The structure shows that the heterocyclic five-membered ring is planar, but due to the bulkiness of the tellurium atom a relatively narrow C–Te–C angle (78.6°) is observed, whereas the C–N–C angle is larger (116.9°) as compared to the angles in a corresponding benzothiazole.

There are short intermolecular Te–Te distances ($3.864 \text{ \AA}$) in the parent 1,3-ditellurole system (**1**) as compared to the covalent radius of Te; the following bond lengths ($\text{\AA}$) and angles were found <85JA6298>.



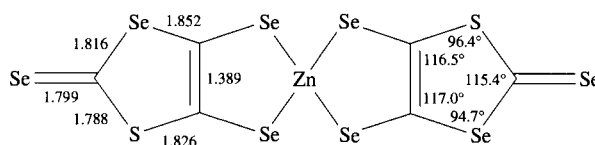
In hexamethylenetetratellurafulvalene (**21**) (Table 2) short intermolecular Te–Te distances are observed (3.583 and $3.743 \text{ \AA}$) as already noted in CHEC-I <82CC1316, 86CL311>. The x-ray analysis of the corresponding bis(dimethylthieno)tetratellurafulvalene (**2**) revealed very different dihedral angles between the tetratelluraethylene core and the exterior dimethylthieno planes, 47.1 (3°) and

at 16.0 (3°), resulting in large deviation from planarity. The x-ray analysis also revealed very short intermolecular Te—Te distances <84JA8303>.



BDMT-TTeF
(2)

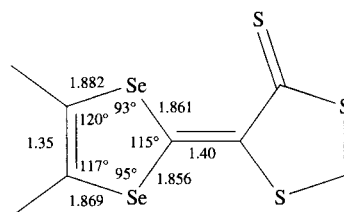
Bis(tetraphenylphosphonium)bis(1,3-thiaselenol-2-selenon-4,5-diselenolato)zincate (**3**) is an important starting material for preparation of 1,3-thiaselenole derivatives, and the result from x-ray analysis gives the following values <92JOM(427)213>.



(3)

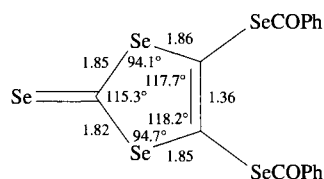
X-ray crystallographic analysis revealing a distorted tetrahedral geometry for the corresponding semiconducting copper(II) complex was also reported <90CL355>.

The crystal structure of a spiro 1,3-oxaselenole is reported <83JCS(P1)333> as well as of the following fulvene system (**4**) <90MI 314-01>.



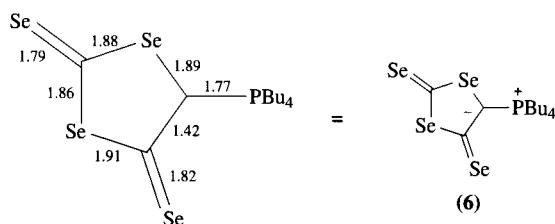
(4)

The crystal structure of the important starting material 4,5-dibenzoylseleno-1,3-diselenole-2-selone (**5**) was reported, and the structure compared with the “all-sulfur” analogue <92JPR72>.



(5)

X-ray crystallographic analysis of the zwitterionic 1,3-diselenole (**6**) showed a planar 5-ring structure with extensive delocalization <85AG1057>.



(6)

3.14.3.2 Nuclear Magnetic Resonance Spectroscopy

3.14.3.2.1 ^1H NMR and ^{13}C NMR spectroscopy

Proton and ^{13}C NMR spectroscopy was covered extensively in CHEC-I and is not treated separately here. NMR spectroscopy has been used in the characterization of new compounds, and consequently NMR data can be found in the majority of the papers cited here.

3.14.3.2.2 ^{77}Se and ^{125}Te NMR spectroscopy

The isotopes of selenium and tellurium, ^{77}Se and ^{125}Te , have an abundance of ca. 7% and therefore NMR spectra can be obtained from both nuclei in natural abundances. ^{77}Se NMR investigations of organic selenium compounds are now routine techniques, and spectral data are available for a number of representative examples of selenium-containing 1,3-dichalcogenoles (see Table 1).

The shift increments for the ^1H , ^{13}C , and ^{77}Se chemical shifts in the 1,3-dichalcogenole derivatives in Table 1 are reported <87PS(29)187>. Linear relationships were observed between the ^{77}Se and ^{125}Te chemical shifts for 2-phenylbenzoselenazole and 2-benzoylbenzoselenazole and the corresponding benzotellurazoles <87MRC129>. Also, the ^{77}Se — ^1H NMR coupling constants and coupling pattern have been reported for the parent 1,3-diselenolylium and the 1,3-thiaselenolylium cations <87ZC369>.

By measurement of the homonuclear ^3J (^{77}Se — ^{77}Se) coupling constants, *cis/trans* assignments were possible for a series of substituted tetraselenafulvalenes, (TSF) (7). Coupling constants 80–100 Hz were observed for *cis*-orientation of the chalcogenes, while the *trans*-chalcogenes have coupling constants in the range 10–25 Hz; the ^{77}Se — ^1H coupling constants were also reported for this series of TSFs <84JA1240>.

The ^{125}Te couplings to ^1H , ^{13}C , and ^{125}Te in the NMR spectra of 1,3-ditellurole (1) are: $^1J(^{125}\text{Te}$ — $^{13}\text{CH}_2$) = 178.7 Hz, $^1J(^{125}\text{Te}$ — ^{13}CH) = 288.3 Hz, $^2J(^{125}\text{Te}$ — ^{13}CH) = 12.3 Hz, $^2J(^{125}\text{Te}$ — $^{13}\text{C}^1\text{H}_2$) = 25.9 Hz, $^2J(^{125}\text{Te}$ — $^{13}\text{C}^1\text{H}$) = 126.5 Hz, $^3J(^{125}\text{Te}$ — $^{13}\text{C}^1\text{H}$) = 33.5 Hz, $^2J(^{125}\text{Te}$ — ^{125}Te) = 260.3 Hz, and $^3J(^1\text{H}$ — ^1H) = 8.12 Hz <86OM1544>.

3.14.3.3 Mass Spectrometry

Mass spectra have been used extensively for the characterization of a large number of the new compounds described in this chapter. It is briefly mentioned if a systematic treatment of the mass spectra is given.

3.14.4 THERMODYNAMIC ASPECTS

3.14.4.1 Electrochemistry and Conductivity

Like their sulfur analogues, tetraselenafulvalenes and the mixed sulfur/selenium systems are excellent electron donors which are able to form radical cation salts and charge transfer complexes with appropriate electron acceptors.

A tetrachalcogenafulvalene can be oxidized in two discrete steps, each step giving rise to a Hückel-type $[4n + 2]$ aromatic delocalized π -system, thus for tetraselenafulvalene (TSF) (7), Scheme 2 results.

Comprehensive reviews covering the electrochemical data for selenium- and tellurium-based tetrachalcogenafulvalenes have appeared, as mentioned in the introduction <87SR155, 93SR245>. Table 2 gives the half-wave oxidation potentials for selected representative examples of the selenium- and tellurium-based donors.

The tetrathiafulvalene (TTF) system (12) has been in focus for a long time due to its unique properties as an excellent reversible and stable π -donor. Interest in the corresponding selenafulvalenes culminated in 1980 <80MI 314-01, 80MI 314-02> when superconductivity in an organic metal was discovered for the first time in a salt of tetramethyltetraselenafulvalene (TMTSF) $_2\text{X}$ (8).

Scheme 3 shows the sulfur- and selenium-based tetrachalcogenafulvalenes, which have given rise to superconducting radical cation salts. It is worth noting from this list, that there are almost as many selenium- as sulfur-based systems that have shown superconductivity, such as (DMET) $_2\text{Au}(\text{CN})_2$ (9)

Table 1 ^{77}Se NMR spectral data for 1,3-dichalcogenoles.

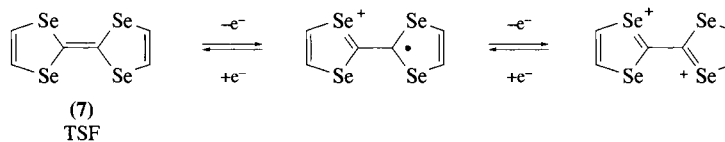
R_1	R_2	X	Y	Z	Chemical shifts, ppm (Me_2Se)		Ref.
					$\delta(\text{Se}, 1/3)$	$\delta(\text{C}=\text{Se}, \text{SeEt})$	

H	H	S	Se	Se	995.5	1027.7	84OMR(22)480
H	H	S	Se	S	939.7		84OMR(22)480
H	H	S	Se	O	658.0		84OMR(22)480
Ph	H	S	Se	Se	1020.0	1058.0	84OMR(22)480
Ph	H	S	Se	S	986.3		84OMR(22)480
Ph	H	S	Se	O	722.6		84OMR(22)480
H	H	Se	Se	Se	1011.7	1193.9	84OMR(22)480
H	H	Se	Se	S	953.9		84OMR(22)480
H	H	Se	Se	O	701.9		84OMR(22)480
Ph	H	Se	Se	Se	1013.9/1041.7	1219.5	84OMR(22)480
Ph	H	Se	Se	S	960.6/991.7		84OMR(22)480
Ph	H	Se	Se	O	719.3/778.5		84OMR(22)480
Me	Me	Se	Se	Se	1068.3	1150.8	84OMR(22)480
PhCOSe	PhCOSe	Se	Se	Se	1074.1	1209.0(Se=C) 621.3(CSeCO)	87ZAAC(544)199
PhCOSe	PhCOSe	S	Se	Se	1120.8	1090.7(Se=C) 702.0(4-Se) 621.8(5-Se)	92JOM(427)213

H	H	Se	Se	Se	855.4	1454.8	84OMR(22)480
H	H	Se	Se	S	804.9		84OMR(22)480
H	H	Se	Se	O	564.5		84OMR(22)480

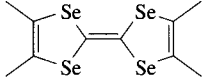
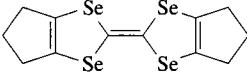
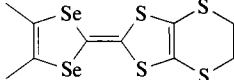
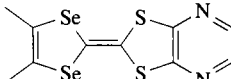
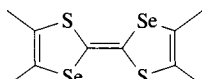
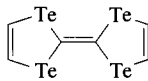
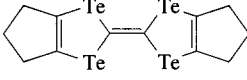
$Z = \text{H}, \text{SeEt}, \text{SEt}, 1\text{-morpholinyl} = \text{A}$

H	H	S	Se	H	1085.5		84OMR(22)480
H	H	S	Se	SeEt	1035.7	602.6(SeEt)	84OMR(22)480
H	H	S	Se	SEt	999.6		84OMR(22)480
H	H	S	Se	A	717.1		84OMR(22)480
H	H	Se	Se	H	1102.6		87PS(29)187
H	H	Se	Se	SeEt	1043.9	649.8(SeEt)	87PS(29)187
H	H	Se	Se	SEt	1003.6		87PS(29)187
H	H	Se	Se	A	722.6		87PS(29)187

**Scheme 2**

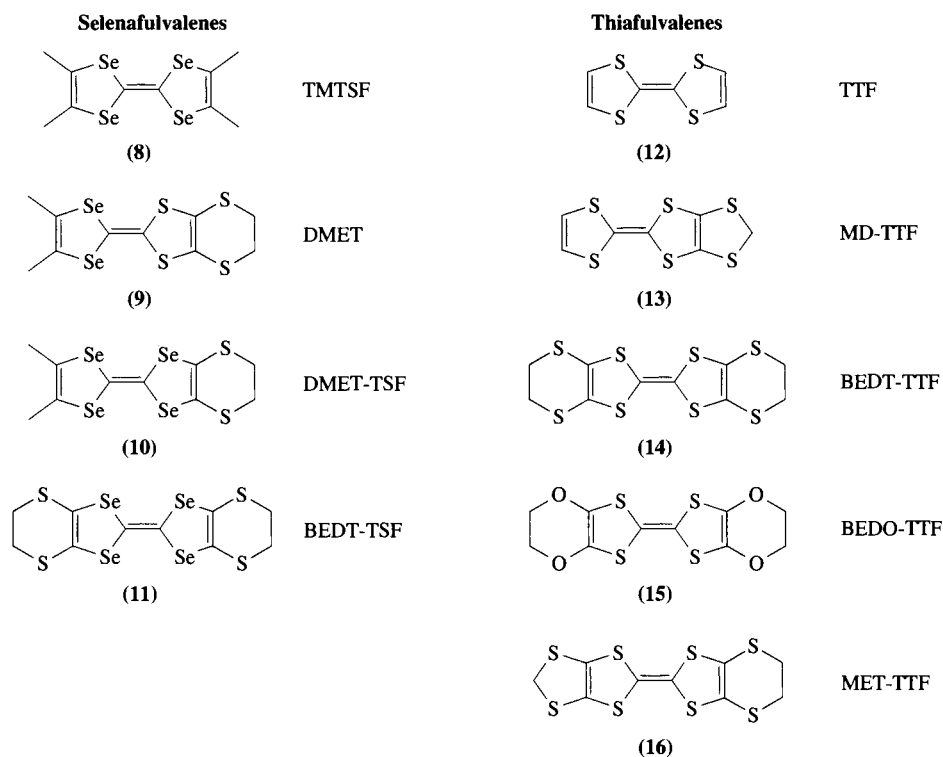
<87CL931> albeit the number of TTF derivatives which have been investigated is many times larger than the number of TSF derivatives <91SCI1501>. Table 3 gives a compilation of the T_c temperatures for the tetrachalcogenafulvalene salts (selenium and mixed sulfur–selenium-based systems) which have shown superconductivity.

Table 2 Half-wave oxidation potentials for selected tetrachalcogenafulvalenes.

Compound/No.	$E_{1/2}(1)/V^a$	$E_{1/2}(2)/V^a$	$\Delta E/V$	Ref.
 TMSF (8)	0.44	0.72	0.28	74CC937
 (17)	0.18	0.45	0.27	88SMB425
 DMET (9)	0.52	0.78	0.26	86CC1472
 (18)	0.69	1.02	0.33	87CL1279
 (19)	0.33	0.68	0.35	83JCP(79)1004
 TTeF (20)	0.59	0.84	0.25	87JA4115
 (21)	0.40	0.69	0.29	83CL503

^a Redox potential in acetonitrile vs. SCE.**Table 3** Selenium-based organic superconductors.

Type	$T_c(K)$	Ref.
(TMTSF) ₂ PF ₆	0.9 (12 kbar)	91SCI1501
(TMTSF) ₂ AsF ₆	1.1 (12 kbar)	91SCI1501
(TMTSF) ₂ SbF ₆	0.4 (11 kbar)	91SCI1501
(TMTSF) ₂ TaF ₆	1.4 (12 kbar)	91SCI1501
(TMTSF) ₂ ReO ₄	1.3 (9.5 kbar)	91SCI1501
(TMTSF) ₂ FSO ₃	2.1 (6.5 kbar)	91SCI1501
(TMTSF) ₂ ClO ₄		91SCI1501
(DMET) ₂ Au(CN) ₂	0.8 (5 kbar)	91SCI1501
(DMET) ₂ I ₃	0.47	91SCI1501
(DMET) ₂ IBr ₂	0.59	91SCI1501
(DMET) ₂ AuCl ₂	0.83	91SCI1501
(DMET) ₂ AuI ₂	0.55 (5 kbar)	91SCI1501
(DMET) ₂ AuBr ₂	1.0 (1.5 kbar)	91SCI1501
κ -(DMET) ₂ AuBr ₂	1.9	91SCI1501
λ -(BEDT—TSF) ₂ GaCl ₄	8	93CL1559
(DMET—TSF) ₂ AuI ₂	0.58	93SM2084



Scheme 3

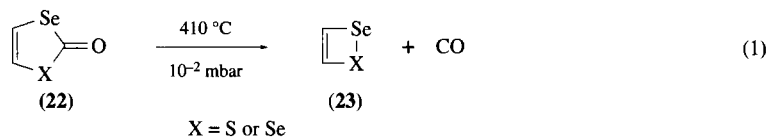
3.14.5 REACTIVITY OF FULLY CONJUGATED RINGS

The 1,3-dichalcogenolylum ions have a diamagnetic ring current and are therefore 6π hetero-aromatic systems. However, reactivity of the conjugated and nonconjugated 1,3-dichalcogenoles as well as chemistry of the corresponding tetrachalcogenafulvalenes are treated in the present chapter because their chemistry is intimately connected.

3.14.5.1 Thermal and Photochemical Reactions Involving No Other Species

3.14.5.1.1 Thermolysis

Thermal and electron-induced fragmentation of 1,3-diselenole-2-ones are parallel as loss of CO is observed in both cases. Vacuum pyrolyses of either 1,3-diselenole-2-one or 1,3-thiaselenole-2-one (**22**) give rise to formation of CO and 1,2-diselenete or 1,2-thiaselenete (**23**), respectively (Equation (1)) <87AG348>.

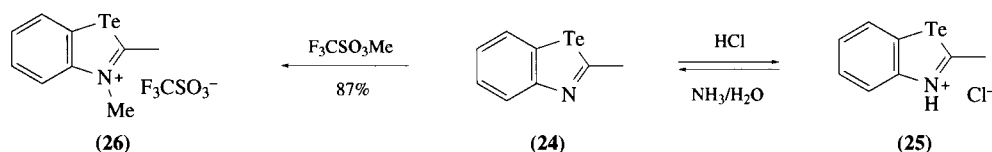


3.14.5.2 Reactions with Electrophiles

3.14.5.2.1 Reactions involving protons or Lewis acids

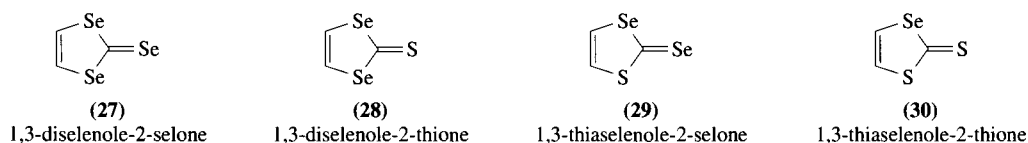
Protonation of a 1,3-benzotellurazole with hydrochloric acid produces the corresponding 1,3-benzotellurazolium chloride (**25**), which may be deprotonated again with aqueous ammonia <86USP4607000>. Reaction of a 1,3-benzotellurazole with a strong alkylating agent such as trifluoro-

methane sulfonate results in *N*-alkylation giving (26) <87USP4661438>. Subsequent reaction with sodium iodide yields the corresponding iodide (Scheme 4).



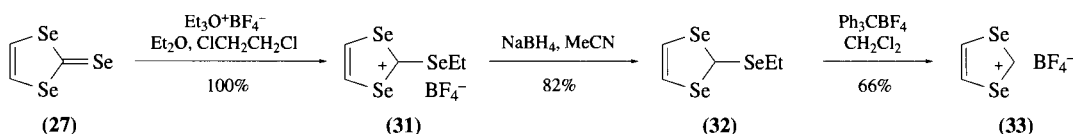
Scheme 4

Chemistry in the sulfur and selenium series of the 1,3-dichalcogenole-2-chalcogenones (Scheme 5) is closely related. For example, alkylation takes place at the 2-chalcogene atom, thus 1,3-diselenole-2-selones such as (27) are readily Se-alkylated with formation of the corresponding 1,3-diselenolylium cation. While such 1,3-dichalcogenolylium cations are recognized as being aromatic 6π electron systems, the 1,3-dichalcogenoles are normally regarded as being nonaromatic.



Scheme 5

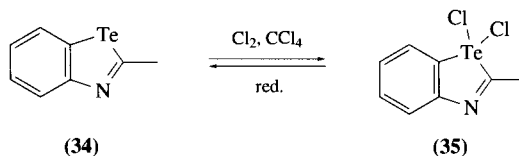
An effective route to the parent cation (33) using Meerwein's reagent, borohydride reduction followed by reaction with triphenylmethyl tetrafluoroborate is illustrative (Scheme 6) <86ZC138>.



Scheme 6

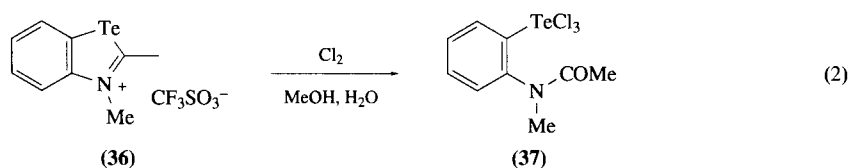
The 1,3-dichalcogenolylium cations are used in the formation of Wittig or Wittig–Horner reagents, see Scheme 16.

Like other telluraheterocycles, oxidation of 1,3-benzotellurazole (34) with chlorine or bromine produces the Te,Te dihalide (35); reduction with aqueous disodium disulfide recovers the 1,3-benzotellurazole (Scheme 7) <88KGS276>.

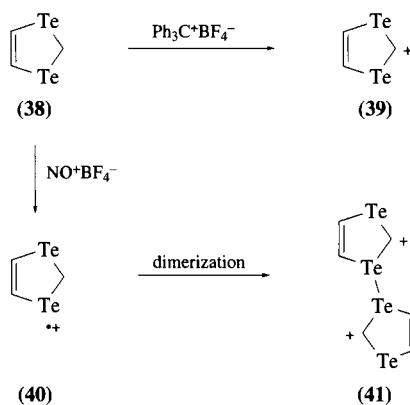


Scheme 7

Te—C bond cleavage is observed when 1,3-benzotellurazolium trifluoromethane sulfonate such as (36) is treated with halogens (Cl_2 or Br_2) (Equation (2)) <87USP4661438>.

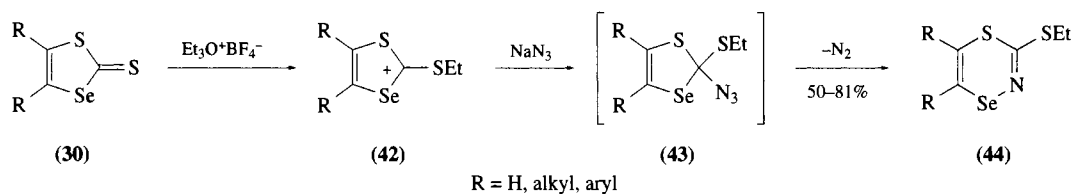


One-electron oxidation of parent 2*H*-1,3-ditellurole (38) with nitrosonium tetrafluoroborate or electrochemically leads to formation of the 1,3-ditellurolylium radical-cation (40) and the corresponding dimer (41); low temperature favors dimer formation (Scheme 8) <85JA6298>.



Scheme 8

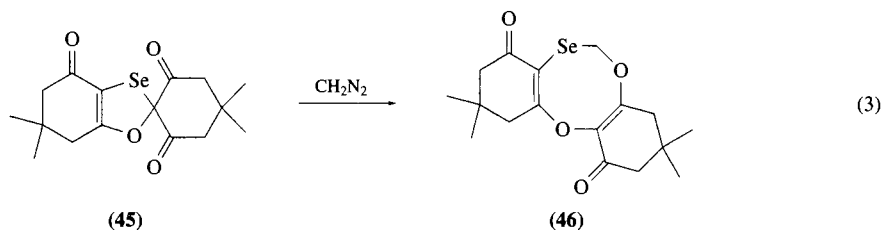
Reaction of a 1,3-thiaselenole (**30**; R = H) with Meerwein's reagent, followed by sodium azide, leads to ring expansion via the azido intermediate (**43**) (Scheme 9) <84S667>.



Scheme 9

3.14.5.2.2 Reactions involving carbenes

Ring expansion of spiro 1,3-oxaselenoles, such as (**45**) derived from dimedone (see Scheme 36) with an excess of diazomethane gives 1,4,6-dioxaselenocine (**46**) in quantitative yield (Equation (3)) <87CPB4967>.

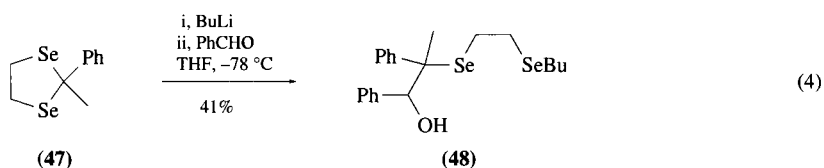


3.14.5.3 Reactions with Nucleophiles

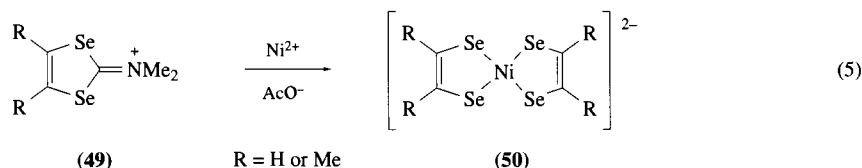
3.14.5.3.1 Reactions with bases

(i) Ring opening reactions

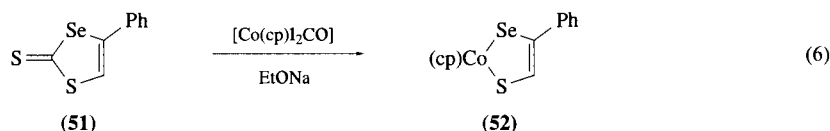
In contrast to the unsaturated 1,3-diselenoles, diselenolanes derived from a 1,3-diselenole such as (**47**) are ring opened by butyllithium in THF (Equation (4)) <93TL8517>.



Reactions of a 1,3-dithiole-2-one ring with base can lead to nucleophilic ring opening, as this ring system is formally a dithiacarbonic ester. A similar nucleophilic opening of a corresponding 1,3-dichalcogenole-2-immonium ring such as (49), is also observed. The diselenolate can be isolated as the nickel(II) (50) complex (Equation (5)) <85IC2864>.

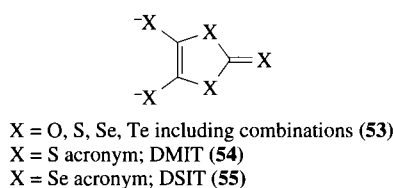


Treatment of 5-phenyl-1,3-thiaselenole-2-thione (51) with sodium ethoxide in the presence of the cyclopentadienyl complex [Co(cp)I₂CO] in ethanol also results in ring opening with formation of the stable cobalt cyclopentadienyl complex (52) (Equation (6)) <89BCJ3266>.



(ii) Deprotonation of ring-carbons, metallation reactions

The dianion of 1,3-dithiole-2-thione-4,5-dithiolate (54) (DMIT) and the selenium analogue (55) (DSIT) are important starting materials for a variety of tetrathiafulvalenes, tetraselenafulvalenes, and dithiadiseleno-fulvalenes. The reactions of DMIT and DSIT, as well as their complexes, with transition metal cations have been intensively studied due to their electrochemical properties and their use as starting materials for organic conductors (Scheme 10) <91CCR115, 91MI 314-01, 91RHA171, 92CCR99>.

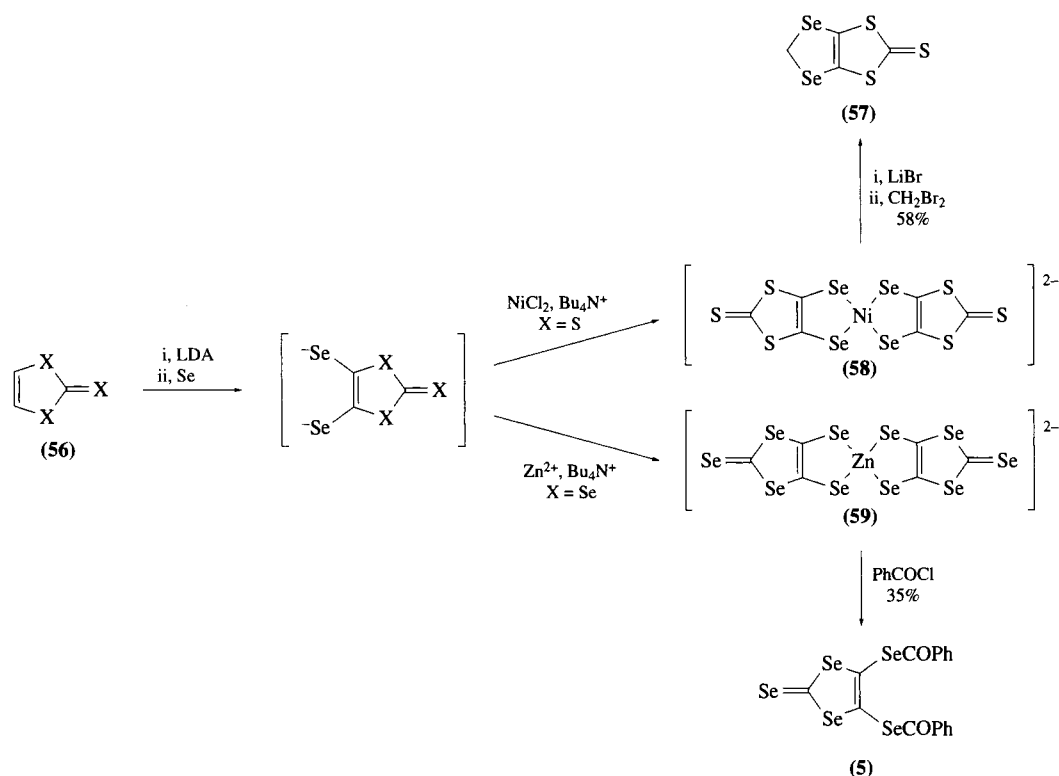


Scheme 10

1,3-Diselenole-2-selone-4,5-diselenolate and its dibenzoate can be prepared from the parent 1,3-diselenole-2-selone (27) via lithiation and seleno insertion at C-4 and C-5 <89ZC250>. The stable dibenzoate (5) is a convenient starting material in the tetraselenafulvalene series similar to the DMIT dibenzoate in the sulfur series. Using this method, starting from 1,3-dithiole-2-thione (56; X = S), the parent 4,5-methylenediseleno-1,3-dithiole-2-thione (57) can be obtained via lithiation with lithium diisopropylamide (LDA) by the route depicted in Scheme 11 <86SRI1351, 90ZAAC(581)59, 92JOM(427)213>.

The tetraphenyl arsonium or phosphonium salts of DSIT-zincate (PPh₄)₂(ZnC₃Se₃)₂ can be prepared in 13% overall yield by sodium metal reduction of carbondiselenide in organic solvents <90JCS(D)115>. This method is similar to the procedure used for the sulfur analogue.

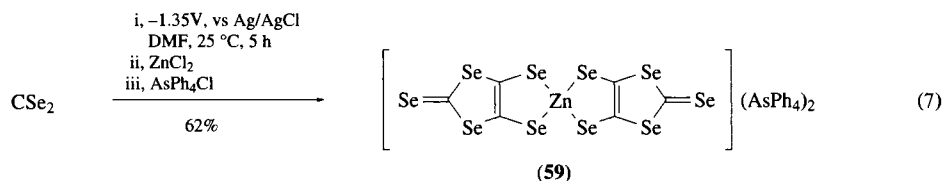
A comprehensive discussion including detailed preparative procedures for conversion into their respective dibenzoates for the selenium-based 1,3-dichalcogenoles described in Scheme 11 is given



Scheme 11

<92JOM(427)213>. Note that this procedure also includes the corresponding 1,3-thiaselenole-2-selone-4,5-diselenolate, and its dibenzoate which is obtained in 68% yield.

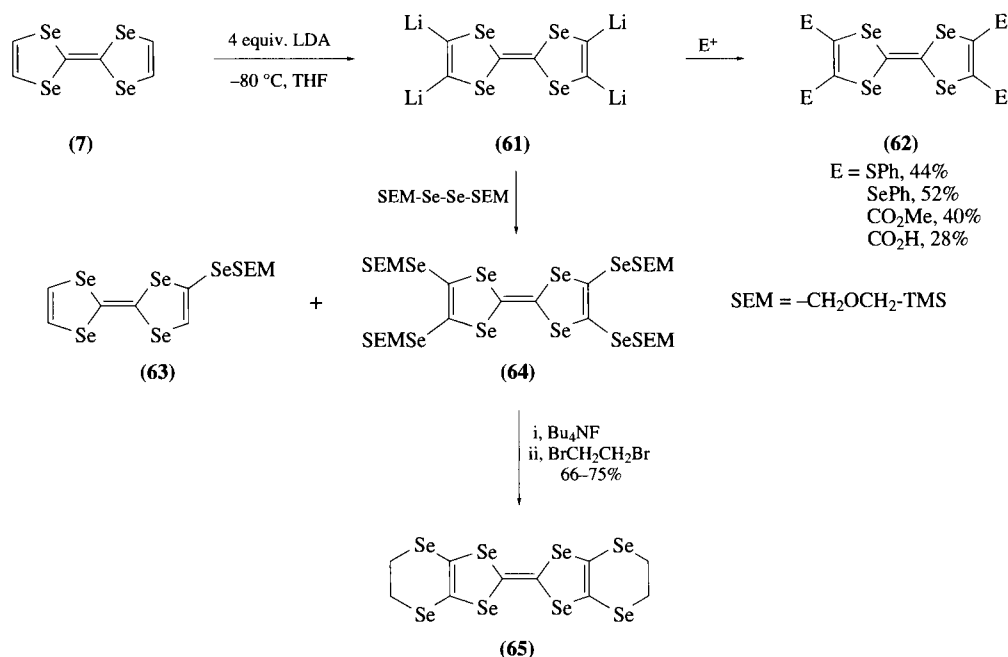
DSIT-zincate (**59**) may also be prepared by electrochemical reduction of carbon diselenide; the method shown in Equation (7) gives the zinc chelate (**59**) in 62% yield based on recovered starting material <84SRI915>.



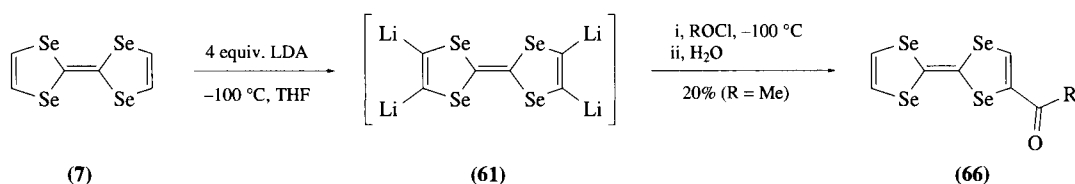
(a) *Metallation in tetraselenafulvalenes.* A tetrachalcogenafulvalene system such as tetrathiafulvalene (**12**) can be metallated at the 4- and 5-carbons using LDA <87JOC3444, 89CC169>. LDA reaction in the tetrathiafulvalene system, followed by reaction with an electrophile, will give a substituted tetrathiafulvalene. These reactions are well documented and very useful for preparation of functionalized TTFs <87CL2399, 88CC1089, 91TL2741>.

Metallation can likewise be used for the synthesis of functionalized TSF-derivatives. In the trimethylsilyl-ethoxymethyl (SEM) reaction (Scheme 12) the LDA metallation results in a mixture of products, thus formation of mono- and disubstituted species is favored. The tetrasubstituted TSF (**64**) is obtained in 10% yield after chromatographic workup. The SEM protecting group (-CH₂OCH₂CH₂-TMS) can subsequently be cleaved and the resulting selenolate realkylated <91TL2741>. As an example, the preparation of the BEDT-TTF analogue BEDS-TSF (**65**) is shown (Scheme 12) <83CC235>.

By working at low temperature, it is possible to avoid formation of mixtures, thus when tetraselenafulvalene (**7**) is tetralithiated at -100 °C followed by reaction with 0.8 equiv. of an acid chloride, only the monoacyl derivative (**66**) is isolated in 20% yield accompanied by 60% recovered starting TSF (**7**) (Scheme 13) <93S465>.



Scheme 12



Scheme 13

Metallation of a 1,3-ditellurole ring is also possible; however, lithiation of the 1,3-ditellurole ring takes place at the 2- or 4-position depending on the structure ^{<83TL237>}; the 4-phenyl derivative (67) gives rise to substitution at C-2 yielding compound (68), whereas the unsubstituted ring (71) results in substitution at C-4 giving (73). As usual in metallation reactions in five-membered heterocycles, control of the temperature is important, thus heating of the lithio-1,3-ditellurole in the presence of TMS-Cl may lead to ring opening and rearrangement, resulting in formation of (70) (Scheme 14).

3.14.5.3.2 Reaction with phosphorus nucleophiles

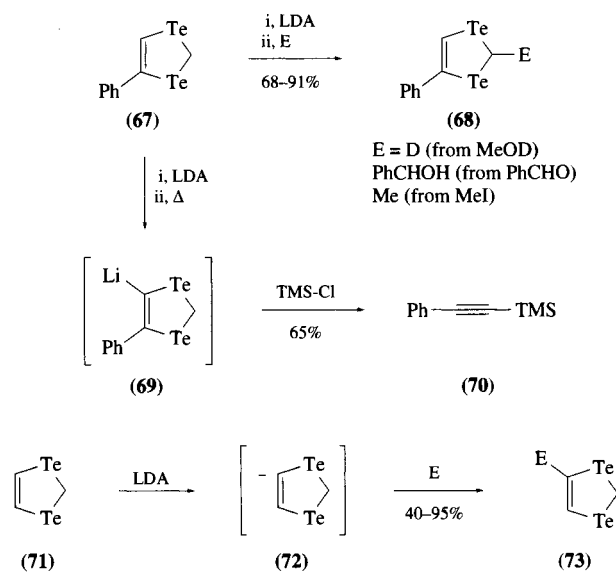
(i) Wittig-type coupling reactions, formation of extended vinylog systems, and fulvenes

For many reasons, such as reducing coulombic repulsion energy or stabilizing dication states, extended or vinylog fulvene systems are of interest, see Section 3.14.7.

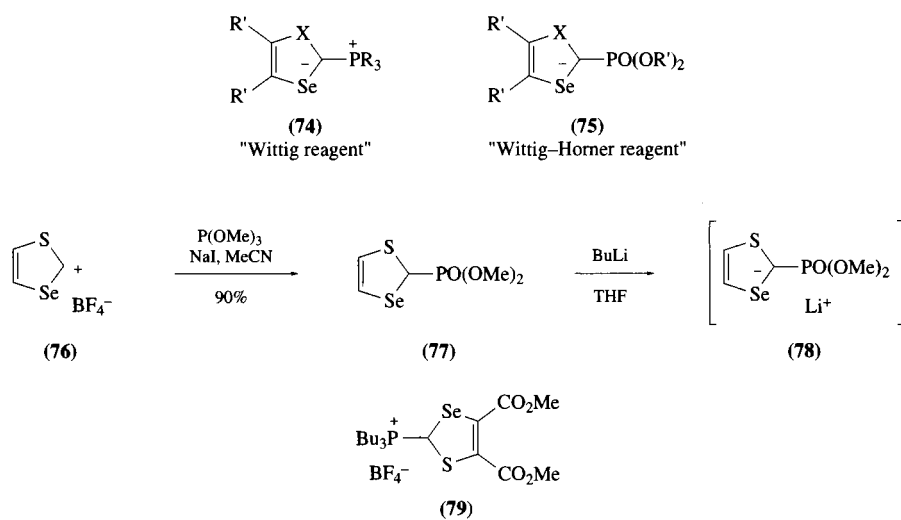
Wittig (74) and Wittig–Horner (75) reagents of 1,3-dichalcogenoles are useful starting materials, and they have been used extensively for synthesis of extended fulvenes in the sulfur series as well as for their selenium analogues. As expected, the phosphonate esters are more reactive nucleophiles in these reactions as compared to the phosphoranes.

The following example (Scheme 15) is representative, as preparation of the Wittig–Horner reagent (77) is typical ^{<90CC470, 91JCS(P)157>}; preparation of the corresponding phosphonium reagent (79) is described ^{<84TL4227, 92JOC5517>}; both reagents are formed in high yields.

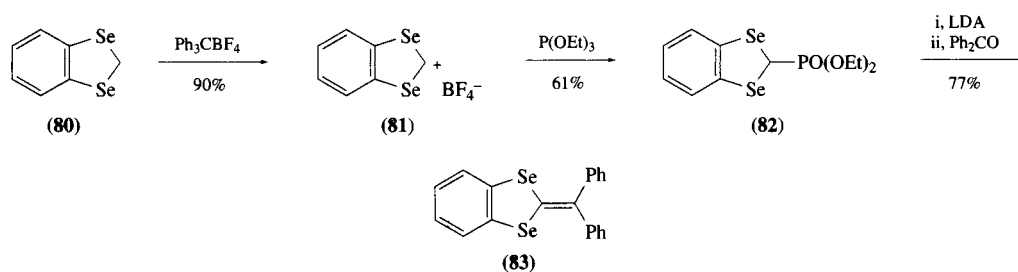
High yield of the phosphonate is also obtained from the benzo-1,3-diselenole (80). Treatment of phosphonate (82) with LDA and subsequent reaction of the ylide, for example with diphenyl ketone, produces the fulvene (83) in high yield (Scheme 16) ^{<88HCA1242>}.



Scheme 14

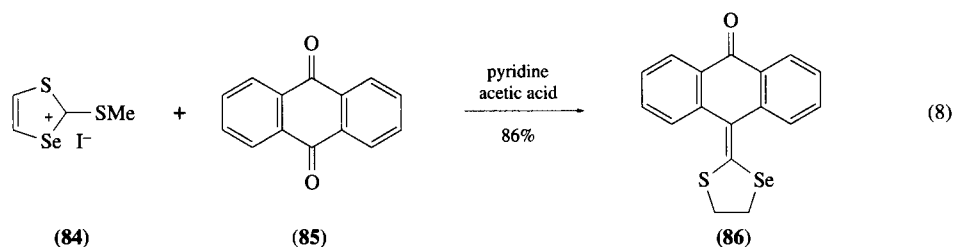


Scheme 15



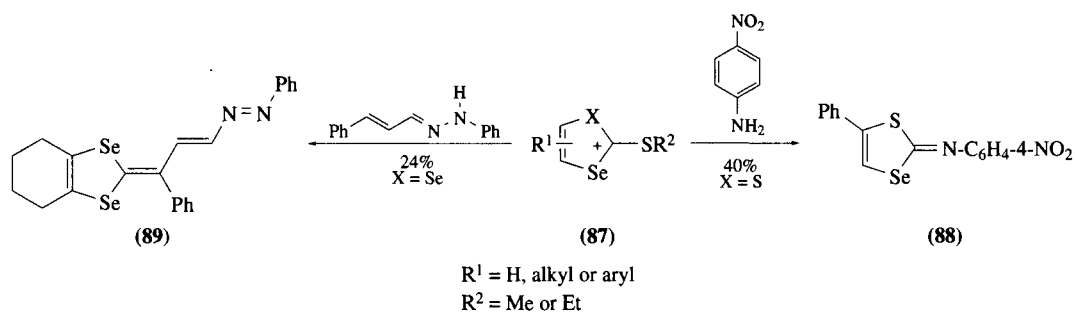
Scheme 16

When a 2-thiomethyl-1,3-selenothiolium iodide such as **(84)** reacts with an aryl ketone **(85)** in pyridine–acetic acid, fulvenes such as **(86)** are obtained; reaction with a Wittig–Horner reagent takes place at both carbonyl groups (Equation (8)) <90PAC473, 91JCS(P1)157>.



The 2-alkylthio group in a 1,3-dichalcogenolium cation **(87)** reacts with a 4-nitro-aniline nitrogen to give an imine **(88)**; subsequent reduction and diazotization give rise to diazo-dyes <88JPR590>. Related polymethin compounds and dyes are reported in patents <84EGP211356, 84EGP215782>.

Reaction of the 2-alkylthio-1,3-dichalcogenolium cation **(87)** with a conjugated hydrazone also takes place at the electrophilic 2-position, in this case resulting in formation of an extended fulvene system **(89)** (Scheme 17) <83S840>.

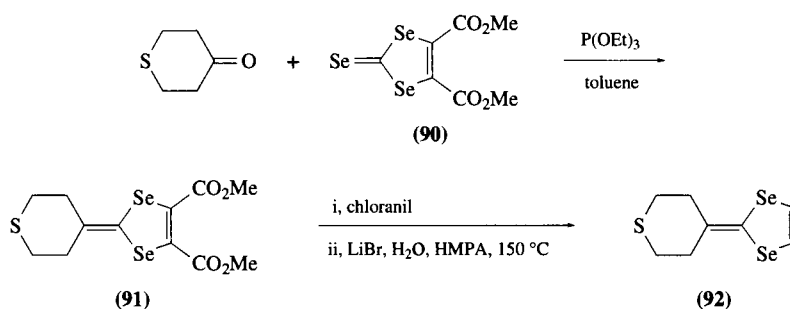


Scheme 17

Reaction of a 1,3-thiaselenole-2-thione with Meerwein's reagent yields the 2-ethylthio-1,3-thiaselenolium cation **(87)** in quantitative yield; subsequent reaction with the nucleophilic azide anion (sodium azide) leads to ring transformation via an azido intermediate <84S667> (cf. Scheme 9).

(ii) *Coupling reactions, dechalcogenations, formation of fulvenes and fulvalenes*

Coupling of an appropriate ketone, thione, or selone with selone **(90)** using a trialkyl phosphite (P(OR)_3 ; $\text{R} = \text{Me or Et}$) has been used extensively for preparation of fulvene systems. An example **(91)** from the dichalcogenafulvene series is shown in Scheme 18; hydrolysis and decarboxylation give the parent system **(92)** <88CC822, 93JCS(P2)1815>.

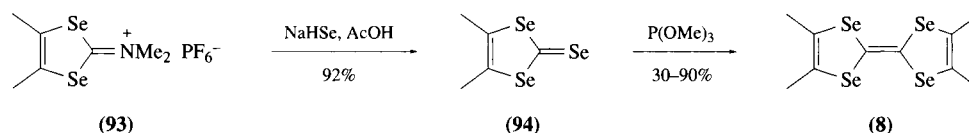


Scheme 18

(a) *Tetraselena- and thiaselenafulvalenes: preparation.* The preparation and functionalization of tetrathiafulvalenes is well advanced and includes numerous reports on physical properties of radical cation salts based on TTFs as mentioned in the introduction.

Selenium is a more electropositive element than sulfur and, in general, the chemistry of organic selenium compounds is more complicated when compared to the sulfur analogues. However, in spite of these difficulties a number of tetraselenafulvalenes and mixed sulfur- and selenafulvalenes have been prepared. A variety of methods have been used, such as: (i) coupling of a 1,3-dichalcogenole with a trialkyl phosphite or dicobalt octacarbonyl (Schemes 19, 22, 23); (ii) ring synthesis with direct formation of the fulvalene by reaction of a 1,2-dichalcogenolate with tetrahalogenoethylene (see ring formation, Section 3.14.9); (iii) coupling of a 2-methylene-1,3-diselenole with iodine/morpholine (Equation (9)); (iv) direct cycloaddition of an ethyne and a carbondichalcogene using high pressure (Scheme 40); and finally (v) functionalization of the parent tetraselenafulvalene system metallation with LDA to give tetralithiotetraselenafulvalene which is subsequently reacted with an electrophile (Scheme 12).

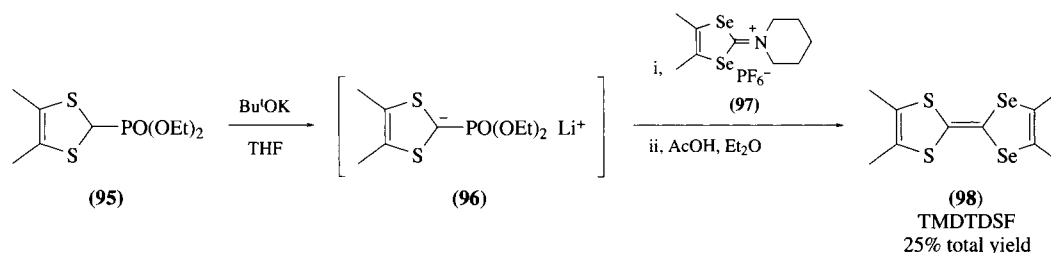
(b) *Trialkylphosphite coupling, symmetric and unsymmetric systems.* A good example of this type of reaction is the preparation of the two fundamental tetraselenafulvalenes, tetraselenafulvalene (**7**) (TSF) <84CC89> and tetramethyltetraselenafulvalene (**8**) (TMTSF) <83JOC388>; the reaction scheme for TMTSF is depicted in Scheme 19. It is important to note that the use of hydrogen selenide gas can be avoided by the use of hydrogen selenide prepared *in situ* as shown here for 4,5-dimethyl-1,3-diselenole-2-selone (**94**); in this case subsequent coupling with trimethylphosphite gives TMTSF (**8**).



Scheme 19

Mixed sulfur and selenium systems are usually prepared by phosphite coupling of two different 1,3-dichalcogenoles followed by separation of the product mixture. This procedure gives rather low yields of the desired coupling products in most cases.

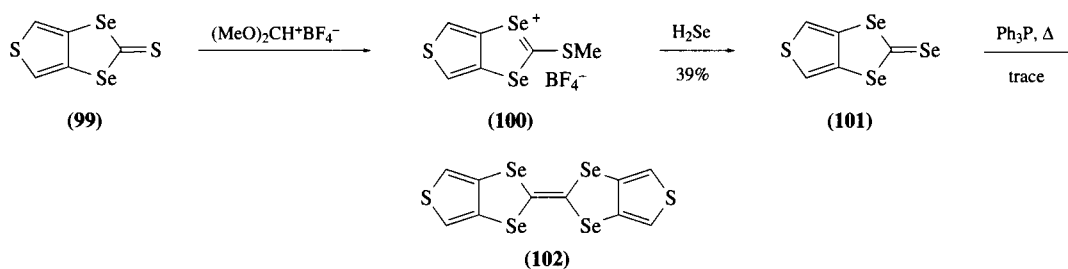
A direct and, in some cases, more effective method to a mixed system yielding a single fulvalene derivative, is based on reaction of a 1,3-dichalcogenole-2-immonium salt (**97**) with an appropriate Wittig–Horner reagent (**96**) as Scheme 20 demonstrates <89MI 314-01>.



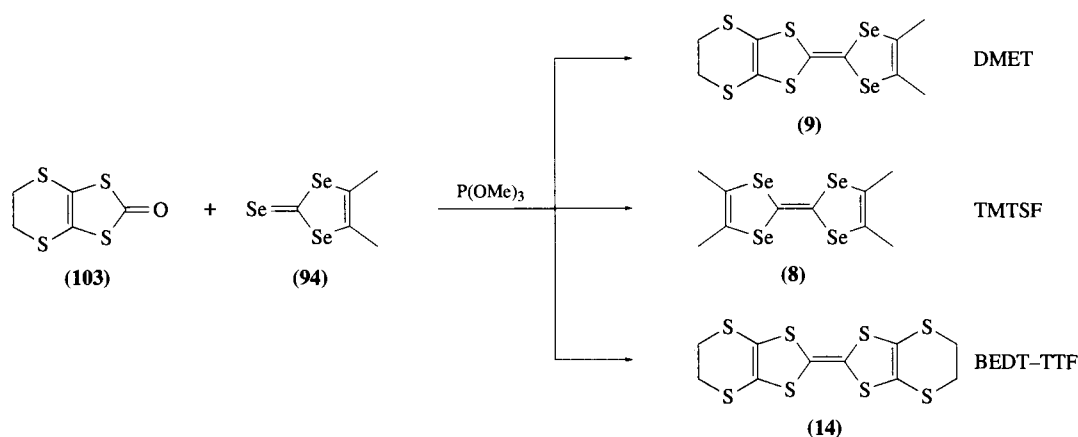
Scheme 20

Usually, coupling of a selone gives better yield than use of the corresponding thione; transformation of a thione into the selone can be done (as shown in Scheme 21) from a 2-alkylthio-1,3-diselenolylium cation (**100**) as the example demonstrates <83JOC4713>. Although coupling of the 1,3-dithiole-2-selone did give the expected TTF derivative, the tetraselenafulvalene (**102**) was only formed in trace amounts.

A large variety of unsymmetric fulvalene systems have been prepared via phosphite-mediated coupling and subsequent separation of the reaction mixture, either by fractionated crystallization or by chromatography <83CC1477, 86SM339, 93SM295>. The ratio of the isomers is dependent on reaction conditions and substituents; a good example is described in Scheme 21. The mixed sulfur-selena fulvalene system DMET (**9**) is prepared in a phosphite cross-coupling between a 2-oxo- (ET) (**103**) and a 1,3-dichalcogenole-2-selone (**94**). Distribution between the three reaction products was found to be: (**9**):(**8**):(**14**) = 1:2:10 (Scheme 22) <86TL4315>.



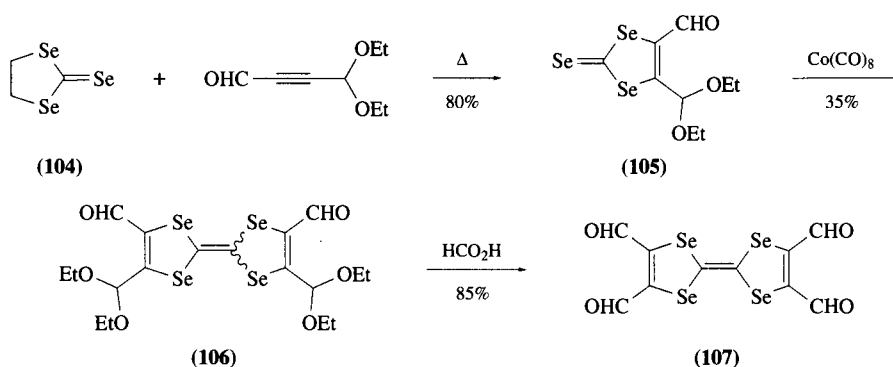
Scheme 21



Scheme 22

DMET (**9**) is a hybrid between two important fulvalene systems which have both previously given rise to superconductors, and this is also the case for the radical cation salt, (DMET)₂Au(CN)₂, see <86CC1472, 87CL1279, 87CL931>; for combination of DMET in other salts see also <87MI 314-02, 87MI 314-03, 87MI 314-04>. Related tetrachalcogenafulvalene systems are described <88TL2185, 91SM2049, 93CL1851, 93SM1978, 93SM2073>.

A final example is the synthesis of the important tetraformyltetraselenafulvalene (**107**) from the monoacetal (**105**) using dicobalt octacarbonyl as the coupling reagent. This reagent can be used where a functional group in the 1,3-dichalcogenole-2-thione or -selone is not compatible with the use of a trialkyl phosphite reagent (Scheme 23) <89CC1520>.



Scheme 23

3.14.6 REACTIVITY OF NONCONJUGATED RINGS

Reactivity of the formally nonconjugated 1,3-dichalcogenole rings is discussed in Section 3.14.5 together with the reactivity of the fully conjugated rings. An overview of the different oxidation stages of the 1,3-dichalcogenole ring system is seen in Figure 1.

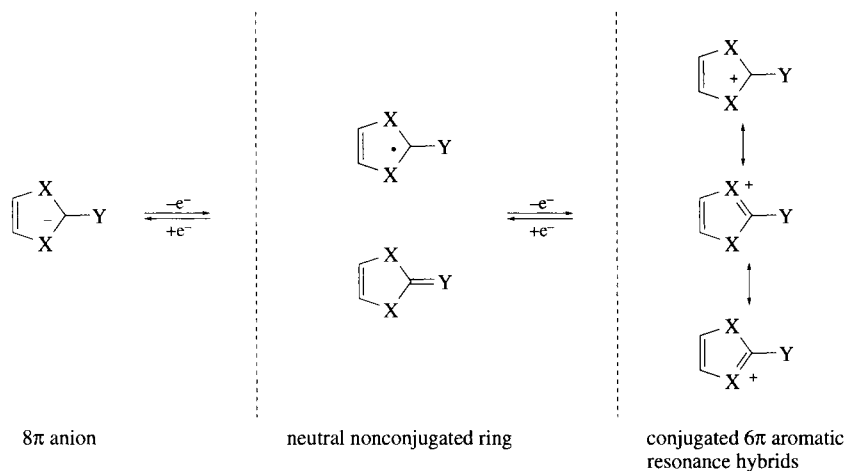
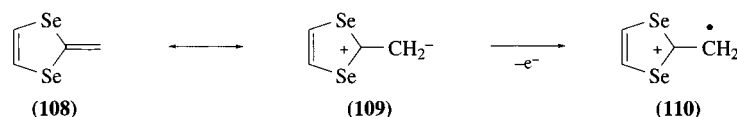


Figure 1

3.14.7 REACTIONS OF SUBSTITUENTS ATTACHED TO RING CARBON ATOMS

3.14.7.1 Reactions of Substituents Attached to Carbon-2

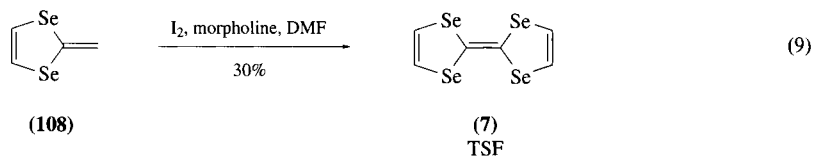
2-Methylene-1,3-diselenole (**108**) is obtained in high yield from acetaldehyde semicarbazone using the selenadiazole route (Scheme 25, see also Scheme 49, Section 3.14.10.1.2). The exocyclic methylene in (**108**) is quite reactive; protonation gives a highly reactive 2-methyl-1,3-diselenolylum ion resulting in polymerization <88JOC3529>. However, the methylene carbon has nucleophilic character due to the contribution from the dipolar mesomeric structure (Scheme 24).



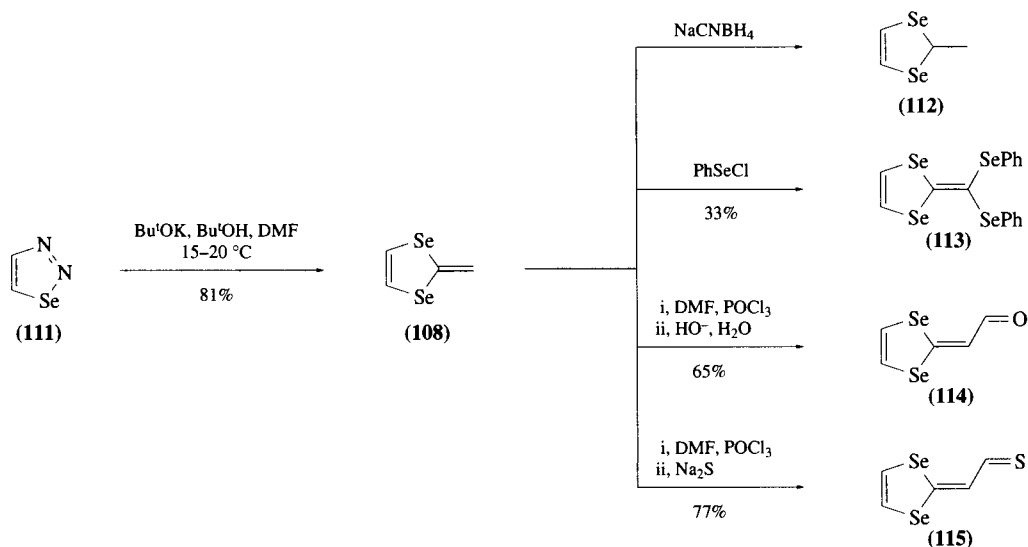
Scheme 24

Electrophilic substitution or reaction via electron transfer at the methylene carbon gives a number of products with electrophiles. Note that the fulvenealdehyde (**114**) and -thioaldehyde (**115**) are stabilized as “push-pull” systems (Scheme 25) <88JOC3529, 87TL5635, 94POL675>.

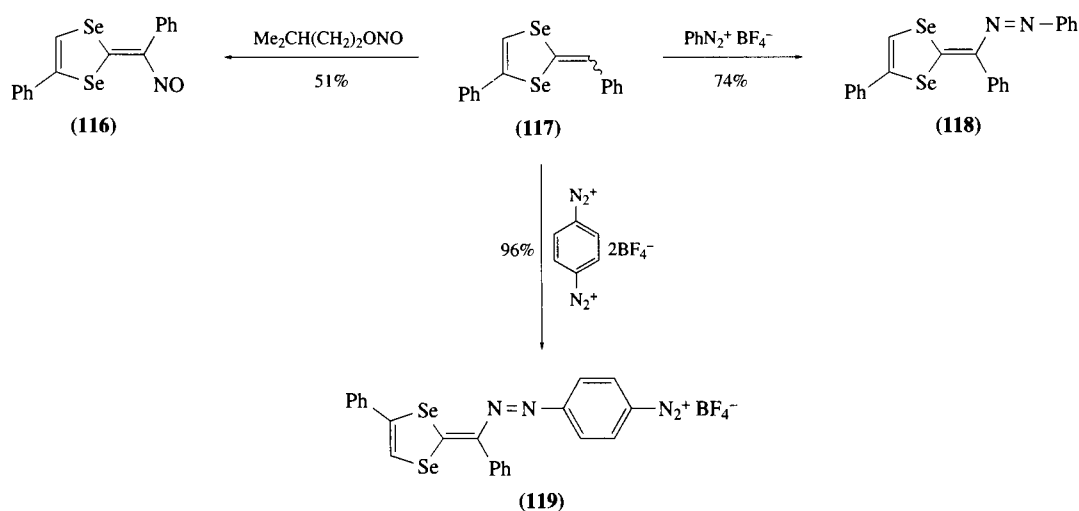
An interesting reaction is the following in which the parent tetraselenafulvalene (**7**) (TSF) is obtained from 2-methylene-1,3-diselenole (**108**) in modest yield. The mechanism probably involves a cycloaddition step (Equation (9)) <87TL5635>.



In the phenyl-substituted fulvene (**117**), reaction with isoamyl nitrite or the phenyl diazonium cation gives the corresponding substitution products (**116**) and (**118**) <88JOC3529>. The reaction with diazonium salts has also been used for the preparation of polymethin-type azo-dyes (**119**) in high yield (Scheme 26) <90JPR43>.

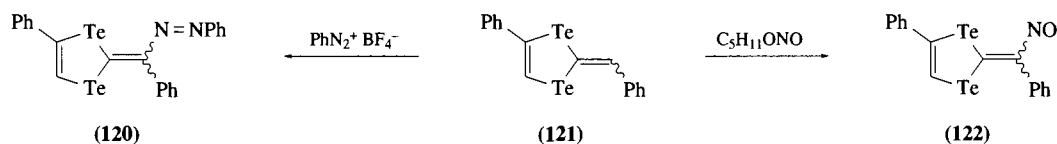


Scheme 25



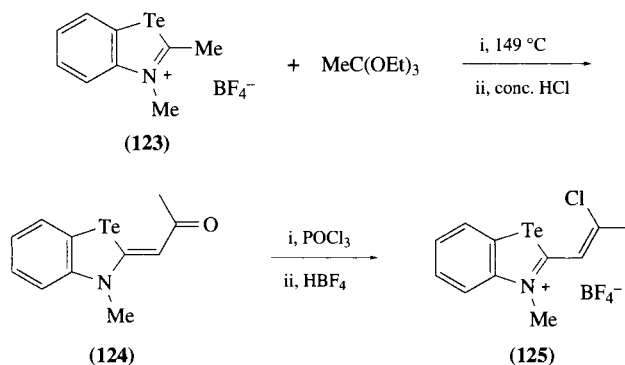
Scheme 26

2,6-diphenyl-1,4-ditellurazulene (121) reacts with electrophiles such as pentyl nitrite and benzene-diazonium tetrafluoroborate analogously to the corresponding selenium and sulfur derivatives (Scheme 27) [81CC828].



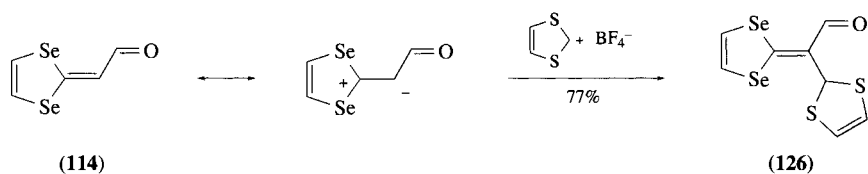
Scheme 27

The methyl group in the 2-methyl-1,3-benzotellurazolium cation (123) is activated and will condense with orthoesters; subsequent reaction of (124) with POCl_3 gives a 1,3-benzotellurazolium derivative (125). These compounds are important starting materials for polymethin dyes (Scheme 28) [86USP4575483].



Scheme 28

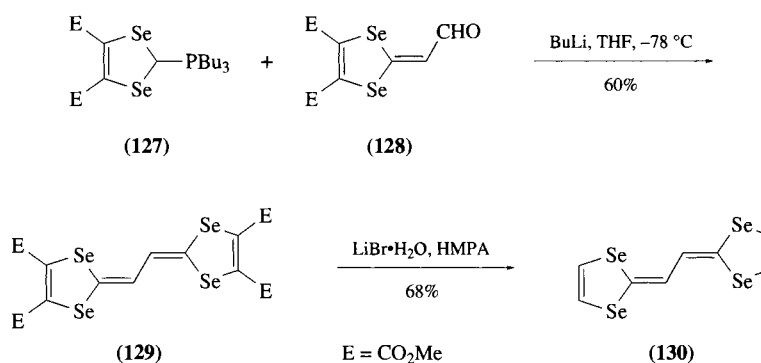
An important type of extension (alkenation) of the 2-(formylmethylene)fulvene (**114**) system is possible using a dithiolylum cation resulting in formation of (**126**) <88JOC3529>.



Scheme 29

3.14.7.1.1 Extended tetrachalcogenafulvalenes

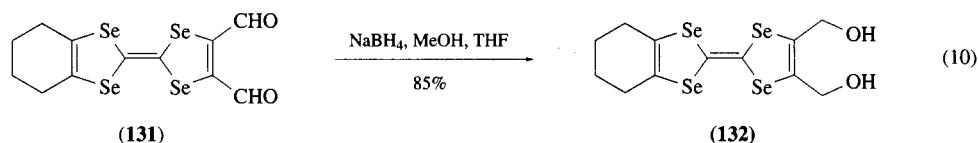
Ethylene analogues of tetrachalcogenafulvalenes such as (**130**) are of interest as π -donors having a more extended π -system. Chemistry developed in the sulfur series can also be used in the corresponding selenafulvalenes, and extended systems can be obtained via Wittig or Wittig–Horner alkenation of an appropriate ketone or aldehyde (see, for example, Equation (8)). The ester groups in (**129**) can be hydrolyzed and decarboxylated with LiBr/HMPA to give the parent system (**130**) in fair yield (Scheme 30) <84JAP59161376, 84TL4227, 87SM569, 89CM535>.



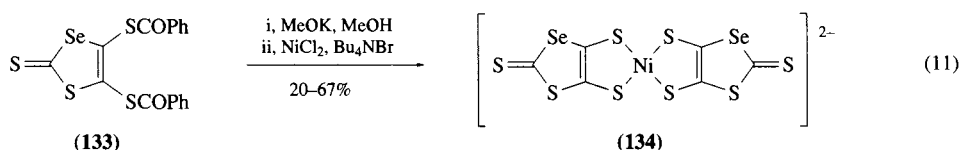
Scheme 30

3.14.7.2 Reactions of Substituents Attached to Ring Carbon-4 and Carbon-5

The formyl group in the tetrachalcogenafulvalene system (**131**) reacts in the normal way, thus borohydride reduction gives access to the corresponding hydroxymethyl-substituted fulvalene (**132**) in excellent yield (Equation (10)) <89CC1520, 93SM1978, 93SM2073>.



As already pointed out, there is considerable interest in metal complexes of 1,3-dithiole-2-thione-4,5-dithiolates (**54**) (DMIT) and in chalcogene analogues such as 1,3-diselenole-2-selone-4,5-diselenate (**55**) (DSIT), due to their use as starting materials for organic conductors <91CCR115, 91MI 314-01, 91RHA171, 92CCR99>. The stable 4,5-dibenzoates of these compounds such as (**133**) (see Scheme 11) can easily be hydrolyzed with ethoxide, and subsequently used for complex formation to give (**134**) as shown in the example (Equation (11)), or for preparation of S-alkylated derivatives by realkylation of the 1,3-thiaselenolate <90ZAAC(581)59>.



3.14.8 REACTIVITY OF SUBSTITUENTS ATTACHED TO RING HETEROATOMS

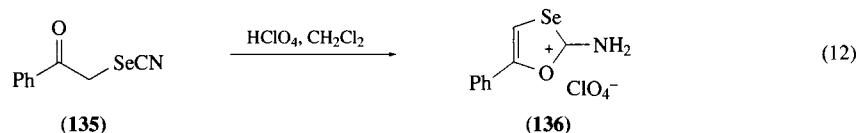
There are no reports on reactivity of substituents attached to the ring chalcogen atoms.

3.14.9 RING SYNTHESIS CLASSIFIED BY NUMBER OF RING ATOMS IN EACH COMPONENT

3.14.9.1 Ring Synthesis from Nonheterocyclic Compounds

3.14.9.1.1 Formation of one bond

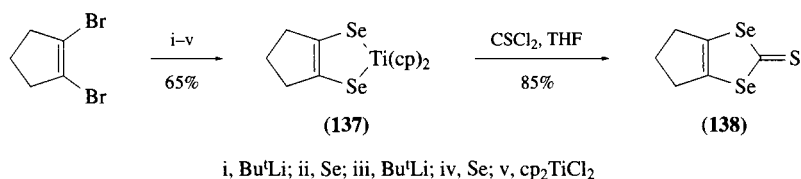
Selenocyanoketones such as (**135**) give high yields of 1,3-oxaselenolylium salts (**136**) (see Equation (12)) <89EGP270530>.



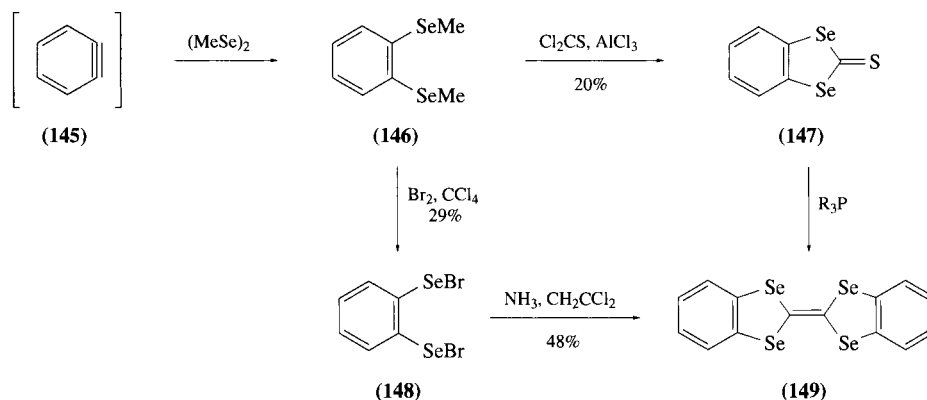
3.14.9.1.2 Formation of two bonds

(i) Formation of two bonds from [4 + 1] atom fragments

The classical route to many 1,3-dichalcogenole-2-thiones starts from a vicinal dihalogenoethene followed by lithiation and reaction with selenium; the intermediate diselenate may be isolated as a titanium-biscyclopentadienyl complex (**137**) as shown in the example in Scheme 31 <93CL1851>.



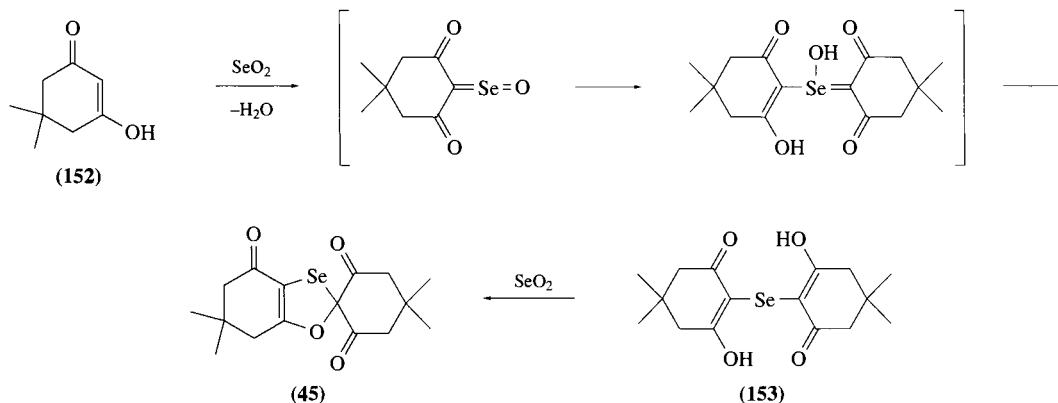
Scheme 31



Scheme 35

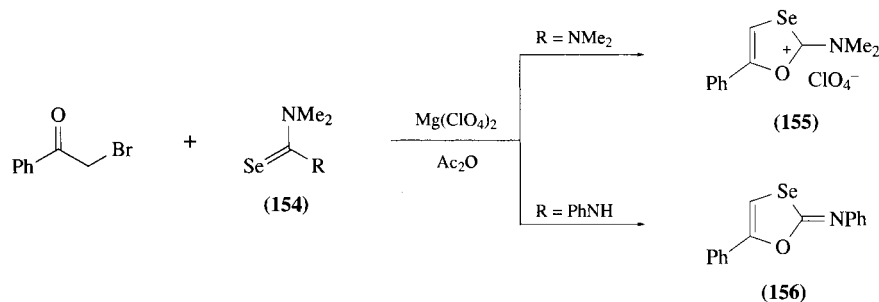
(ii) Formation of two bonds from [3 + 2] atom fragments

(a) *1,3-oxaselenoles*. Spiro 1,3-oxaselenoles are obtained by selenium dioxide oxidation of cyclohexane-1,3-dione such as (152) in a (2 + 3) two-component synthesis. The reaction pathway involves a Pummerer rearrangement, as selenium dioxide oxidation of (153) also gives rise to (45) (Scheme 36) <83JCS(P1)333>.



Scheme 36

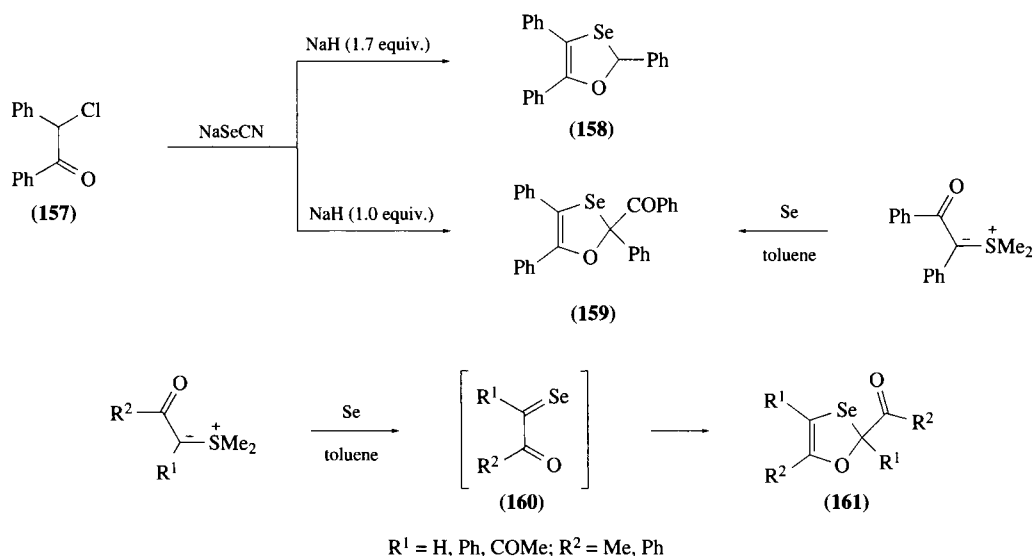
A fairly general [2 + 3] reaction based on selenourea derivatives and α -selenoketones gives high yields of either 1,3-oxaselenoles (156) or the corresponding 1,3-oxaselenolylium salts (155) depending on the reaction conditions (Scheme 37) <87ZC95, 88EGP254734, 89EGP270530>.



Scheme 37

The same type of reaction using desylchloride (157) and sodiumselenocyanate yields aryl 1,3-oxaselenoles; depending on the ratio of base, either (158) or (159) is obtained <84JOC2057>.

Cycloaddition of selenium and carbonyl stabilized sulfonium ylides gives 1,3-oxaselenoles in high yield via an α -oxoselenocarbonyl derivative (**160**) (Scheme 38) <85TL2201, 87TL4423>.



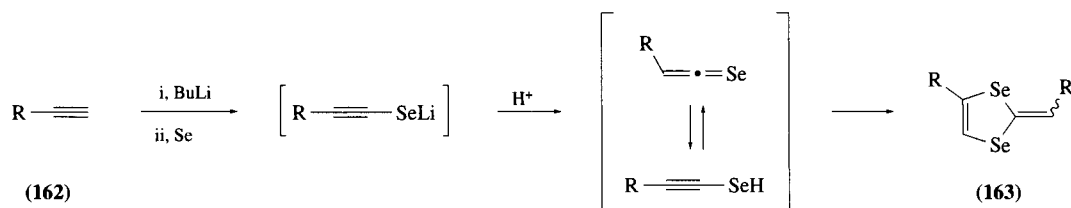
Scheme 38

Potassium selenocyanate in acetic anhydride reacts with epoxides to give 2-acetyl-amino-1,3-oxaselenole derivatives <93JCS(P2)351>. Low yields of 1,3-oxaselenoles are obtained in the reaction of selenium with ethyne in aqueous base <89ZOR2283>.

(b) *1,3-Thiaselenoles and 1,3-diselenoles*. A full account of the electrochemical reduction of CSSe and CSe_2 in DMF to 1,3-dichalcogeno-2-chalcogenon-4,5-dichalcogenolate (including the important starting material DSIT) and a complete preparative procedure including the stable dibenzoate is reported <87ZAAC(544)199> (see Scheme 11).

If an ethyne (**162**) is used as starting material and the reaction is carried out without the presence of CX_2 ($\text{X} = \text{S}$ or Se), the cycloaddition will take place as a 1,3-anionic cycloaddition between the ketene-intermediate and the acetylide, resulting in formation of a mixture of the (*Z*)- and (*E*)-fulvenes (**163**) (Scheme 39) <81ZOR667, 90BCJ835, 93CL1469>. See also Scheme 49.

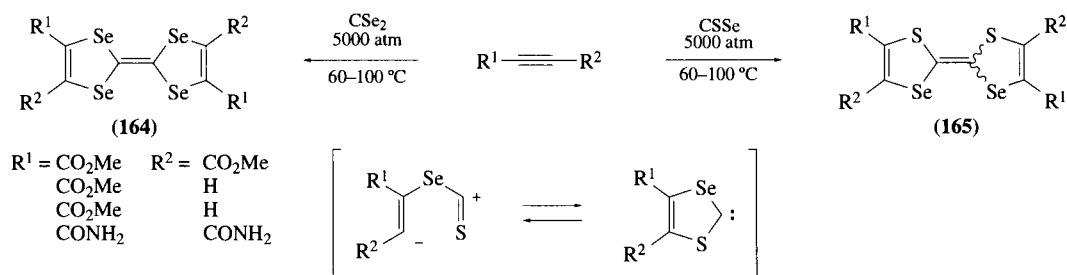
In this reaction, improved yield (79%) with formation of the (*Z*)-isomer of (**163**) is obtained when the reaction is carried out in the presence of SnCl_2 ($\text{R} = \text{Ph}$) <89ZOR524>.



Scheme 39

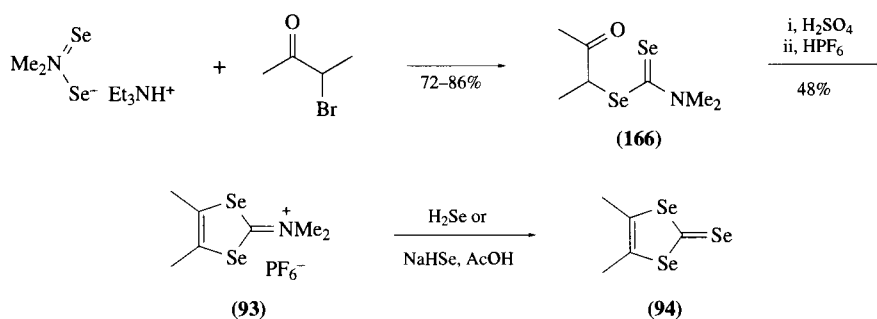
(c) *Direct formation of a fulvalene system, cycloaddition*. Mixed tetrachalcogenafulvalenes (**164**) and (**165**) can be prepared in an apparently effective way by cycloaddition under very high pressure (5000 atm) of ethynes substituted with electron-withdrawing groups and carbon disulfide, diselenide, or the mixed system carbosulfoselenide. This one-pot method gives high yields as compared to most of the fulvalene coupling reactions described previously (see, for example, Scheme 22). The reaction mechanism in the high pressure reaction is likely to involve a carbene species of the type shown in Scheme 40 <82H(18)191>.

Direct cyclization to the 1,3-diselenolylium cation takes place when a β -formyl-*N,N*-dialkyl-diselenocarbamate is treated with acid; subsequent reaction with hydrogen selenide gives the parent 1,3-diselenole-2-selone <84CC89>. Excellent yield (83%) of 4,5-dimethyl-1,3-diselenole-2-selone (**94**)



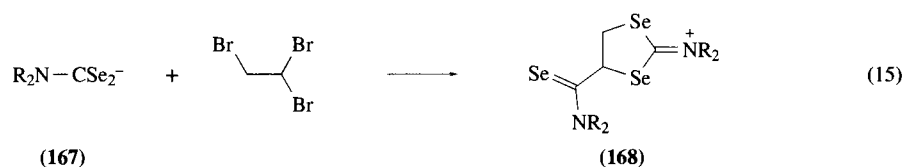
Scheme 40

by subsequent treatment with H_2Se is obtained following this route using the method described in (Scheme 41) <83JOC388, 86IS131>. See also Scheme 19.

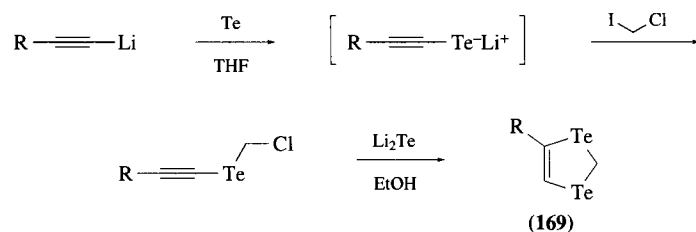


Scheme 41

Saturated 1,3-diselenolane-2-iminium salts (**168**) can be prepared in high yield (85%, $R = \text{---}(\text{CH}_2)_4\text{---}$) from *N,N*-dialkylaminocarbodiselenoic acid *N,N*-dialkylammonium salts (**167**) by reaction with 1,1,2-tribromoethane (Equation (15)) <93USP5237067>.



(d) *1,3-Ditelluroles*. The main route to 1,3-ditelluroles (**169**) is based on the intramolecular nucleophilic addition of a telluroate anion to a triple bond (Scheme 42) <82TL1531>.

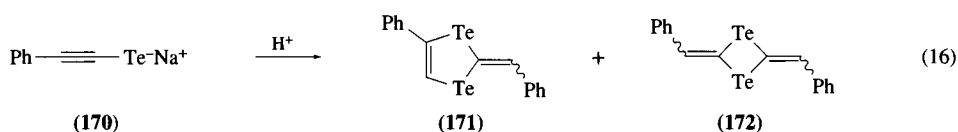


$R = \text{H, Me, Bu}^t, \text{Ph}$ = (67)
4–65% yield

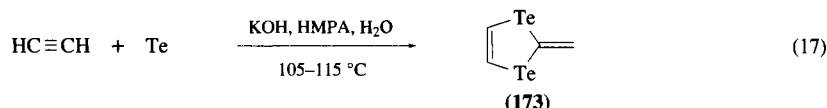
Scheme 42

In the now classical synthesis, protonation of sodium phenyl ethynyltelluroate (**170**) yields mixtures of the isomeric ditellurofulvene (**171**) <81CC828>; however, the four-membered 1,3-ditelluraethane derivative (**172**) becomes the main product when the reaction is carried out in HCl /

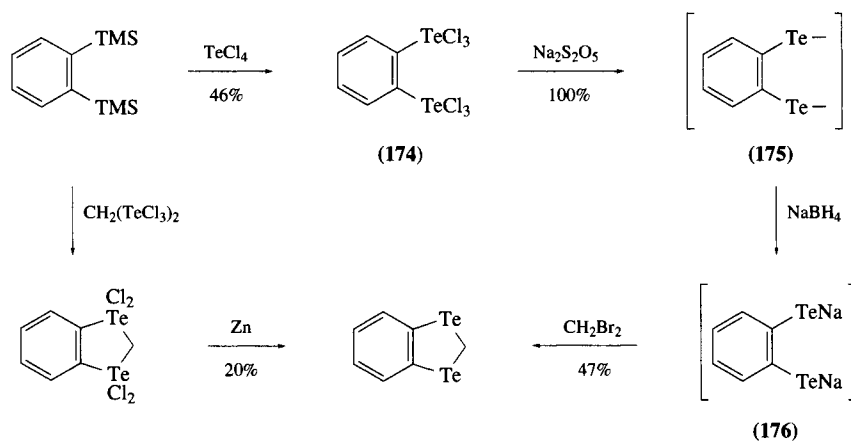
diethylether <81TL1495, 89TL441>. (For reaction of phenylethynyl tellurolate (**170**) with CS₂, see (Equation (16)) <81ZOR2064>).



This type of reaction on an ethyne only gives a 1% yield of the parent 2-methylene-1,3-ditellurole (**173**) <91SUL143>; lower temperature favors the isomeric 1,4-ditellurine (Equation (17)).

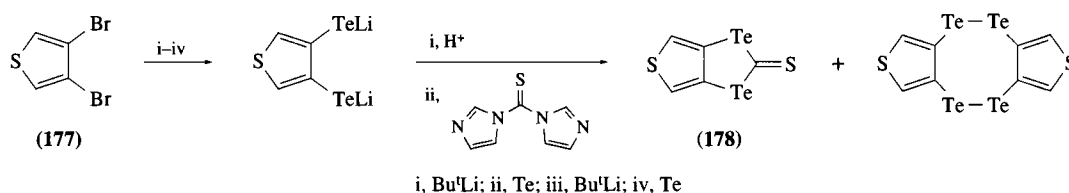


(e) *Benzo-1,3-ditelluroles*. Benzo-1,3-ditellurole (**176**) can be prepared starting from *o*-dihalo-genobenzene via the *o*-bis(trichlorotelluro)benzene (**174**) which, in quantitative yield, gives poly(*o*-phenylditelluride) (**175**) (Scheme 43) <88KGS1144, 91HAC307>.



Scheme 43

A related synthesis, starting from a 3,4-dibromothiophene (**177**), leads to the thieno[3,4-*d*][1,3]ditellurole-2-thione (**178**) <83JOC4713> with the dimer as an inseparable by-product (Scheme 44).

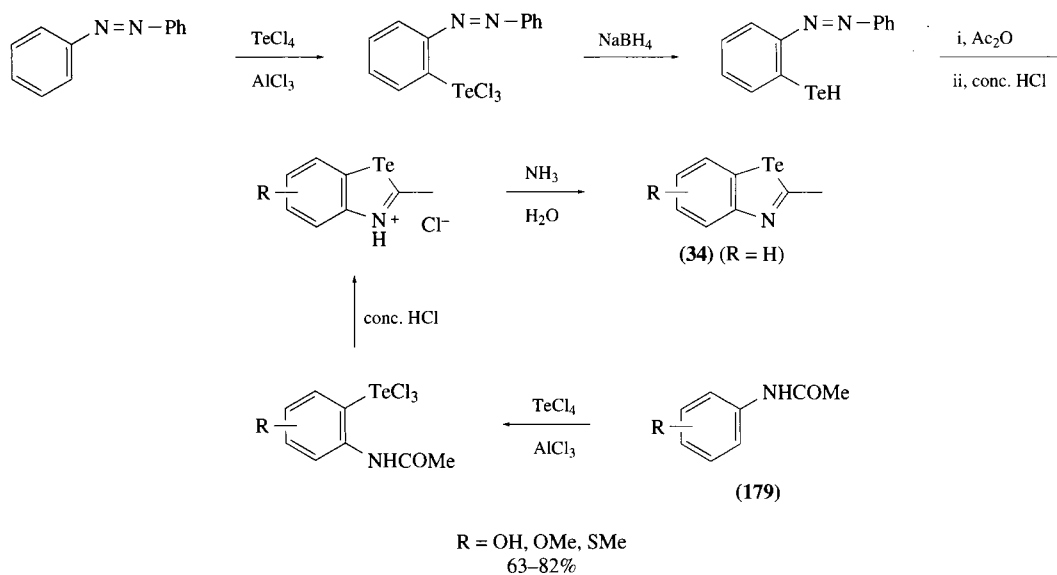


Scheme 44

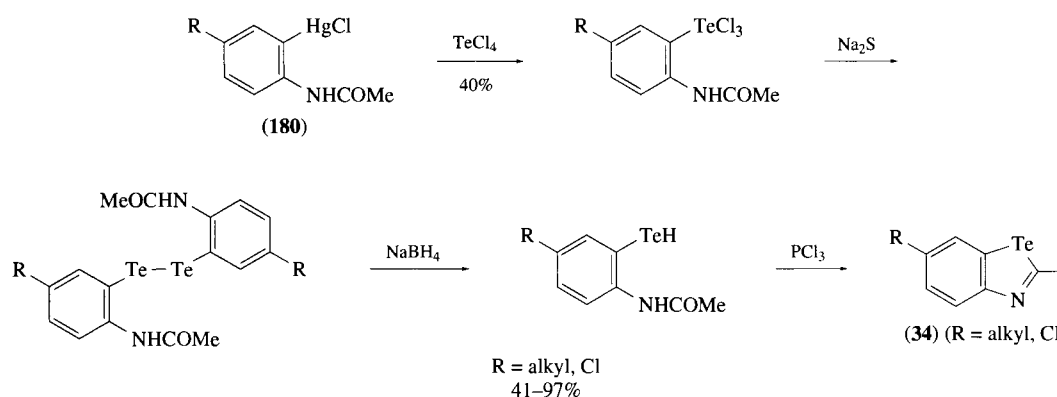
(f) *1,3-Benzotellurazoles*. 1,3-Benzotellurazoles are of interest as dyes and related uses in photography, and a number of synthetic methods have been developed for this class of heterocycles.

The main reaction pathway in their synthesis involves a 2-aminobenzene tellurole derivative which is subsequently acylated and cyclized with acid. It is also possible to start from an acetanilide (**179**) and tellurium tetrachloride <86USP4607000, 87USP4661438>. This method is compatible with a variety of substituents (Scheme 45).

A related method starts from an appropriate 2-aminophenyl mercury chloride derivative (**180**) (Scheme 46) <88PS(38)121>.

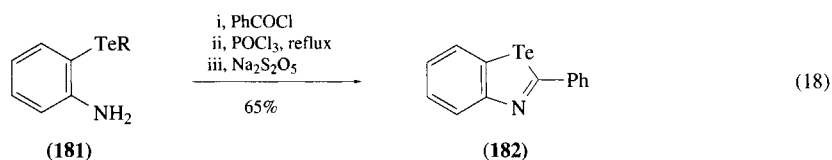


Scheme 45



Scheme 46

Finally, 2-phenyl-1,3-benzotellurazole (182) can be obtained by cyclization of a 2-(*N*-acylamino)-phenylalkyl telluride, derived from (181) in a three-step reaction (Equation (18)) <83TL5873, 88KGS276>.



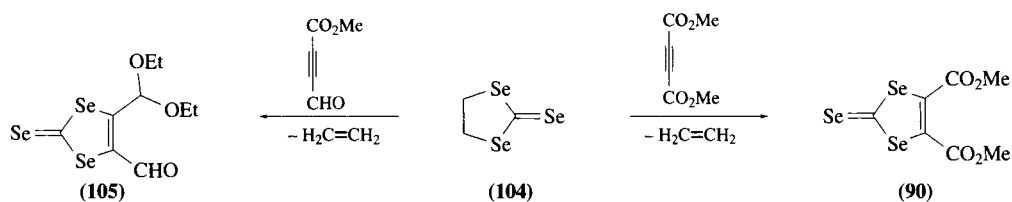
(g) 1,3-Tellurazoles, nonfused. Knowledge of tellurium chemistry and tellurium-containing heterocycles has been much developed in the last decade and, for example, a number of thienoannulated and nonannulated 1,3-tellurazoles are described in patent literature as being useful for color photography materials and in photographic imaging. Examples of this type are represented in patents <86JAP61272734, 86JAP61277942, 86JAP61282834, 87JAP62254146>.

3.14.10 RING SYNTHESIS BY TRANSFORMATION OF ANOTHER RING

3.14.10.1 Synthesis Involving Heterocyclic Compounds

3.14.10.1.1 The ethyne diselenolane cycloaddition route

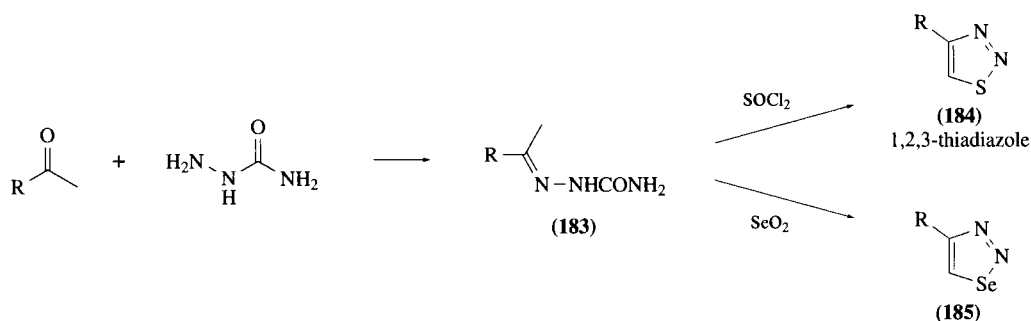
Using a classical multistep route, 4- and 5-substituted-1,3-diseleno-2-selones (**105**) and (**90**) are obtained by cycloaddition of 1,3-diselenolane-2-selone (**104**) and an ethyne ($R = CO_2Me$); hydrolysis in hydrochloric acid followed by decarboxylation in pyridine yield the parent 1,3-diselenole-2-selone (**27**) <76IZV179>. This cycloaddition route is quite versatile as it gives access to a starting material for the important tetraformyltetraselenafulvalene; the reaction is carried out in refluxing toluene and gives the cycloaddition product in 35% yield (Scheme 47) <89CC1520>.



Scheme 47

3.14.10.1.2 The 1,2,3-selenadiazole route

The thiadiazole route to 1,3-dithiole-2-thiones and 1,3-diselenole-2-thiones or selones is quite versatile as 1,2,3-thia- (**184**) or selenadiazoles (**185**) are readily prepared from an appropriate methyl ketone semicarbazone (**183**) (Scheme 48).



Scheme 48

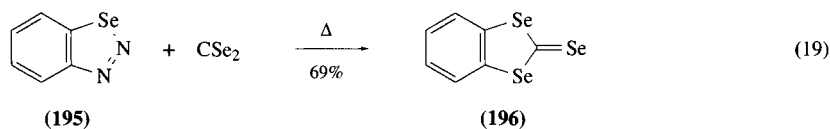
Like their sulfur analogues, the 1,2,3-selenadiazoles are readily deprotonated at C-5 with KOH in ethanol or dioxane with subsequent ring opening and loss of N_2 . Corresponding thermolysis or photolysis, in the presence of selenium, eventually gives low yields of fulvenes amongst other products. The general scheme outlines the scope of these reactions by cycloaddition from (**186**).

The parent 1,3-diselenole-2-selone (**27**) may be prepared in a convenient method via the 1,2,3-selenadiazole route by reaction of 1,2,3-selenadiazole (**185**; $R = H$) with potassium *t*-butoxide in the presence of carbon diselenide to give (**27**) in 40% yield <86ZC138>.

Scheme 49 shows the general scheme of the selenadiazole route for the formation of 1,3-dichalcogenoles by cycloaddition from (**186**). The references corresponding to each reaction are: (**187**), (**188**) <84S512>; (**189**) <82ZOR514, 91ZOR1394>; (**190**) <90ZOR179>; (**191**), (**192**) <86JHC(23)861, 88JPO317>; (**193**) <89NKK1447>; (**194**) <87JOM(334)C39, 88CL657, 89LA435, 90MI 314-02>.

The selenadiazole route is superior to the lithium acetylide route (Scheme 39) <75JOC387>.

Entry into the benzo-1,3-diselena-2-selone (**196**) series is possible by heating 1,2,3-benzo-selenadiazole (**195**) with CSe_2 <83CC295> (preparation of carbondiselenide, see Equation (19) <72IJS(A)133, 81IC856>).



3.14.11 SYNTHESIS OF A PARTICULAR CLASS OF COMPOUNDS AND A CRITICAL COMPARISON OF THE VARIOUS ROUTES AVAILABLE

One of the most versatile preparations of the 1,3-diselenole ring system is the 1,3-cycloaddition. An overview of the cycloaddition route of 1,3-diselenoles either from a 1,2,3-selenadiazole or by the acetylide route is given in Scheme 49.

3.14.12 IMPORTANT COMPOUNDS AND APPLICATIONS

Aspects of the application of a number of 1,3-dichalcogenole systems and especially the corresponding fulvalenes have already been mentioned in Section 3.14.4.1. Scheme 3 gives a compilation of the presently known sulfur and selenium tetrachalcogenafulvalenes which have given rise to

superconductors. Furthermore, Table 3 gives a compilation of the T_c temperature for the presently known selenium-based superconductors, while the half-wave oxidation potentials for a range of selected tetrachalcogenafulvalenes are shown in Table 2.

A comprehensive discussion and introduction to organic conductors including tetraselenafulvalenes is found in CHEC-I (84CHEC-I(1)347).

3.15

Two Adjacent Heteroatoms with at least One Phosphorus, Arsenic, or Antimony

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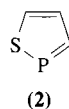
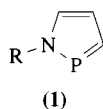
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3.15.2	SPECTRA, STRUCTURE, AND BONDING	710
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3.15.4	1,2-THIAPHOSPHOLES	711
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3.15.1 INTRODUCTION

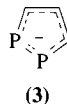
Aside from very rare exceptions, full π -conjugation in a phosphorus heterocycle necessitates the phosphorus ring member(s) to be two-coordinate. This chapter as well as the other chapters on five-membered phosphorus heterocycles (see 3.16 and 4.22) will therefore concentrate on such systems, generally termed heterophospholes $\langle$ B-90MI 315-01 $\rangle$. The same applies to the heterocycles of the heavier congeners of phosphorus.

Fully unsaturated five-membered ring systems with one other heteroatom adjacent to phosphorus have only been known only since 1986 $\langle$ 86CB410 $\rangle$ and therefore no representative is contained in *Comprehensive Heterocyclic Chemistry, First Edition* (CHEC-I) $\langle$ 84CHEC-I(1)523 $\rangle$. They include now 1,2-azaphospholes (**1**) and 1,2-thiaphospholes (**2**) and are mentioned in several reviews $\langle$ B-89MI 315-01, B-90MI 315-01 $\rangle$. The known compounds are listed in a compilation of phosphorus-31 chemical shifts $\langle$ 88PS(36)217 $\rangle$ and in a review on anellated heterophospholes $\langle$ 94T7675 $\rangle$.

In five-membered aromatic rings with several phosphorus atoms $\langle$ 94CCR1 $\rangle$ all of them must be



two-coordinate and, if they are the only heteroatoms, the ring consequently must be negatively charged. Rings with two adjacent phosphorus atoms, i.e. 1,2-diphospholides (**3**), are known as ferrocene derivatives and since very recently also as lithium salts or as zwitterions.



3.15.2 SPECTRA, STRUCTURE, AND BONDING

3.15.2.1 Quantum Chemical Calculations

Among other azaphospholes 1,2-azaphosphole (**1**) has been studied for an isodesmic ring fragmentation reaction and compared to pyrrole and pyrazole. The calculated heats suggest that in conjugative interaction $\text{P}=\text{C}$ is more comparable to $\text{C}=\text{C}$ than to $\text{N}=\text{C}$ <93JPC4011>.

The phosphorus analogues of the cyclopentadienyl anion $\text{P}_n(\text{CH})_{5-n}^-$ have been examined by SINDO1 for their aromaticity. For $n=0$ and 5 the aromaticity index is comparable to that of benzene. Of the two diphospholides ($n=2$), the 1,3-isomer (88%) has a slightly higher relative aromaticity than the 1,2-isomer (86%) <92JOC3694>.

3.15.2.2 X-ray Structure Analyses

The structure of the five-membered ring of the diphosphonio-1,2-diphospholide (**35**) is in accord with a cyclic delocalized system. Its $\text{P}-\text{P}$ -bond length of 207.7(1) pm is only somewhat longer than that of acyclic *trans*-diphosphenes (202–204 pm). On bromination it widens to 221.6(2) pm <96CEJ221>.

3.15.2.3 Phosphorus-31 NMR Spectra

A low field chemical shift is characteristic for heterophospholes in general with most of the shifts between $\delta^{31}\text{P} = 50$ and 300 <88PS(36)217, B-90MI 315-02, B-91MI 315-01>. Within this range, the shift depends mainly on the ring members adjacent to phosphorus <B-90MI 315-01> and is found for 1,2-azaphospholes at $\delta^{31}\text{P} = 180$ –238 and 1,2-thiaphospholes at $\delta^{31}\text{P} = 198$ –211.

1,2-Diphospholide anions (**30**) are characterized by $\delta^{31}\text{P} = 152$ –206 and by a large coupling constant $^1J_{\text{PP}}$ of roughly 440 Hz. The signals of their mono- and bis(triphenylphosphonio) derivatives (**39**) and (**35**) are found much more downfield at $\delta^{31}\text{P} = 218$ –317 and show a still increased coupling $^1J_{\text{PP}} = 465$ –480 Hz <94AG708, 94AG(E)663, 96CEJ221>. Methylation of a ring phosphorus atom in (**35**) apparently does not destroy the π^6 system as in the case of other phospholides and leaves the $\text{P}-\text{P}$ bond length unchanged <96CB>.

3.15.2.4 Proton and Carbon-13 NMR Spectra

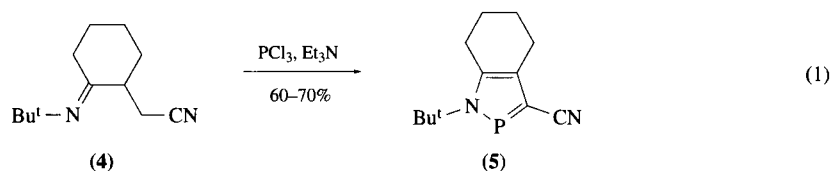
Proton and carbon-13 NMR data is available for 1,2-azaphospholes (**10**) and (**11**) <86CB410>, 1,2-benzazaphospholes (**12**) <89PS(46)31>, 1,2-thiaphospholes (**20**) <94BCJ2785>, dihydro-1,2-diphospholes (**29**) <95AG623, 95AG(E)590>, and for the 1,2-diphosphaindenide (**39**) <94AG708, 94AG(E)663>.

3.15.2.5 Mass Spectra

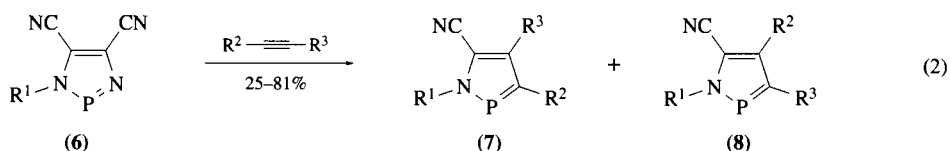
In the mass spectra of 1,2-thiaphospholes (**14**) and (**20**), M^+ gives the base peak and $\text{M}^+ - \text{PS}$ a characteristic fragment peak <88TL4535, 94BCJ2785>. The base peak of lithium diphospholides (**30**; $\text{R} = \text{Et}, \text{Ph}$) corresponds to the mass of the anion <95AG623, 95AG(E)590>.

3.15.3 1,2-AZAPHOSPHOLES

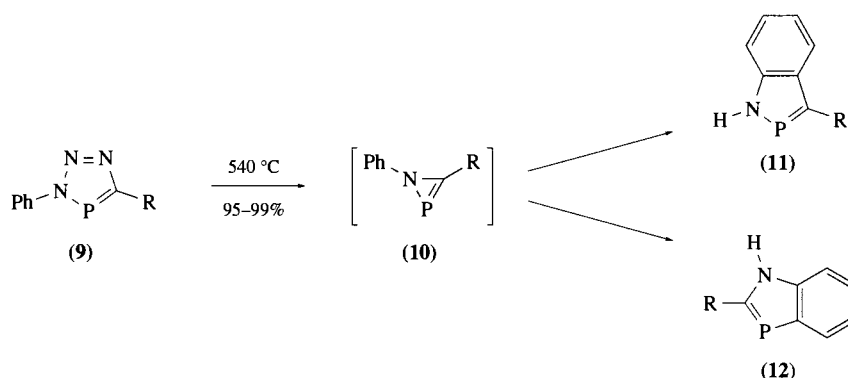
1,2-Azaphospholes such as (5) with a cyano, nitroaryl, or other electron-withdrawing substituent in 3-position can be prepared by condensating the appropriate β -methylene ketimine (4) with PCl_3 or PBr_3 and a base (89EGP268704). The yield can be improved if DABCO is used in place of triethylamine (Equation (1)).



4,5-Dicyano-1,3,2-diazaphospholes (6; $\text{R}^1 = \text{Me}$, TMS) are converted to 5-cyano-1,2-azaphosphopholes (1,2-azaphosphole-5-carbonitriles) (7) by reaction with alkynes $\text{R}^2\text{-C}\equiv\text{C-R}^3$, $\text{R}^2/\text{R}^3 = \text{H}/\text{Pr}^n$, H/Bu^n , $\text{H}/\text{CH}_2\text{NMe}_2$, H/Ph , $\text{H}/\text{CO}_2\text{Et}$, Me/Me , $\text{Me}/\text{CO}_2\text{Me}$, $\text{Ph}/\text{CO}_2\text{Et}$, Ph/OCOPh , $\text{CO}_2\text{Me}/\text{CO}_2\text{Me}$. In some cases of asymmetrical alkynes, the other isomer (8) also forms. The preference for position 3 increases in the order $\text{H} < \text{CO}_2\text{Et} < \text{Ph} < \text{alkyl}$ (Equation (2)). The products are remarkably stable both to oxidation and hydrolysis. Compound (7), $\text{R}^1 = \text{Me}$, $\text{R}^2 = \text{H}$, $\text{R}^3 = \text{Ph}$, taken as an example, does not react with elemental sulfur or methanol or both of them (typically a reactive combination towards other azaphospholes) (86CB410).



3-Phenyl-1,2,3,4-triazaphosphole (9; $\text{R} = \text{Bu}^t$) prepared from the [3 + 2]-cycloaddition of the phosphalkyne with phenyl azide, on flash vacuum pyrolysis splits off dinitrogen. The intermediate azaphosphirene (10) may open the ring to give either a carbene or a phosphinidene. These species subsequently undergo [1,5]-electrocyclization followed by proton migrations to form anellated azaphospholes: the 1,2-benzazaphosphole (11), and the 1,3-benzazaphosphole (12) in a ratio 4 : 1. The isomer mixture can be separated by medium pressure chromatography. An analogous reaction is observed for the 3-naphthyl-1,2,3,4-triazaphosphole and gives the two isomers in a ratio of 3 : 1 (Scheme 1) (87T3247, 89PS(46)31).

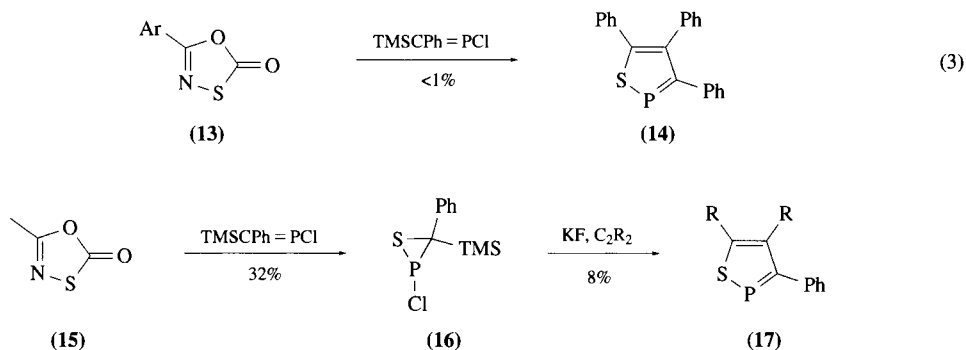


Scheme 1

3.15.4 1,2-THIAPHOSPHOLES

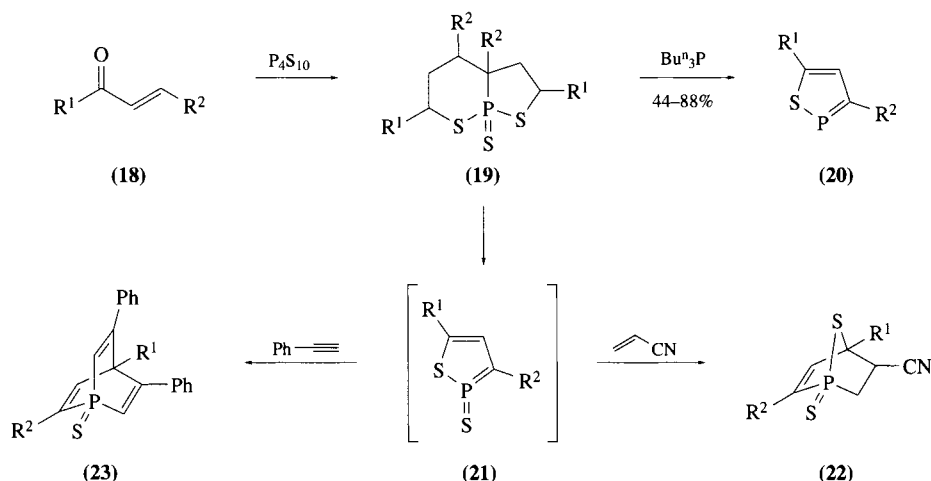
The first representative, 3,4,5-triphenyl-1,2-thiaphosphole (14) was observed as side product and isolated in low yields (1% or below) along with 3,5-diphenyl-1,2,4-thiadiphosphole from the reaction of 1,3,4-oxathiazol-2-ones (13), $\text{Ar} = 2\text{-MeC}_6\text{H}_4$, $2,6\text{-Cl}_2\text{C}_6\text{H}_3$, and a 1-chloro-2-trimethylsilyl phosphalkene (Equation (3)) (88TL4535). The corresponding reaction of the methyl derivative (15)

yields *E/Z*-mixtures of 2-chloro-3-trimethylsilyl thiaphosphiranes (**16**). Reaction with methyl ethyne dicarboxylate in the presence of KF (18-crown-6) gives the 1,2-thiaphosphole (**17**; R = CO₂Me) in poor yield (Scheme 2) <89TL4501>.



Scheme 2

3,5-Diaryl-substituted 1,2-thiaphospholes (**20**; R¹, R² = Ph, 4-MeC₆H₄, 4-MeOC₆H₄, 2-thienyl, styryl) can efficiently be prepared from α,β -unsaturated ketones (**18**). Reaction with excess P₄S₁₀ in the presence of triethylamine gives 2,9-dithia-1-phosphabicyclo[4.3.0]nona-3,7-diene 1-sulfides (**19**) <82TL1263>. Their treatment with Buⁿ₃P affords the thiaphospholes (Scheme 3) <93CL1563, 94BCJ2785>.

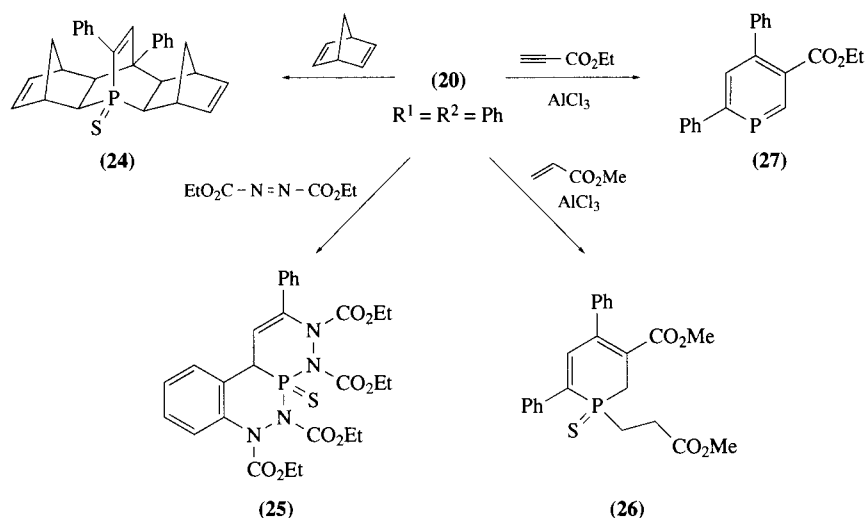


Scheme 3

Thermolysis of (**19**) in absence of a phosphine generates 1,2-thiaphosphole 2-sulfides (**21**) which can be trapped with suitable dienophiles such as acrylonitrile, styrene, butyl vinyl ether, and norbornene. The [4 + 2] cycloadducts such as (**22**) are formed regiospecifically <85BCJ667>. The reaction with dimethyl ethynedicarboxylate or phenyl ethyne affords 1-phosphabarrelene 1-sulfides (**23**) (Scheme 3) <86BCJ2047>.

The 1,2-thiaphospholes (**20**) react thermally with norbornadiene, norbornene, or diethyl azodicarboxylate to produce double Diels–Alder cycloadducts (**24**) and (**25**). With mixtures of norbornadiene and methyl acrylate or acrylonitrile, crossed double Diels–Alder cycloadducts are obtained. In the presence of AlCl₃ the 1,2-thiaphospholes (**20**) react with acrylic esters, acrylonitrile or methyl vinyl ketone to give tandem Diels–Alder/Michael adducts such as (**26**). The AlCl₃-promoted reaction of (**20**) with ethyl propiolate affords with the elimination of a sulfur atom the stable phosphinine (**27**) (Scheme 4) <94BCJ2785>.

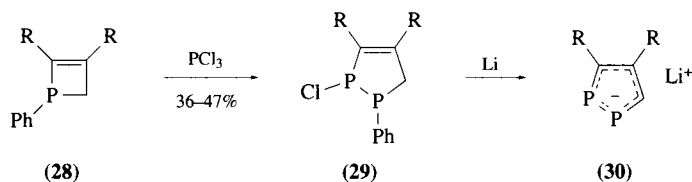
An attempt to synthesize 1,2-thiaphospholes and 1,2-selenaphospholes from triphenylphosphoniumylidyl thioxophosphines and selenoxophosphines, respectively, and phenacyl halides failed <95ZN(B)1543>.



Scheme 4

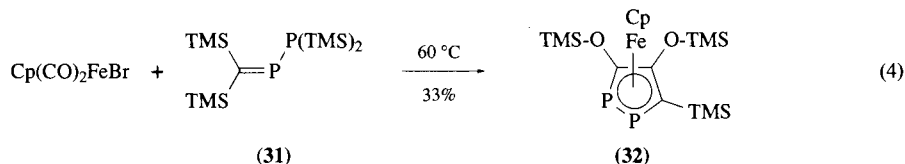
3.15.5 1,2-DIPHOSPHOLIDES

1,2-Dihydrophosphetes (28), accessible from titanacyclobutenes and dihalophosphines undergo a ring enlargement reaction with PCl_3 and at the same time act as reducing agent. The resulting 1,2-diphosphacyclopent-3-enes (29; $R = \text{Et}, \text{Ph}$) are further reduced by lithium in THF to yield the lithium 1,2-diphospholides (30) (Scheme 5). They can be used for the preparation of 1,2-diphosphoferrocenes (95AG623, 95AG(E)590).



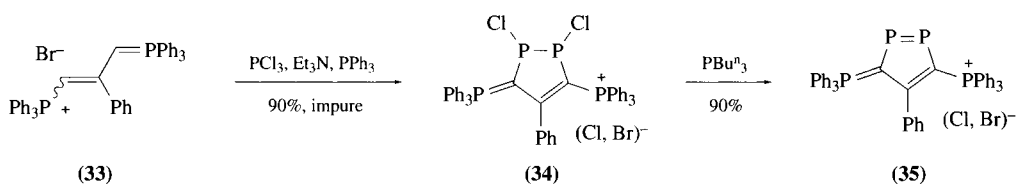
Scheme 5

Other 1,2-diphosphoferrocenes had been obtained earlier by direct synthesis (91CC1293, 91CC1659, 93OM731). The 1,2-diphosphoferrocene (32) for example results from the persilylated phosphinomethylenephosphine (31) by complex formation and thermal rearrangement of the primary complex (Equation (4)).



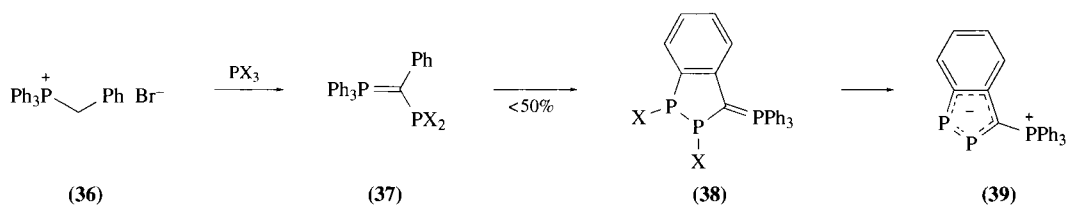
Condensation of the 1,3-diphosphonio-propenide cation (33) with two equivalents each of phosphorus trichloride and triethylamine as well as with triphenylphosphine yields the 1,2-dichloro-1,2-dihydro-1,2-diphospholide cation (34). Its reduction by tributylphosphine gives the 3,5-bis(triphenylphosphonio)-1,2-diphospholide cation (35) in form of a mixed chloride/bromide (96CEJ221). The cation is stable to hydrolysis, adds chlorine, bromine or iodine to the PP-bond and can be regained from these adducts (Scheme 6).

The reaction of benzyltriphenylphosphonium bromide (36) with phosphorus trichloride or tribromide and triethylamine leads via the C-dihalophosphino-C-phenyl ylides (37) to the 1,2-dihalo-3-triphenylphosphorane-1,2-diphosphaindanes (38). Their yield increases with reaction time, and for $X = \text{Br}$ the product (38) can account for up to 50% of the reacted trihalide. The corresponding reactions of (3-methylbenzyl)triphenylphosphonium bromide yield mixtures of the 5-



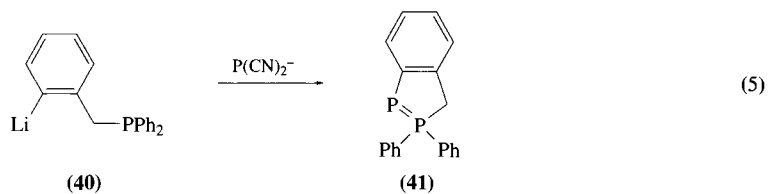
Scheme 6

Me and 7-Me derivatives. The bromides (38) have been reduced with magnesium in THF to yield the 3-triphenylphosphonio-1,2-diphosphaindenide (39) (Scheme 7) <94AG708>.



Scheme 7

An unstable diphenyl-1,2 λ^5 -diphosphaindene (41) has been observed from the reaction of *o*-lithiobenzyl diphenylphosphine (40) and dicyanophosphide (Equation (5)) <85ZN(B)1306>.



3.16

Two Nonadjacent Heteroatoms with at least One Phosphorus, Arsenic, or Antimony

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3.16.1 INTRODUCTION

Heterophospholes were introduced in Chapter 3.15.1. The first fully unsaturated phospholes with a nonadjacent second heteroatom were 1,3-benzazaphospholes (**1**). They were first described in 1978 <78TL441> and were consequently mentioned in the first edition of *Comprehensive Heterocyclic Chemistry* (CHEC-I) <84CHEC-I(1)523>, together with 1,3-benzothiaphospholes (**2**) and 1,3-benzodiphospholes (**3**) <80TL3483>. 1,3-Benzazarsoles (**4**) were also first studied at that time <78JOM(154)1>.

Today the family of 1,3-heterophospholes contains monocyclic 1,3-azaphospholes (**5**), 1,3-oxaphospholes (**6**), 1,3-thiaphospholes (**7**) and 1,3-selenaphospholes (**8**), as well as the benzo derivatives (**1**), (**2**), (**9**) of (**5**)–(**7**) and a naphtho derivative (**10**). While the benzo derivatives (**1**) result formally from the 4,5-anellation to (**5**), 1,5- and 1,2-anellation leads to two isomeric bicyclic systems such as (**11**) and (**12**) with a bridgehead nitrogen atom. Strictly speaking they therefore belong in Volume 8. However, they are also described here as they are closely related to the monocyclic 1,3-azaphospholes (**5**). The 1,5- and 1,2-anellated 1,3-azaphospholes embrace the pyrido derivatives, that is, the 2-phosphaindolizines (**12**), the isoquinolo derivatives (**13**) and (**14**), the pyridazo derivatives (**15**) and (**16**), the phthalazo derivative (**17**), the pyrazo derivatives (**18**) and (**19**), and the benzthiazolo derivative (**20**). In (**21**) the 1,3-azaphosphole is fused both with its 1,2- and its 1,5-bond to further rings and becomes part of a tetracyclic system. In other examples not shown here, the fused ring is not fully unsaturated. According to the fusion nomenclature compounds (**11**), (**12**), and (**20**) are [1,3]azaphospholo[1,5-*a*]pyridines, -[1,2-*a*]pyridines and -[5,1-*b*]benzothiazoles.

In neutral 1,3-diphospholes (**22**) the second heteroatom is a three-coordinate pyramidal phosphorus atom which is not at all or only very weakly conjugated to the remaining π -system. Full cyclic conjugation occurs only in their anions, that is, in the 1,3-diphospholide anions. The same applies to the 1,3-benzodiphospholides (**3**) and their anions. The known monocyclic and fused 1,3-heterophospholes and 1,3-diphospholes are shown in Table 1.

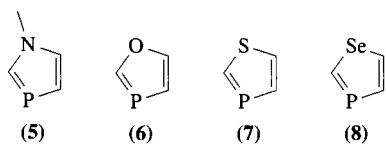
The family of 1,3-heteroarsoles is less developed than that of the 1,3-heterophospholes. It contains 1,3-azarsoles (**23**) as well as 1,3-benzazarsoles (**4**) and 1,3-benzoxazarsoles (**24**). Among the 1,3-azarsoles, a 1,2-fused derivative with a bridgehead nitrogen atom, (i.e. a 1-arsaindolizine (**25**)) is also known. Finally, the 1,3-phosphaarsolide ion (**26**) contains both a two-coordinate phosphorus and an arsenic atom as nonadjacent ring members. Table 2 shows the known monocyclic and fused 1,3-heteroarsoles.

Azaphospholes and, more general, heterophospholes were reviewed in 1989 <B-89MI 316-01> and 1990 <B-90MI 316-01>, respectively, and annellated heterophospholes in 1994 <94T7675>. A further review put special emphasis on 1,3-heterophospholes <94MI 316-01>. 1,3-Diphospholides were covered in a review on polyphosphacyclopentadienide anions <94CCR1>. A comprehensive list of compounds was given in a compilation of phosphorus-31 chemical shifts <88PS(36)217>, and in a review of annellated heterophospholes <94T7675>.

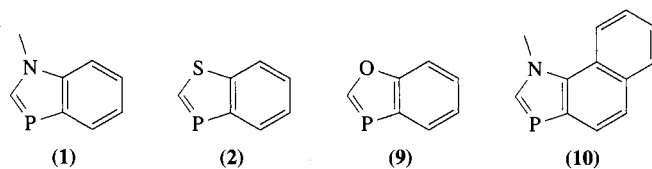
The use of 2-substituted cycloiminium salts in azaphosphole synthesis <95S361> and the use of phosphalkynes as building blocks for heterophosphole synthesis <90CRV191, B-90MI 316-02,

Table 1 The known monocyclic and fused 1,3-heterophospholes and 1,3-diphospholes.

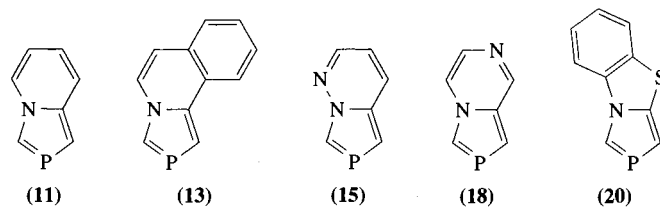
Monocyclic 1,3-heterophospholes



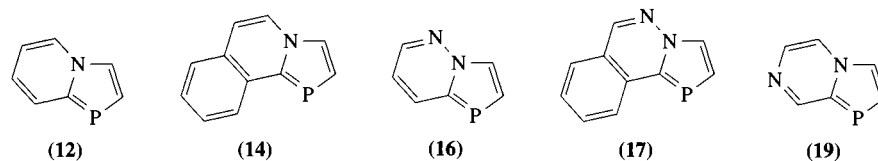
1,3-Benzoheterophospholes and 1,3-naphthoheterophospholes



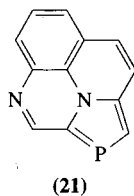
1,5-Annellated 1,3-azaphospholes



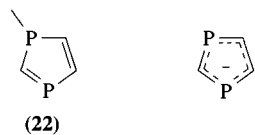
1,2-Annellated 1,3-azaphospholes



1,2- and 1,5-Annellated 1,3-azaphospholes



1,3-Diphospholes and 1,3-diphospholides



1,3-Benzodiphospholes and 1,3-benzodiphospholides

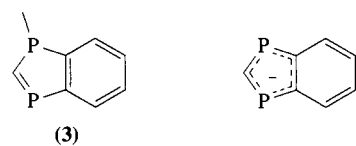
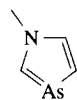


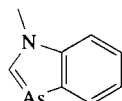
Table 2 The known monocyclic and fused 1,3-heteroarsoles.

Monocyclic 1,3-azarsoles

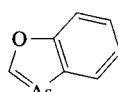


(23)

1,3-Benzazarsoles and 1,3-benzoxarsoles

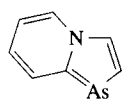


(4)



(24)

1-Arsaindolizines



(25)

1,3-Phosphaarsolides



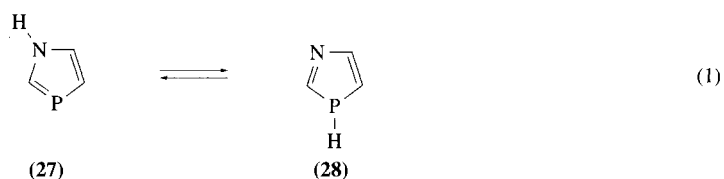
(26)

B-90MI 316-03> have been surveyed. Syntheses of 1,3-diphospholide anions were mentioned in a review on the chemistry of 1,2-dihydro-1,2-diphosphetes <92MI 316-01>. The reactivity of 1,3-heterophospholes is discussed in some of the cited reviews. A review on cycloaddition reactions to $P=C$ and $As=C$ double bonds <86PS(26)203> mentions 1,3-benzoxaphospholes and 1,3-benzoxarsoles as examples. Besides that, only one 1978 and one 1994 review deal with 1,3-heteroarsoles <B-78MI 316-01, 94MI 316-01>.

3.16.2 SPECTRA, STRUCTURE, AND BONDING

3.16.2.1 Theoretical Methods and PE Spectra

The electronic structure of 1,3-azaphospholes (5) (and of other azaphospholes, see Chapter 4.22) has been investigated by means of *ab initio* quantum chemical calculations and HeI photoelectron spectroscopy <92JPC623, 92JA9080>. Equation (1) shows the isomers 1*H*-1,3-azaphosphole (27) and 3*H*-1,3-azaphosphole (28). The calculated total energy of the 3*H*-isomer is significantly higher than that of the 1*H*-isomer and the aromatic stabilization—as measured by the heats of bond separation reactions—changes in a similar way. While the aromaticity of the 1*H*-isomer is found to be similar to that of imidazole, the 3*H*-isomer is much less aromatic and generally even considered nonaromatic and nonconjugated. While the 1*H*-isomer is planar with calculated bond lengths between those of isolated single and double bonds, the 3*H*-isomer is nonplanar, the arrangement around the phosphorus atom pyramidal, and the C—P bond length close to the single bond value.



UV and PE spectra of 3-alkyl 1,3-benzazaphospholes and 1,3-benzazarsoles are consequently completely different from those of their 1*H*-isomers <94MI 316-01>.

Earlier MNDO calculations are in accord with the results above <91PS(56)189>. Their main emphasis is on 1,3-benzazaphospholes (1) and 1,3-benzodiphospholes (3) and their anions. The drastic reactivity differences caused by the homologous N/P-exchange is readily explained. Other MNDO and CNDO/2 calculations and HeI photoelectron spectra <89JOM(373)49, 89JOM(373)57, 94MI 316-01> include 1,3-benzazarsoles (4) as well as 1,3-benzoxaphospholes (9) and 1,3-benzoxarsoles (24). Their HOMO has predominantly P=C or As=C character although this unit strongly interacts with the benzo π -system. As compared to phosphinine and arsinine the results indicate for them a lower electrophilicity and a lower reactivity in addition reactions. The thermodynamic stabilization by aromaticity decreases in the order (5) > (4) > (9) > (24).

Comparison of π -ionization energies of a series of compounds including 1,3-azaphospholes (5), 1,3-benzazaphospholes (1), and 1,3-benzoxaphospholes (9) and of ring fragmentation reaction heats suggests that in conjugative interactions P=C is more comparable to C=C than to N=C π -systems <93JPC4011>.

Charge densities calculated by MNDO for indolizine and its 2-phospha derivative (11) and 1-phospha derivative (12) show the π -electron excess in the five-membered ring to increase in this order. This result suggests that the phosphorus atom in (11) will be less likely to act as a donor than in (12) <91CB475>. As a dicoordinate phosphorus atom lowers the π -electron density at the adjacent carbon atoms, 2-phosphaindolizines are less reactive towards electrophiles in position 1 and 3 than indolizines.

Aromaticity of the 1,3-diphospholide anion was found to be somewhat higher than that of the 1,2-isomer <92JOC3694>.

3.16.2.2 X-ray Structure Investigations

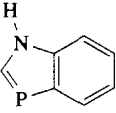
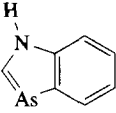
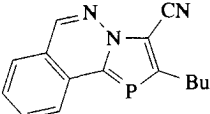
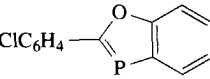
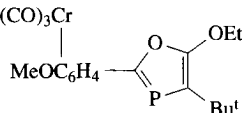
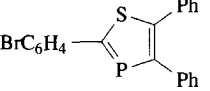
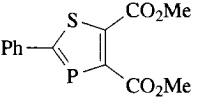
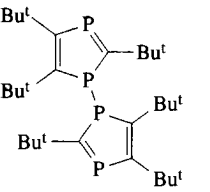
Several structures of 1,3-heterophospholes, 1,3-diphospholes and 1,3-heteroarsoles have been determined by x-ray diffraction techniques. The bond distances within the ring and the bond angle at the two-coordinate phosphorus or arsenic atom are given in Table 3. In part they are also contained in a review <88MI 316-01>. In general the structures show a planar five-membered ring with averaged bond distances. The angle at the phosphorus atom clearly depends on the size of the second heteroatom: in the case of O and N it ranges from 88 to 90°, and in the case of S and P from 94 to 100°.

The P—C bond lengths from Table 3 cover almost the whole range between the average values for a localized single (185 pm) and for a localized double (167 pm) bond <88MI 316-01, B-90MI 316-04>. Of the two bonds connecting the two-coordinate phosphorus to the carbon atoms the bond 2,3 is always shorter than the bond 3,4. The difference may serve as straightforward indicator of cyclic delocalization: the more the two lengths deviate from each other, the less pronounced it is. The difference is small (2–5 pm) for 1,2-anellated 1,3-azaphospholes and 1,3-thiaphospholes, larger (7–11 pm) for 1,3-benzazaphospholes and 1,3-benzoxaphospholes and largest (14 pm) for the 1,3-diphosphole. In the latter case the phosphorus atom in 1-position is pyramidal and does not participate in the π -system which therefore is not cyclic but of diene character. Consequently the two PC bond lengths are close to those of localized single and double bonds.

For two of the compounds of Table 3, aromaticity indices were derived from the molecular dimensions (1,3-oxaphosphole: 38, 1,3-thiaphosphole: 55). According to them, aromaticity is not greatly reduced if dicoordinate nitrogen in a five-membered heterocycle is replaced by phosphorus <90T5697>.

The structures of lithium and potassium salts and of some transition metal η^5 -complexes of 1,3-diphospholide ions have been determined by x-ray diffraction <87CC1146, 90AG575, 90CC472, 92AG1082, 92MI 316-01, 92JOM(430)C10, 93JOM(462)319, 93PS(77)254>. They all demonstrate full cyclic delocalization.

Table 3 Bond lengths (pm) in 1,3-heterophosphole, 1,3-diphosphole, and 1,3-heteroarsole rings and the angle at the two-coordinate phosphorus or arsenic atom from x-ray structure analyses.

	Bonds					Angle (°)	Ref.
	1.2	2.3	3.4	4.5	1.5		
	135.1	169.5	180.7	142.2	137.1	88.2	86ZAAC(540)336
	133	182.2	192.0	140	138	83.3	83ZAAC(501)146
	136.5	173.4	175.4	137.1	137.2	89.9	92TL1049
	136.9	171.2	178.8	139.3	137.4	88.1	85ZAAC(520)107
	136.9	170.5	177.2	133.9	135.5	89.5	89CC788 93T5577
	172.3	169.1	171.9	136.3	167.7	96.3	87TL2119
	169.9	171.5	176.1	136.5	171.3	93.8	92TL4421
	178.4	167.3	181.6	139.7	181.9	100.5	93CC267

The lithium diphospholide from $\text{Bu}^t\text{C}\equiv\text{P}$ and $\text{LiP}(\text{TMS})_2$ (see Section 3.16.4.5.3) forms a double salt with $\text{LiSi}(\text{TMS})_3$ with lithium ions centered to both sides of the diphospholide ring (96PC316-01).

3.16.2.3 NMR Spectra

3.16.2.3.1 Phosphorus-31 NMR

Phosphorus-31 NMR data of 1,3-heterophospholes have been compiled (88PS(36)217, 94T7675) and discussed several times (B-89MI 316-01, B-90MI 316-01, B-90MI 316-05, 94MI 316-01). The typical shift range is $\delta^{31}\text{P} = 50\text{--}180$ with a high field extreme of $\delta = -5$ and a low field extreme of $\delta = 235$. Table 4 lists characteristic monocyclic examples and their benzo derivatives. The low field chemical shifts observed for monocyclic 1,3-thiaphospholes (and 1,3-selenaphospholes) are ascribed to a transannular electron repulsion (94MI 316-01). Benzoannellation is generally accompanied by a significant upfield shift.

Table 4 Characteristic chemical shifts $\delta^{31}\text{P}$ of 1,3-heterophospholes, 1,3-diphospholes, 1,3-diphospholides, and their benzo derivatives.

92	70	-5
86TL5699	78TL441	81ZAAC(481)22
118	85	
93T5577	85PS(25)345	
217	71	
87TL2119	80TL3483	
223		
91SL356		
303	263	104
25, $^2J_{\text{pp}} = 24 \text{ Hz}$	-85, $^2J_{\text{pp}} = 23 \text{ Hz}$	2, $^2J_{\text{pp}} = 27 \text{ Hz}$
93CC267	90JOM(382)53	81TL4475
188	145	84
89POL849	90JOM(382)53	88ZC255

In 1,3-azaphospholes electron donating 2- or 4-substituents cause an upfield shift, and electron withdrawing 2-substituents a downfield shift, increasing, for example, in the order $\text{C}_6\text{H}_5 < \text{C}_6\text{H}_4\text{NO}_2 < \text{CO}_2\text{Et}$, $\text{CN} < \text{COPh}$ (91CB475, 94T7675). The effects correspond to those of α -substituents in acyclic two-coordinate phosphorus compounds (86PS(29)73, B-87MI 316-01, B-90MI 316-05). For 1,5-annellated 1,3-azaphospholes $\delta^{31}\text{P}$ depends on the nature of the fused ring and decreases in the order benzthiazole > oxazoline > thiazoline > pyridine over a range of $\Delta\delta = 20$. The shifts of 1-phosphaindolizines (20) and 2-phosphaindolizines (11) are found well separated in different regions of this range, the former at the high-field end, $\delta = 68\text{--}76$ (87TL1511), and the latter at the low-field end, $\delta = 121\text{--}184$ (91CB475, 92IJC(B)254). They thus reflect the difference in charge density as calculated (see Section 3.16.2.1).

The two-coordinate phosphorus signals of 1,3-diphospholes are found further downfield than those of 1,3-heterophospholes (Table 4) and are particularly sensitive to substituent effects. This

reflects the absent interaction of the three-coordinate phosphorus atom with the π -system. In accordance with this, the chemical shift of the two-coordinate phosphorus hardly changes if the three-coordinate phosphorus atom is oxidized $\langle 90\text{JOM}(382)53 \rangle$. It compares well with the $\delta^{31}\text{P}$ of electron-poor phosphalkenes $\langle 86\text{PS}(29)73 \rangle$.

As compared to the signals of the two-coordinate neutral phosphorus, 1,3-diphospholes, the signals of 1,3-diphospholide anions are observed at a much higher field (Table 4), those of monocyclic representatives being in the narrow range of $\delta^{31}\text{P} = 190 \pm 5$ $\langle 89\text{POL}849, 90\text{AG}575, 92\text{POL}601 \rangle$. The effects of benzoanellation and of electron-donating substituents are similar to those in 1,3-heterophospholes. Coupling constants $^2J_{\text{pp}}$ in 1,3-diphospholes $\langle 93\text{CC}267 \rangle$, 1,3-benzodiphospholes $\langle 90\text{JOM}(382)53 \rangle$ and 1,3-diphospholides $\langle 92\text{POL}601 \rangle$ range from 9 to 39 Hz.

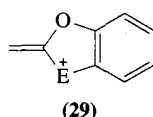
3.16.2.3.2 Proton and Carbon-13 NMR

For most of the newly synthesized 1,3-heterophospholes, 1,3-diphospholes, and 1,3-heteroarsoles ^1H and ^{13}C NMR spectra are given and discussed in the references for their synthesis. Coupling constants $^2J_{\text{PH}}$ are typically large, ranging from 30 to 50 Hz. The coupling constants $^1J_{\text{PC}}$ vary between 20 and 60 Hz.

As compared to 1,3-azaphospholes $\langle 86\text{TL}5699 \rangle$ and 1,3-benzazaphospholes $\langle 78\text{TL}441 \rangle$ the arsenic analogues $\langle 89\text{ZC}71, 78\text{JOM}(154)1 \rangle$ exhibit a strong downfield shift of the C-2 signal ($\delta^{13}\text{C} = 164 \rightarrow 180$ and $160 \rightarrow 173$, respectively) and also of the 2-H signal ($\delta^1\text{H} = 8.53 \rightarrow 9.75$). The ^1H NMR spectrum of 2-methyl 1,3-azarsole indicates an easier proton exchange from the NH group than in 1,3-azaphospholes $\langle 89\text{ZC}71 \rangle$.

3.16.2.4 Mass Spectra

Mass spectra have been reported for 1,3-azaphospholes (**5**) $\langle 87\text{TL}1089, 87\text{CB}1809, 88\text{JOM}(338)329 \rangle$, 1,3-azarsoles (**23**) $\langle 89\text{ZC}71 \rangle$, 1,3-benzazaphospholes (**1**) $\langle 78\text{TL}441, 81\text{ZAAC}(481)22, 82\text{TL}3643 \rangle$, 1,3-benzazarsoles (**4**) $\langle 78\text{JOM}(154)1 \rangle$, 1,3-azaphospholes with 1,2-anellated pyridine (**12**) $\langle 87\text{TL}1511 \rangle$ and 5,1-anellated oxazoline rings $\langle 94\text{PS}(86)139 \rangle$, 1,3-benzoxaphospholes (**9**) $\langle 80\text{ZC}342 \rangle$, 1,3-benzoxarsoles (**24**) $\langle 80\text{JOM}(186)39 \rangle$, 1,3-thiaphospholes (**7**) $\langle 87\text{TL}2119 \rangle$, and 1,3-benzodiphospholes (**22**) $\langle 81\text{TL}4475, 90\text{JOM}(382)53 \rangle$. While 1,3-benzazaphospholes and -arsoles (**1**), (**4**) give mass spectra with few lines and the loss of nitrile as an important fragmentation step, the fragmentation of 1,3-benzoxaphospholes and -arsoles (**9**), (**24**) is complex and favors the cation (**29**; E = P, As).



3.16.2.5 UV and IR Spectra

UV spectra have been reported and discussed for 1,3-heterophospholes $\langle 78\text{TL}441, 80\text{ZC}342, 81\text{ZAAC}(481)22, 82\text{TL}3643, 83\text{JOM}(258)257, 85\text{PS}(25)345, 86\text{TL}5699, 89\text{ZC}410 \rangle$ and 1,3-heteroarsoles $\langle 78\text{JOM}(154)1, 80\text{JOM}(186)39, 88\text{ZC}250, 89\text{ZC}71 \rangle$, both including their benzo derivatives, as well as for a 1,3-benzodiphosphole $\langle 90\text{JOM}(382)53 \rangle$. By comparison, the electronic similarity of 1,3-azaphospholes (**5**) and 1,3-azarsoles (**23**) with pyrroles and imidazoles, that of 1,3-benzazaphospholes (**1**) and 1,3-benzazarsoles (**4**) with indoles and benzimidazoles or that of 1,3-benzoxaphospholes (**9**) and 1,3-benzoxarsoles (**24**) with benzofuranes and benzoxazoles were shown $\langle 94\text{MI}316-01 \rangle$. Replacing a two-coordinate nitrogen atom in an azole by phosphorus, then replacing this by arsenic, is accompanied by a bathochromic shift of the absorption maximum. As compared to pyrrole, imidazole and oxazole, 1,3-azaphospholes and 1,3-azarsoles, like thiazoles, show an additional $\pi \rightarrow \pi^*$ band $\langle 86\text{TL}5699 \rangle$.

2-Aryl 1,3-benzoxaphospholes exhibit a strong blue fluorescence ($\lambda = 416$ nm) in the concentration range 10^{-2} to 10^{-4} M $\langle 85PS(25)345 \rangle$.

Little use has been made of IR and Raman spectra of 1,3-heterophospholes and 1,3-diphospholes.

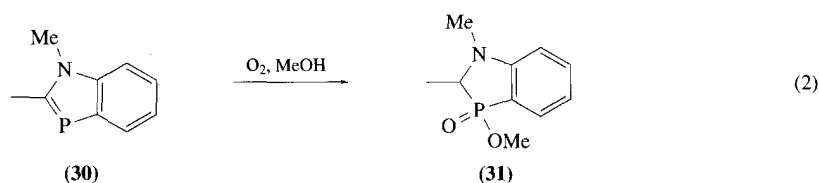
3.16.3 REACTIVITY

Reviews on 1,3-heterophosphole reactivity are mentioned in Section 3.16.1.

3.16.3.1 1,3-Azaphospholes/Arsoles and 1,3-Benzazaphospholes/Arsoles

3.16.3.1.1 General stability

1,3-Azaphospholes (**5**) and -arsoles (**23**), and 1,3-benzazaphospholes (**1**) and -arsoles (**12**) are colorless to yellow oils or solids which are generally stable in air for some time $\langle 78JOM(154)1, 78TL441, 81ZAAC(481)22, 82TL3643, 83JOM(258)257, 84PS(20)347, 86TL5699, 87TL1511, 89ZC71 \rangle$. 1,2-Dimethyl-1,3-benzazaphosphole (**30**), for example, seems air-stable as a solid but is slowly oxidized in methanol solution to give phosphinic ester (**31**) (Equation (2)) $\langle 94MI 316-01 \rangle$.



In contrast to most of the azaphospholes with more than the two heteroatoms (which are covered in Chapter 4.22) 1,3 azaphospholes/arsoles and 1,3-benzazaphospholes/arsoles are not (or only slowly) attacked by water, dilute acids or bases, alcohols and amines. Concentrated acetic acid reconverts (**1**) to 2-aminophenylphosphine.

3.16.3.1.2 Tautomerism

In accordance with the calculated energies (see Section 3.16.2.1) for *N*-unsubstituted representatives, only the 1*H*-isomers are observed spectroscopically and no 3*H*-isomer can be detected. The lower thermal stability of *N*-unsubstituted 1,3-benzazarsoles as compared to 1-methyl 1,3-benzazarsoles could be due to traces of the labile 3*H*-isomer in the tautomeric equilibrium $\langle 83JOM(258)257 \rangle$. For 1-trimethylsilyl-1,3-benzarsoles no silatropic equilibrium is observed $\langle 94MI 316-01 \rangle$. 4-Hydroxy-1,3-azaphospholes/arsoles do not form the keto tautomer $\langle 87TL1089, 88TL3387 \rangle$.

3.16.3.1.3 Reactivity towards electrophiles

N-Unsubstituted 1,3-benzazaphospholes and 1-methyl 1,3-benzazaphospholes are not basic and are not extracted from an organic phase by dilute sulfuric acid. They do not react with methyl iodide but are *P*/*As*-alkylated by $\text{Me}_3\text{O}^+\text{BF}_4^-$ $\langle 83JOM(258)257, 94MI 316-01 \rangle$. A *P*-Cr(CO)₅ complex of 2-phenyl 1,3-benzazaphosphole is known $\langle 81ZAAC(481)22 \rangle$.

1,3-Benzazaphospholes undergo *N*-substitution with PCl_3 . 1,3-Benzazaphospholes/arsoles are only *N*-acylated and *N*-trimethylsilylated after deprotonation with LiBu or more conveniently with LiNEt_2 ; they are, however, *P*/*As*-alkylated by methyl iodide. 1,3-Azaphospholes react in the same way $\langle 81ZAAC(481)22, 83JOM(258)257, 86TL5699 \rangle$. The lithium 1,3-azaphospholides and 1,3-benzazaphospholides/arsoles are intensely colored and can be isolated as monoetherates. 2-Substituents (TMS, $\text{CO}_2\text{-TMS}$, SMe) are introduced in 1-methyl-1,3-benzazaphospholes/arsoles by 2-lithiation and subsequent reaction with the electrophile $\langle 82TL3643, 83JOM(258)257, 86TL5699, 88ZC250 \rangle$. Addition of LiBu^t to the $\text{P}=\text{C}$ bond is a side reaction to the metalation, however.

3.16.3.1.4 Reactivity towards nucleophiles

1,3-Azaphospholes/arsoles and 1,3-benzazaphospholes/arsoles neither add hard nucleophiles (as mentioned above) nor soft nucleophiles such as PhSH or PhAsH₂. Exceptions are Me₃SnH which adds to the As=C bond of 1,2-dimethyl-1,3-benzazarsole on heating to 130 °C <94MI 316-01>, and LiBu^t as described above.

3.16.3.1.5 Cycloaddition reactions

1,2-Dimethyl-1,3-benzazarsole adds 2,3-dimethylbutadiene on heating to 130 °C to the As=C bond and the corresponding phosphole (30) adds *o*-chloranil in a 1 : 2 ratio to the phosphorus atom <83TL5481>.

3.16.3.1.6 Substituent reactivity

4-Trimethylsiloxy-1,3-azaphospholes/arsoles (see Section 3.16.4.1.4), on treatment with methanol or sodium methoxide and acyl chloride, are converted to the hydroxy or acyloxy derivatives <87TL1089, 88TL3387>.

The 1-methyl-1,3-benzazaphospholyl-2-carboxylic silylester (see Section 3.16.3.1.3) is quickly hydrolyzed to the acid <82TL3643>.

3.16.3.2 1,2- and 1,5-Annellated 1,3-Azaphospholes/arsoles

3.16.3.2.1 General stability

Depending on their substituents, 2-phosphaindolizines (11) are hydrolyzed more or less readily. The ring is first opened at the P=C bond <91CB475>. 1,3-Azaphospholo[1,5-*b*]benzothiazoles (20) hydrolyze rapidly <92HAC359>.

In contrast to 2-phosphaindolizines (11) which are stable in dry air and which cannot be alkylated <91CB475>, 1-phosphaindolizines (12) and 1-arsa-indolizines (25) readily decompose in air and form indolizinium salts with methyl iodide <87TL1511>. This is in accordance with the higher positive charge at the phosphorus atom in (11) than in (12) (see Section 3.16.2.1).

3.16.3.2.2 Reactivity towards electrophiles

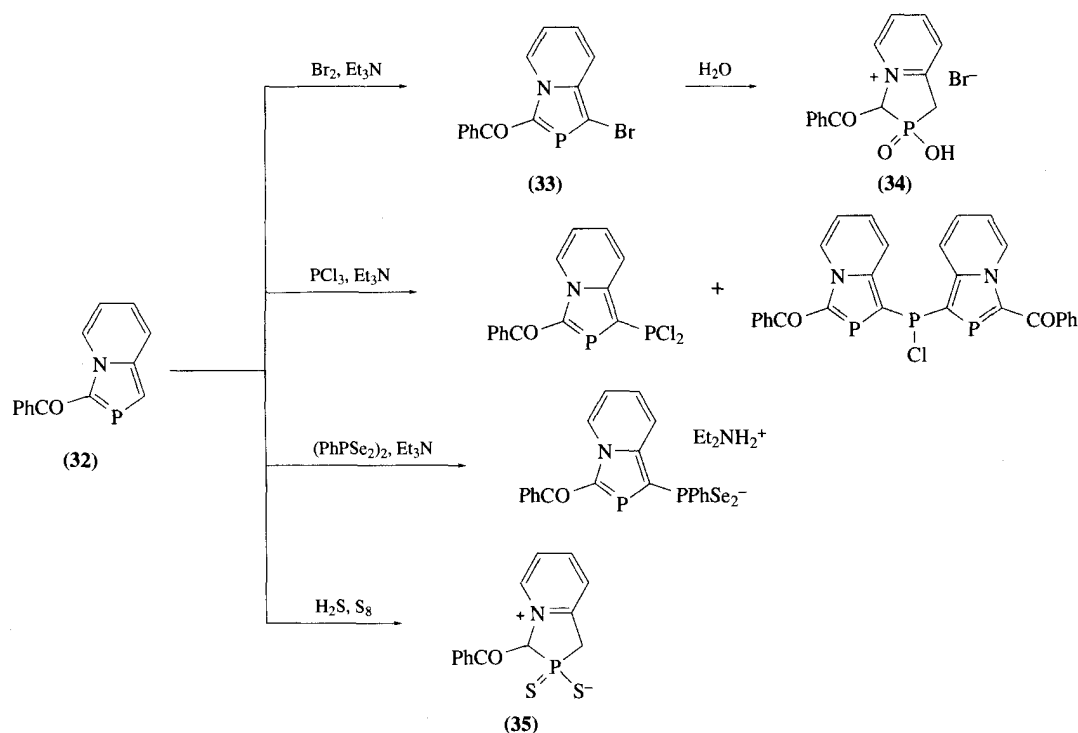
As shown for the representative (32), 2-phosphaindolizines (11) can be brominated in 1-position to (33) with bromine in presence of a base or with NBS, and are substituted by PCl₃, PhPCl₂ (but not by Ph₂PCl, MeCOCl or PhCOCl) or by perselenophosphonic anhydride <92HAC359, 93PS(77)235>. Hydrolysis of the bromo derivative (33) interestingly involves the debromination of C-1 coupled to the oxidation of the phosphorus atom to (34) (Scheme 1).

3.16.3.2.3 Reactivity towards nucleophiles

2-Phosphaindolizines such as (32) add H₂S in the presence of elemental sulfur to yield zwitterionic dithiophosphinates such as (35). The selenium analogue is also known <93PS(77)235>.

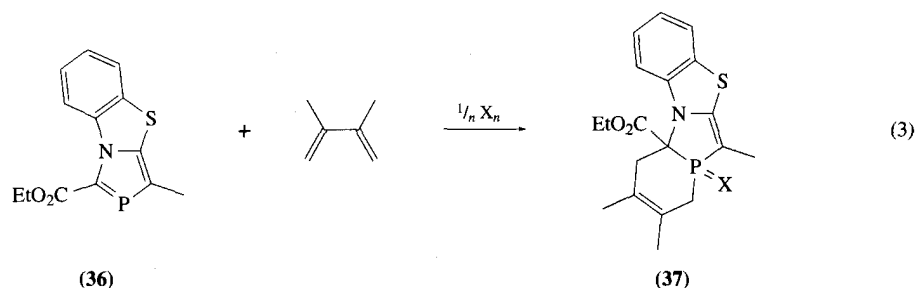
3.16.3.2.4 Cycloaddition reactions

The 1,3-azaphospholo[5,1-*b*]benzothiazole (36) does not react with 2,3-dimethylbutadiene or with isoprene alone. However, if the reaction is carried out in the presence of O₂, S₈ or Se_n, the [4 + 2]-cycloadduct (37; X = O, S, Se) with pentavalent phosphorus is obtained (Equation (3)). The reaction with isoprene occurs regioselectively <93PS(77)235>. It is suggested that the phosphorus is first oxidized to give a transient species with a three-coordinate pentavalent phosphorus, which subsequently



Scheme 1

undergoes cycloaddition $\langle 94\text{T}7675 \rangle$. This reaction is analogous to that of 2-phenyl-4,5-dimethylphosphinine $\langle 84\text{CC}508, 90\text{HAC}37 \rangle$.



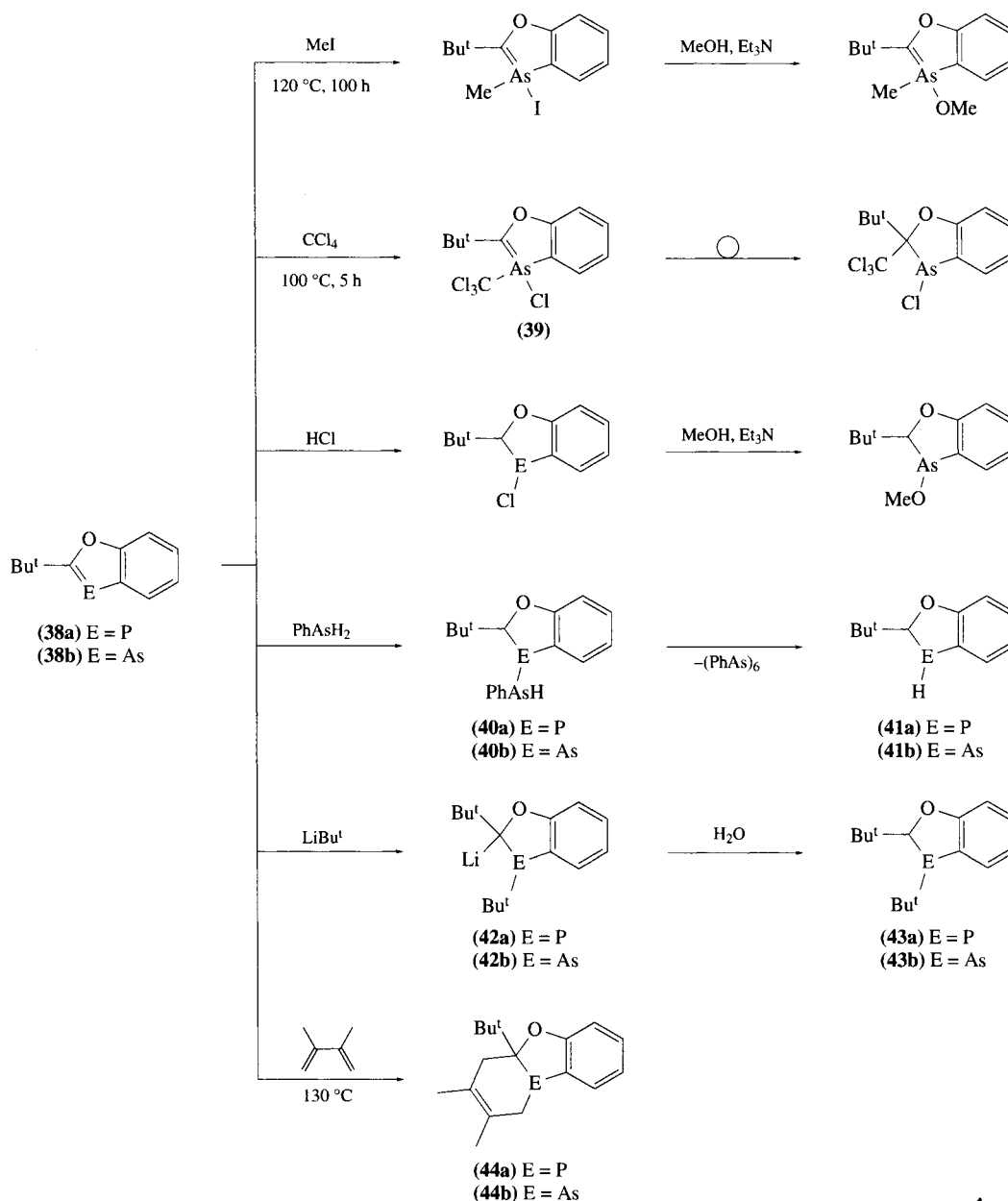
3.16.3.3 1,3-Benzoxaphospholes/arsoles

3.16.3.3.1 General stability

The family of 1,3-benzoxaphospholes (9) and -arsoles (25) includes the 2-alkyl-1,3-benzoxaphospholes/arsoles, which are colorless liquids, thermally stable up to 130°C . The 2-aryl derivatives are yellow crystalline solids $\langle 80\text{JOM}(186)39, 80\text{ZC}342, 83\text{ZC}439, 85\text{PS}(25)345 \rangle$. Air oxidation of the alcoholic solution is fast for the 2-methyl, medium for the 2-*t*-butyl, and slow for the 2-phenyl derivatives. It probably proceeds via cycloaddition of the triplet oxygen to the $\text{P/As}=\text{C}$ bond, and its subsequent fission.

3.16.3.3.2 Reactivity towards electrophiles

2-*t*-Butyl derivatives (38) have mostly been used to investigate reactivity. While the 1,3-benzoxaphosphole (38a) does not react with MeI , MeCOCl , TMS-Cl or PCl_3 , the 1,3-benzoxarsole (38b) adds MeI or CCl_4 to the $\text{As}=\text{C}$ bond on heating, with subsequent rearrangement of the adduct (39) in the latter case (Scheme 2) $\langle 84\text{PS}(20)347 \rangle$.



Scheme 2

3.16.3.3 Reactivity towards nucleophiles

Like 1-methyl-1,3-benzazaphospholes/arsoles, the 1,3-benzoxaphospholes/arsoles (**38**) are unreactive to water, alcohols or amines. However, in contrast to them they add HCl, PhSH, and PhAsH_2 , and in the presence of AIBN they also add Me_3SnH . In this reaction (**38a**) is always less reactive than (**38b**); PhMePH only adds to (**38b**). Adducts (**40**) undergo a dismutation to yield the dihydro derivatives (**41**). (**41**) also results from (**38a**) and Me_3SnH .

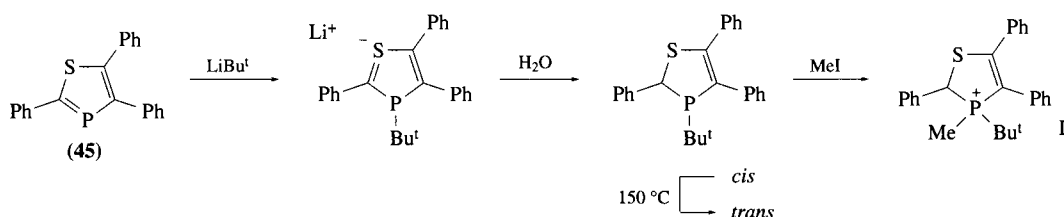
At -60°C (**38**) and LiBu^t rapidly give the adducts (**42**) which on hydrolysis furnish (**43**) as 1 : 9 mixtures of *cis/trans* isomers (Scheme 2) <84PS(20)347>.

3.16.3.3.4 Cycloaddition reactions

On prolonged heating with 2,3-dimethylbutadiene compounds (38) form the cycloadducts (44). Tetrachloro-*o*-benzoquinone adds in the same way but much more quickly; in a subsequent reaction a second molecule adds to the phosphorus atom (83TL5481).

3.16.3.4 1,3-Thiaphospholes

1,3-Thiaphospholes (7) are colorless to pale yellow air-stable crystalline solids. The addition of LiBu^t to the 2,4,5-triphenyl derivative (45), and the subsequent reactions shown in Scheme 3, seem the only ones to have been described (87TL2119).

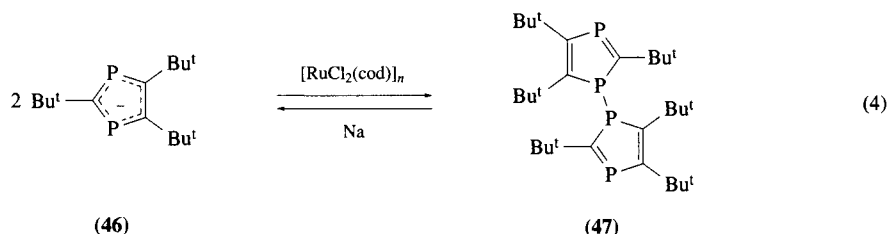


Scheme 3

3.16.3.5 1,3-Diphospholides and 1,3-Benzodiphospholides/diphospholes

3.16.3.5.1 Reactivity towards electrophiles, oxidation, and complex formation

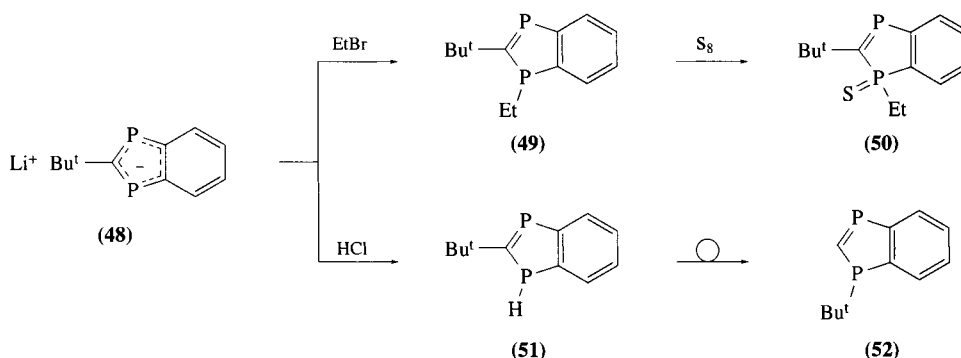
Protonation of the 1,3-diphospholide anion $(\text{PhC})_2\text{P}_2\text{CH}^-$ generates the transient 2*H*-1,3-diphosphole $(\text{PhC})_2\text{P}_2\text{CH}_2$ which can be trapped (91OM2835). Oxidation of the anion (46) gives the 1,1'-biphospholyl (47) (Equation (4)) (93CC267). Protonation or oxidation of a mixture of the anions $(\text{Bu}^t\text{C})_2\text{P}_3^-$ and (46) gives the tricyclic system $\text{H}_2(\text{Bu}^t\text{C})_5\text{P}_5$ (90CC1307) or the cage compound $(\text{Bu}^t\text{C})_5\text{P}_5$ (89JOM(375)C31), respectively.



Lithium 2-*t*-butyl-1,3-benzodiphospholide (48) reacts with ethyl bromide and pivaloyl chloride to give the 1-substituted products, such as (49), which can be oxidized to (50). Hydrogen chloride (but not methanol) yields the 1,3-benzodiphosphole (51), which immediately rearranges to the isomer (52) (Scheme 4). The same rearrangement is observed for the 1-TMS and 1-PPH₂ derivatives (90JOM(382)53, 90PS(49)355). Lithium 2-trimethylsiloxy-1,3-benzodiphospholide becomes 1-trimethylsilylated (88ZC250), lithium 2-anilido-1,3-benzodiphospholide both *N*- and 1-trimethylsilylated (85ZAAC(529)216).

The reactivities of 1,3-benzazaphospholes (1) and 1,3-benzodiphospholes (3) as well as those of their anions have been compared (91PS(56)189).

A variety of transition metal complexes has been prepared from 1,3-diphospholide anions (94CCR1). In these complexes the ligand may be $\eta^1(\text{P})$ -bonded (91OM2835), $\eta^3(\text{PCP})$ -bonded (89JOM(373)C17, 90CC472), or η^5 -bonded (87CC1146, 90CC472, 90AG575, 91JOM(415)C15, 92OM459, 92POL601, 93CC311). Of the 1,3-benzodiphospholide anion (48), $\eta^1(\text{P})$ - and η^5 -complexes are known as well as a η^1 -complex of the 1,3-benzodiphosphole (49) (90JOM(382)53, 90PS(49)355).



Scheme 4

3.16.3.5.2 Reactivity towards nucleophiles

The 1,3-benzodiphosphole (49) adds HCl and MeOH as well as LiBu to its P=C bond <90JOM(382)53, 90PS(49)355>. The addition of HCl and ROH to a 2,4,5-tri-*t*-butyl-1,3-diphosphole is also known <88TL5867>.

3.16.3.5.3 Cycloaddition reactions

Compound (49) gives a Diels-Alder addition of 1,4-diphenylbutadiene to its P=C bond <90JOM(382)53, 90PS(49)355>.

3.16.4 SYNTHESSES

For reviews on the synthesis of 1,3-heterophospholes and 1,3-diphospholes, see Section 3.16.1.

3.16.4.1 1,3-Azaphospholes/arsoles and 1,3-Benzazaphospholes/arsoles

3.16.4.1.1 Survey of synthetic routes

Several synthetic routes to 1,3-azaphospholes (5) and -arsoles (23), and 1,3-benzazaphospholes (1), (10) and -arsoles (4) may be distinguished in view of the fragments from which the ring is formed.

(i) NCCP/As + C

The procedure by which the first representatives were obtained <78TL441, 78JOM(154)1> proved very effective. It starts with the four-membered chain of a 2-aminoalkylphosphine/arsine or 2-aminophenylphosphine/arsine and completes the ring by condensation with a carboxylic acid derivative. In the former case full unsaturation is reached by thermolysis of the condensation product <94MI 316-01>.

(ii) CNCC + Electrophilic P/As

This procedure was first developed for the synthesis of 1,5-annellated 1,3-azaphospholes like 2-phosphaindolizines <91CB475>. It needs a four-membered chain with reactive methylene groups at both ends for condensation with phosphorus trichloride to form the ring. For 1,5-annellated 1,3-

azaphospholes, 1,2-dialkyl cycloiminium ions are used (see Section 3.16.4.2); for monocyclic 1,3-azaphospholes, a ketene *N*-methylaminal. To yield 1,3-benzazaphosphole/arsole according to this pattern, phenyl isonitrile can serve as starting material.

(iii) *CNCC + Nucleophilic P/As*

Here the fragment pattern is the same as before but the condensation reaction is of inverse polarity. Oxazolium ions or zwitterionic münchnones contribute the CNCC chain and tris(trimethylsilyl)phosphine/arsine contributes the fifth ring member.

(iv) *CNC + CP*

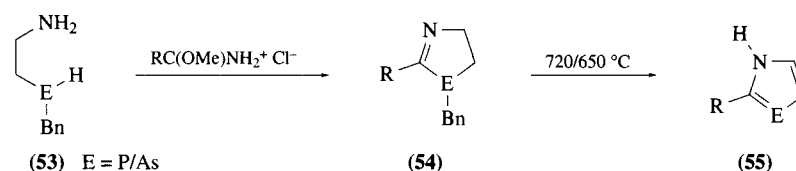
This route involves the cycloaddition of phosphalkynes $RC\equiv P$ or phosphalkenes $R(TMS)C=PCl$, which lose $TMSCl$ in the course of the reaction. Reaction partners are 1,3-dipoles such as nitrile ylides, or their precursors.

(v) *CCNCP*

As mentioned in Chapter 3.15.3, 1,3-benzazaphospholes and the corresponding naphtho derivatives result from the electrocyclization of intermediate phenyl- or naphthyliminoacyl phosphinidenes $\langle 87T3247, 89PS(46)31 \rangle$.

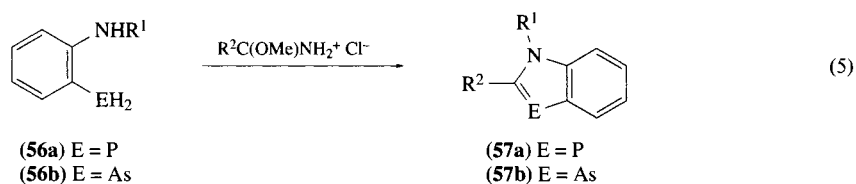
3.16.4.1.2 Synthesis from 2-aminophosphines/arsines

2-Aminoethyl benzylphosphine/arsines (**53**) are condensed with iminoester hydrochlorides, $R = H, Me, Et, Ph$. Flash vacuum pyrolysis of the products (**54**) yields 1,3-azaphospholes/arsoles (**55**) (Scheme 5) $\langle 76JPR409, 86TL5699, 86ZC407, 89ZC71, 91CB493 \rangle$.



Scheme 5

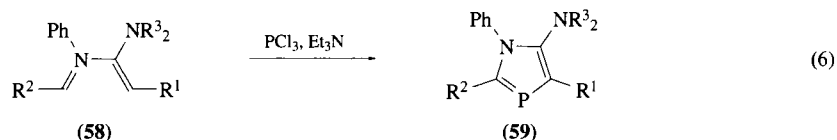
1,3-Benzazaphospholes/arsoles (**57**) are obtained from the condensation of 2-amino-phenylphosphines (**56**), $R^1 = H, Me$, with iminoester hydrochlorides, $R^2 = H, Me, Bu^t, Ph$ (Equation (5)). A broader variety of carboxylic acid derivatives can be used for the condensation of (**56a**) $\langle 78JOM(154)1, 78TL441, 81ZAAC(481)22, 82TL3643, 83JOM(258)257 \rangle$. This synthesis has also been used for specially substituted compounds of type (**57a**) $\langle 95BSF306 \rangle$.



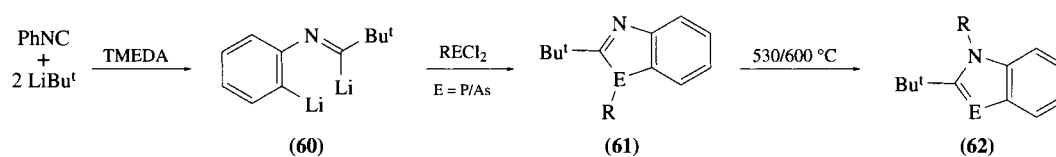
In another version of this route, 2-aminophenylphosphine is first persilylated. The product, on reacting with diphenylcarbodiimide followed by the action of methanol, affords 2-anilino-1,3-benzazaphosphole (**57a**; $R^1 = H, R^2 = NHPh$) $\langle 89ZC410 \rangle$.

3.16.4.1.3 Synthesis from chlorophosphines/arsines

Condensation of ketene aminals (**58**; $R^1 = \text{H, alkyl, aryl}$, $R^2 = \text{CN, C}_6\text{H}_4\text{NO}_2\text{-4}$) with phosphorus trichloride or tribromide gives 1,3-azaphospholes (**59**) (Equation (6)) <89EGP268702>.



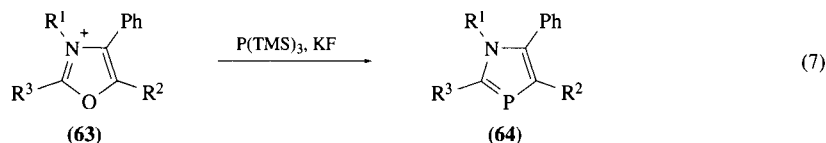
The reagent (**60**) generated *in situ* from the action of LiBu^t on phenyl isonitrile and *t*-butyl dichlorophosphine or methyl dichloroarsine gives the 3*H*-1,3-benzazaphosphole/arsole (**61**) which is converted to the 1*H*-1,3-benzazaphosphole/arsole (**62**) by flash vacuum pyrolysis (Scheme 6) <89JOM(364)C17>.



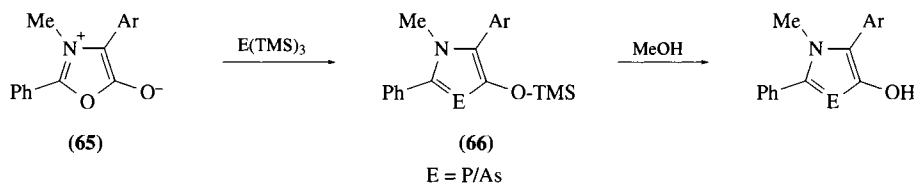
Scheme 6

3.16.4.1.4 Synthesis from tris(trimethylsilyl)phosphine/arsine

Oxazolium perchlorates (**63**) enter a KF assisted condensation with tris(trimethylsilyl)phosphine to give 1,3-azaphospholes (**64**; $R^1 = \text{Me, Et, Bu}^t$, $R^2 = \text{H, Me, Et, Ph}$, $R^3 = \text{H, Me, Et, Ph}$) (Equation (7)). Suitably substituted chloromethylene iminium chlorides can also be used for the condensation <86TL4419>.



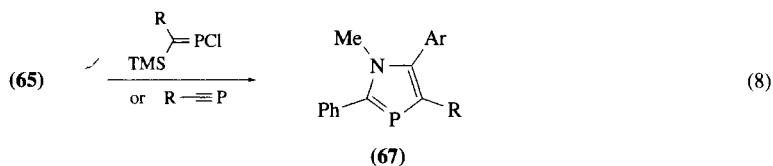
Münchnones (**65**) and tris(trimethylsilyl)phosphine/arsine give 4-trimethylsiloxy 1,3-azaphospholes/arsoles (**66**; Ar = Ph, C₆H₄OMe-4) (Scheme 7) <87TL1089, 88TL3387>.



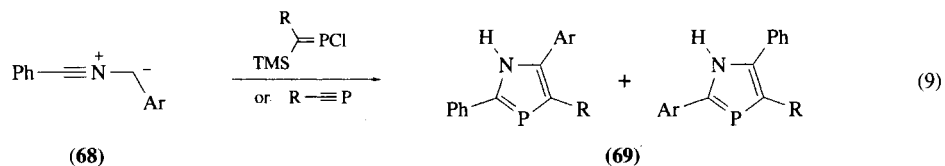
Scheme 7

3.16.4.1.5 Synthesis from phosphalkynes/alkenes

Reaction of münchnones (**65**; Ar = Ph, C₆H₄OMe-4) and a trimethylsilyl chlorophosphalkene, R = Ph, <86TL4419> or phosphalkynes, R = H, Bu^t <87CB1809, 88AG1541, 88JOM(338)329> give 1,3-azaphospholes (**67**) (Equation (8)).



Cycloaddition of diphenyl nitrile ylide (**68**; Ar = Ph, and the phosphalkene, R = Ph) <88TL785>, or of (**68**; Ar = C₆H₄NO₂-4), and phosphalkynes, R = Bu^t, CMe₂Et, 1-adamantyl, yields 1-unsubstituted 1,3-azaphospholes (**69**). The cycloaddition of the phosphalkynes is regioselective; however, the constitution of (**69**) could not be determined with certainty (Equation (9)) <90CRV191>.



3.16.4.2 1,2- and 1,5-Annellated 1,3-Azaphospholes/arsoles

3.16.4.2.1 Survey of synthetic routes

A variety of annellated 1,3-azaphospholes (11)–(21) (Table 1) have been synthesized by variants of three procedures which are also used for monocyclic 1,3-azaphospholes <94T7675>.

(i) NCCC + electrophilic P

This procedure parallels the classical indolizine synthesis <69CB669>. A 2-methyl cycloiminium ion provides the four-membered chain which is joined to the five-membered ring by condensation with phosphorus trichloride <95S361>.

(ii) CNCC + nucleophilic P/As

As in the case of monocyclic 1,3-azaphospholes/arsoles (Section 3.16.4.1.4) tris(trimethylsilyl)phosphine/arsine provides the phosphorus/arsenic ring member by replacing the oxygen atom of an oxazolium ring.

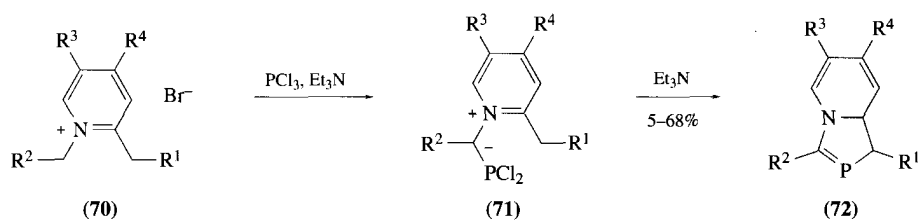
(iii) CNC + CP

Azomethine ylides of pyridine, quinoline, isoquinoline, and related nitrogen heterocycles undergo [3 + 2] cycloaddition with a variety of dipolarophiles leading to fused heterocycles <73S469>. This method has been extended to the use of a phosphalkyne as dipolarophile.

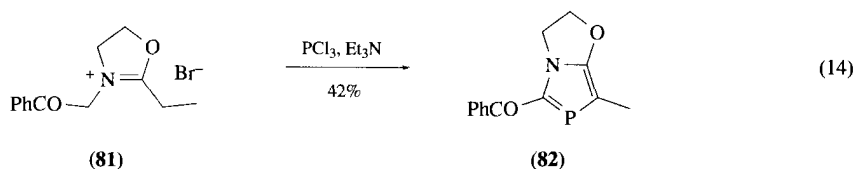
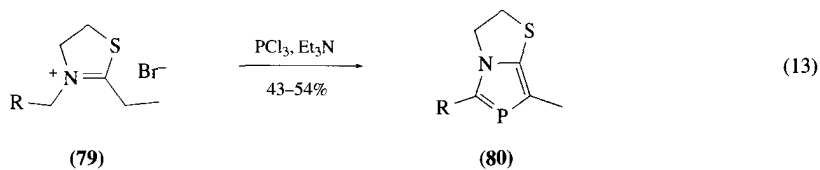
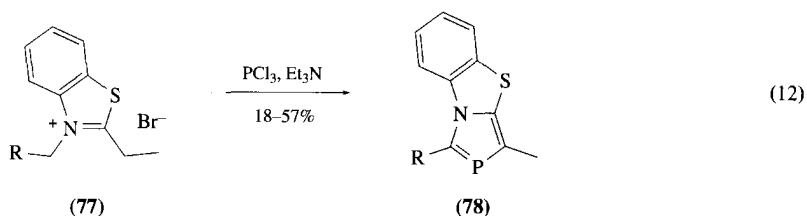
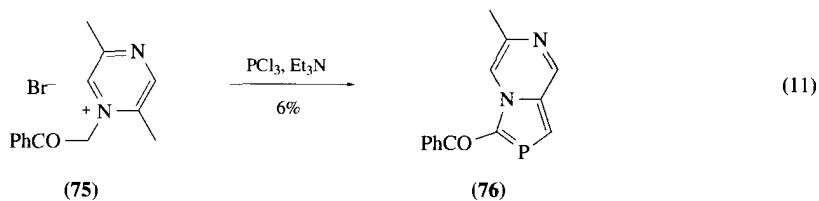
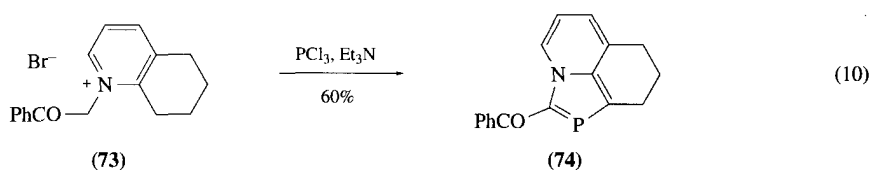
3.16.4.2.2 Synthesis from phosphorus trichloride

Salts resulting from the *N*-alkylation, R² = C₆H₄NO₂-4, CPh, CO₂Et, CN, of 2-alkylpyridines (**70**; R¹ = H, Me, Ph, R^{3,4} = H, Me, Bu), (**73**), 2,5-dimethylpyrazine (**75**), 2-alkylbenzothiazoles (**77**), 2-methylthiazoline (**79**), and 2-ethyloxazoline (**81**) undergo a cyclocondensation with PCl₃ to give 1,3-azaphospholo[1,5-*a*]pyridines (2-phospha-indolizines) (**72**), (**74**) and -[1,5-*a*]pyrazine (**76**) (Scheme 8, Equations (10), (11)) <90PS(49)349, 91CB475, 92IJC(B)254>, 1,3-azaphospholo[5,1-*b*]benzothiazoles (**79**), [5,1-*b*]thiazolines (**80**), and [5,1-*b*]oxazoline (**82**) (Equations (12)–(14)) <92HAC351, 94PS(86)139>, respectively. A PCl₂-substituted pyridinium ylide (**71**) and benzothiazolium ylide have

been isolated as intermediates. The site of the primary reaction in 1,2-dialkylpyridinium halides (**70**) is determined by the relative activation of the 1- and 2-methylene groups <96PS(112)121>.

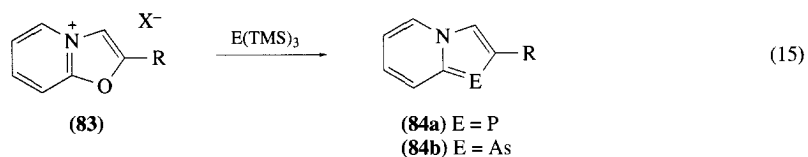


Scheme 8



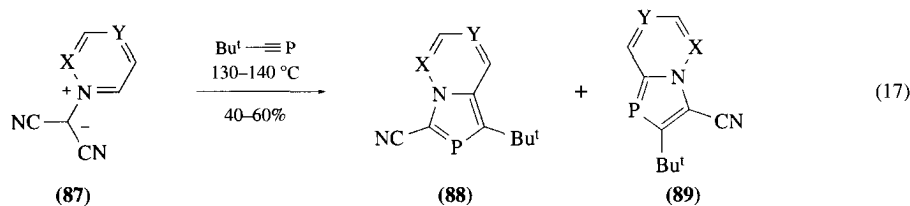
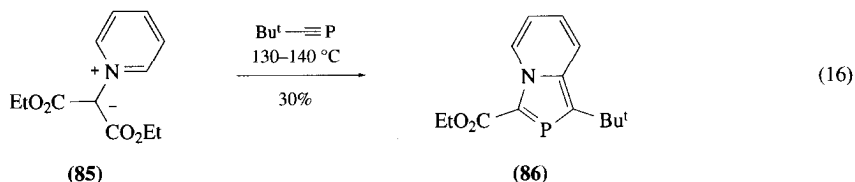
3.16.4.2.3 Synthesis from tris(trimethylsilyl)phosphine/arsine

1,3-Oxazolo[3,2-*a*]pyridinium salts (**83**; R = Me, Pr^i , Bu^i , Ph) react with $\text{P}(\text{TMS})_3/\text{As}(\text{TMS})_3$, or $\text{LiP}(\text{TMS})_2$ to afford 1-phospha/arsaindolizines (**84**) (Equation (15)) <87TL1511>.



3.16.4.2.4 Synthesis from phosphalkynes

The pyridinium ylide (**85**) undergoes regioselective [3 + 2] cycloaddition with *t*-butylphosphaethyne to give the 2-phosphaindolizine (**86**) (Equation (16)). Cycloadditions of pyridinium (**87**; X = CH, Y = CH), pyridazinium (**87**; X = N, Y = CH), and pyrazinium (**87**; X = CH, Y = N) dicyanomethylides are not regioselective and a mixture of the two isomers (**88**) and (**89**) is obtained in each case (Equation (17)). However, regioselectivity is observed when *t*-butyl and isopropoxy groups are introduced in the 4-position of (**87**; X = CH, Y = CH). With isoquinolinium and phthalazinium ylides the reaction is again regioselective, though the dipole orientation is reversed as compared to the formation of (**86**), yielding tricyclic systems of type (**14**) and (**17**) <92TL1049>.



1,3-Dipoles generated from 3*H*-pyrido[1,2-*de*]quinoxalinium bromides react analogously with *t*-butyl phosphaethyne and yield regioselectively phosphazaullacines of type (**21**) <94CC1121>.

3.16.4.3 1,3-Oxaphospholes and 1,3-Benzoxaphospholes/arsoles

3.16.4.3.1 Survey of synthetic routes

Monocyclic 1,3-oxarsoles are unknown up to 1996.

(i) OCCP/As + C

This synthesis of the 1,3-benzoxaphospholes (**9**) and 1,3-benzoxaarsoles (**24**) is analogous to that of 1,3-benzazaphospholes/arsoles (**57**) in Section 3.16.4.1.2, using 2-phosphino/arsinophenols to start with.

(ii) COCC + P

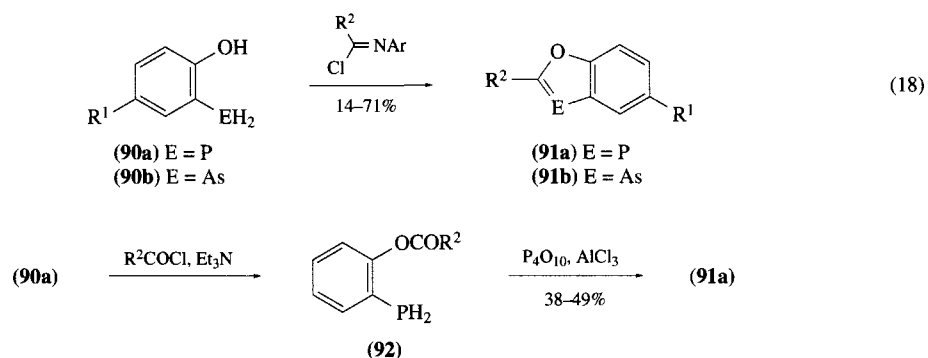
Monocyclic 1,3-oxaphospholes (**6**) can be prepared like 1,3-azaphospholes (**5**) from ketene aminals. The procedure is covered in Section 3.16.4.1.3.

(iii) $CO + C + CP$

This synthesis of (6), like the synthesis of (5) in Section 3.16.4.1.5 uses a phosphaaalkyne. Its reaction with a chromium pentacarbonyl carbene complex provides a carbon monoxide and a carbene unit as the other ring constituents.

3.16.4.3.2 Synthesis from 2-phosphino/arsinophenols

Condensation of 2-phosphino/arsinophenols (90) with *N*-arylimidoyl chlorides gives 1,3-benzoxaphospholes/arsoles (91) (Equation (18)) <80JOM(186)39, 80ZC342, 85PS(25)345>. Compounds (91a) are also obtained by acylation of (90a) and dehydration of the intermediate (92) (Scheme 9).



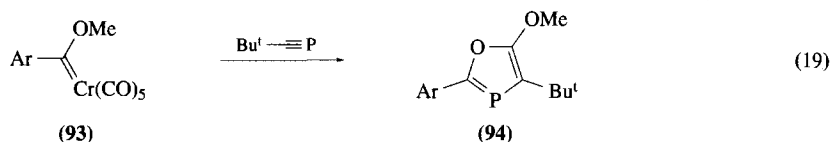
Scheme 9

3.16.4.3.3 Synthesis from phosphorus trihalides

Condensation of α -(4-nitrobenzyl)oxy- or α -cyanomethoxy-substituted enamines with PCl_3 or PBr_3 and a tertiary amine leads to 1,3-oxaphospholes <89EGP268700>. 1,3-Thiaphospholes <89EGP268701> and 1,3-selenophospholes <89EGP268703> are obtained analogously.

3.16.4.3.4 Synthesis from phosphaaalkynes

Chromiumpentacarbonyl arylmethoxycarbene complexes (93; Ar = Ph, 2-naphthyl, 2-furyl, 2-thienyl, 3,4-dimethoxyphenyl, 2-(1,4-dimethoxy)naphthyl) react with *t*-butyl phosphaaacetylene to give 1,3-oxaphospholes (94) together with phosphahydroquinone derivatives (Equation (19)). Depending on Ar, the ratio varies from 1 : 1 to 1 : 0 <89CC788, 90NJC433, 93T5577>.



3.16.4.4 1,3-Thia/Selenaphospholes and 1,3-Benzothiaphospholes

3.16.4.4.1 Survey of synthetic routes

No arsenic analogues to 1,3-thia/selenophospholes (7), (8) and 1,3-benzothiaphospholes (2) seem to be known.

(i) *SCCP + C*

1,3-Benzothiaphospholes (**2**) are prepared from 2-phosphinothiophenol in the same way as the 1,3-benzoxaphosphole (**9**) is made from 2-phosphinophenol (see Section 3.16.4.3.2).

(ii) *CS/SeCC + P*

This synthesis of (**7**) and (**8**) is analogous to that of (**6**) in Section 3.16.4.3.4 and covered there.

(iii) *SCP + CC*

This synthesis of (**7**) involves the cycloaddition of an alkyne to an intermediate thiobenzoyl phosphinidene and is thus related to the electrocyclization of the phenyliminoacyl phosphinidene mentioned in Chapter 3.15.3.

(iv) *CSC + CP*

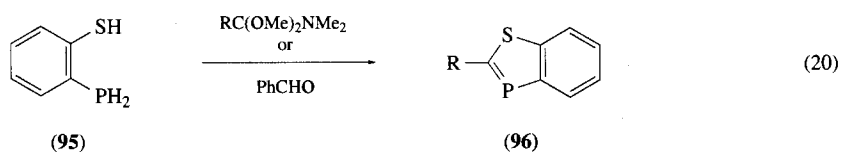
As in Section 3.16.4.1.5 this route involves the cycloaddition of a phosphalkene. Here the reaction partner is a 1,3-dithiolium-4-olate.

(v) *CCSe + CP*

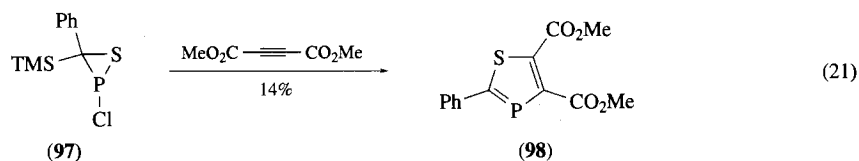
The cycloaddition of a phosphalkyne to an intermediate selenocarbonyl carbene yields a 1,3-selenaphosphole (**8**).

3.16.4.4.2 Synthesis from 2-phosphinothiophenol

2-Phosphinothiophenol (**95**) undergoes condensation with amide acetals or with benzaldehyde to give 1,3-benzothiaphospholes (**96**) (Equation (20)) <80TL3483>.

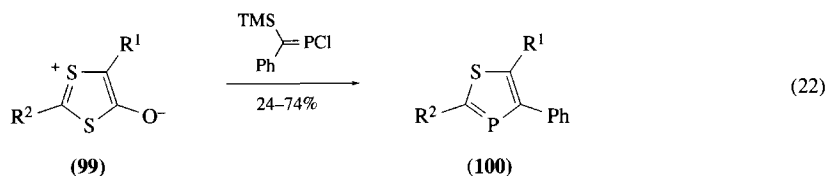
**3.16.4.4.3 Synthesis from a thiaphosphirane**

The thiaphosphirane (**97**) reacts with dimethyl ethyne dicarboxylate in presence of KF, 18-crown-6 to the 1,3-thiaphosphole (**98**) (Equation (21)).



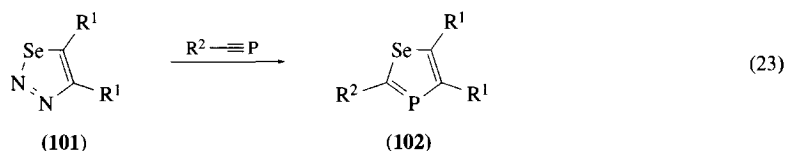
3.16.4.4.4 Synthesis from phosphalkenes

1,3-Thiaphospholes (**100**; $R^1 = \text{Me, Ph, 1-piperidyl, 1-morpholyl}$, $R^2 = \text{Ph, C}_6\text{H}_4\text{Me-4, C}_6\text{H}_4\text{Br-4, C}_6\text{H}_4\text{OMe-4}$) are prepared by 1,3-dipolar cycloaddition of 1,3-dithiolium-4-olates (**99**) and a phosphalkene (Equation (22)) <87TL2119>.



3.16.4.4.5 Synthesis from phosphalkynes

Photolysis or thermolysis of 1,2,3-selenadiazoles (**101**) in the presence of phosphalkynes, $R^2 = \text{Bu}^t, \text{CMe}_2\text{Et, 1-adamantyl}$, gives rise to 1,3-selenaphospholes (**102**) (Equation (23)) <91SL356>.



3.16.4.5 1,3-Diphospholides/diphospholes, 1,3-Phosphaarsolides and 1,3-Benzodiphospholides/diphospholes

3.16.4.5.1 Survey of synthetic routes

As pointed out in the introduction (Section 3.16.1) neutral 1,3-diphospholes and 1,3-benzodiphospholes contain a pyramidal phosphorus atom and are not fully conjugated; their anions, however, are. Synthesis is therefore generally aimed at these anions, i.e. at alkali metal 1,3-diphospholides (**11**) and 1,3-benzodiphospholides (**3**). In some cases they can be converted to neutral diphospholes by protonation, alkylation, silylation, acylation, or oxidation (see Section 3.16.3.5.1). 1,3-Diphospholes and 1,3-benzodiphospholes have also been prepared by direct synthesis. 1,1,1,3,3-Pentaphenyl-1 λ^5 ,3 λ^5 -benzodiphospholes have also been reported <95AG2186>.

(i) PCCP/As + C

This is the only pattern for specific syntheses. Starting materials are 1,2-diphosphinoalkenes or -benzenes, preferably in their metalated form. The former are obtained from the reductive cleavage of 1,2-dihydro-1,2-diphosphetes <92MI 316-01>. Condensation partners are the carboxylic or carbonic acid derivatives.

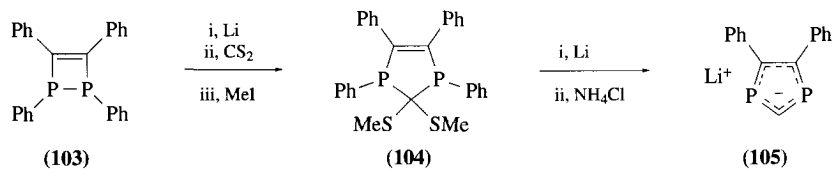
(ii) CP + CP + C

The 1,3-diphosphole ring forms by this pattern from phosphalkynes in disproportionation reactions.

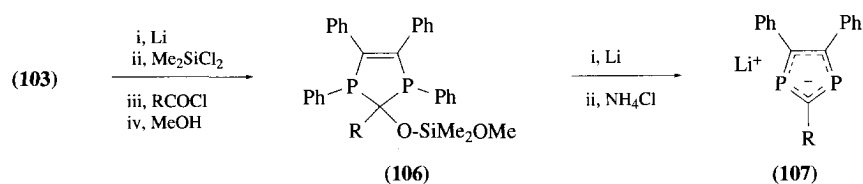
3.16.4.5.2 Synthesis from 1,2-diphosphines/phosphinoarsines

Reaction of dihydro-1,2-diphosphetes (**103**) and (**108a**) with lithium metal and carbon disulfide, methyl iodide <90AG575>, or dimethyldichlorosilane, acyl chloride, methanol <92OM459>, or dichloromethane <92POL601> gives dihydro-1,3-diphospholes (**104**), (**106**), and (**109a**), respectively. Reaction

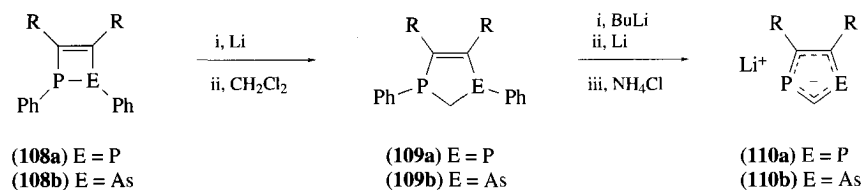
with excess lithium converts them into diphosphole dianions of unknown structure which are monoprotonated by dry ammonium chloride to **(105)**, **(107; R = (CH₂)_{3/2}, Bn, Ph)**, and **(110a; R = Me, Et, Bu^t)** (Schemes 10–12). Related to the second step is the reduction of the octaphenyl tetraphosphafulvalene to give the 2,2'-bis(1,3-diphospholyl) dianion <92AG1082>.



Scheme 10



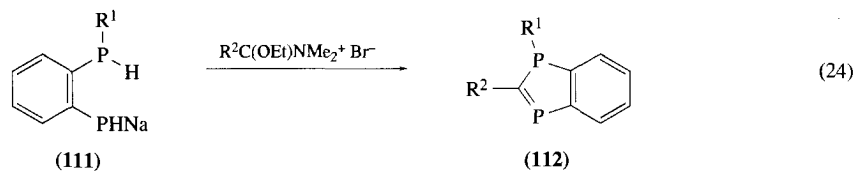
Scheme 11



Scheme 12

The 1,3-phosphaarsolide **(110b; R = Et)** is accessible from the dihydro-1,2-phosphansete **(108b)** <93BSF521, 93PS(77)254>.

Condensation of sodium 1,2-diphosphino benzene **(111)** with carbonic or carboxylic acid derived carbenium salts gives 1,3-benzodiphospholes **(112; R² = H, Me, NMe₂)** (Equation (24)) <81TL4475, 83PS(18)15, 87JOM(330)17>.

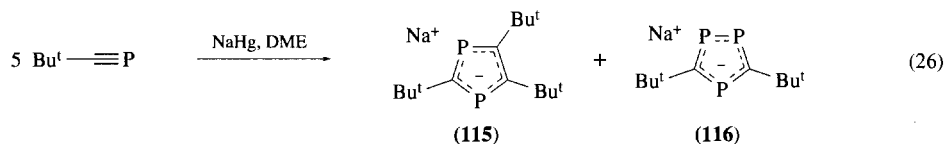


Tetrakis(trimethylsilyl)-1,2-diphosphinobenzene **(113)** after lithiation reacts with carbon dioxide, diphenyl carbodiimide, and acylchlorides to give lithium 1,3-benzodiphospholides **(114)** (Equation (25)), R = O-TMS <88ZC255>, NPhLi <85ZAAC(529)216>, Me, Bu^t, Ph, Mes <90JOM(382)53, 90PS(49)355>. Dihydro-1,3-benzodiphospholes have also been prepared from 1,2-diphosphino benzenes <84ZAAC(519)75>.

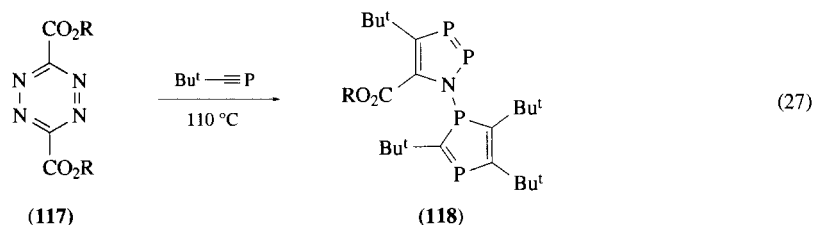


3.16.4.5.3 Synthesis from phosphalkynes

The 1,3-diphospholide anion (**115**) is formed in the reaction of $\text{LiP}(\text{TMS})_2$ and $\text{Bu}^t\text{C}\equiv\text{P}$ <85MI 316-01, 87CC1146>. Reduction of *t*-butyl phosphacetyne with sodium amalgam <89POL2407> or a low-valent tantalum species leads to a 1:1 mixture of the sodium 1,3-diphospholide (**115**) and 1,3,4-triphospholide (**116**) which can be separated by fractional crystallization (Equation (26)) <89POL849>. Mixtures of $\text{Pr}^i\text{C}\equiv\text{P}$ and $\text{Bu}^t\text{C}\equiv\text{P}$ have also been reduced <91JOM(415)C15>.



Heating 1,2,4,5-tetrazine dicarboxylates (**117**) with *t*-butyl phosphacetyne yields a 1,2,3-azadiphospholyl-1,3-diphosphole (**118**; R = Me, Et) (Equation (27)) <88TL5867>.



3.17

Two Adjacent Heteroatoms with at least One Boron

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3.17.1 INTRODUCTION

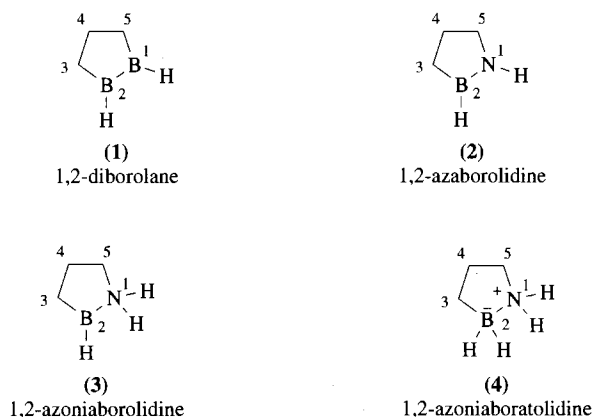
3.17.1.1 Relations to *Comprehensive Heterocyclic Chemistry, First Edition*

Five-membered heterocycles with two adjacent heteroatoms with at least one boron atom were discussed very sparsely in the first edition of *Comprehensive Heterocyclic Chemistry* (CHEC-I) <84CHEC-I(1)637>. Only the class of 1,2-azaborolines was described a little more comprehensively. Other types such as 1,2-azaborolidines, the 1,2-oxaborolanes, and the 1,2-oxaboroles were completely neglected. For that reason it seems appropriate to discuss these heterocycles in more detail. This requires partial consideration of literature before 1982.

3.17.1.2 Types of Rings; Nomenclature

As was done in CHEC-I <84CHEC-I(1)630>, the nomenclature in this chapter follows the borane and the borate nomenclature. Systematic rules are avoided if trivial names are available. If this is not the case, the general nomenclature of heterocycles is used. The following description of the different types of compounds elucidates structures and nomenclature (1)–(22).

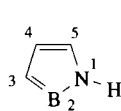
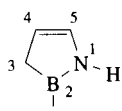
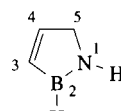
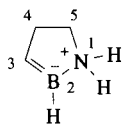
Diborolanes (1) consist of fully saturated five-membered rings with two boron atoms in 1,2 or in 1,3 position (see 3.18). They exist only in a few examples which have been described by Siebert *et al.* (see Section 3.17.9). 1,2-Azaborolidines (2), saturated boron–nitrogen heterocycles, are numerous described in the literature, as well as the 1,2-azoniaborolidines (3) with a quaternary nitrogen atom, and the 1,2-azoniaboratolidines (4) with an additional fourfold boron atom. “Azonia” and “borat”, respectively, express the existence of the formally positively charged nitrogen atom, and the negatively charged boron atom.



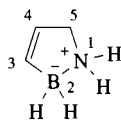
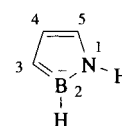
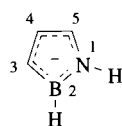
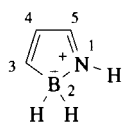
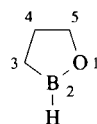
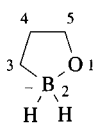
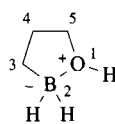
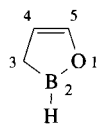
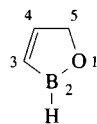
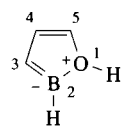
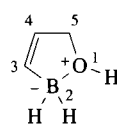
1,2-Azaboroles (5) exist only as 2,3-dihydro (6) or as 2,5-dihydro (7) derivatives. The generation of these unsaturated rings has already been mentioned in CHEC-I <84CHEC-I(1)648>. Quaternization of nitrogen and boron gives the 1*H*-2,5-dihydro-1,2-azoniaboratoles (8) and (9). 1*H*-1,2-Azaboroles can easily be deprotonated to form the 1*H*-1,2-azaboratoles (10), which are better described as fully conjugated 6π electron systems (11), usually called “1,2-azaborolyl” rings, following the term “cyclopentadienyl” which is used for the isosteric and isoelectronic C₅H₅ ring. 1,2-Azaborolyl rings are manifold complex ligands and can be regarded as BN-perturbed aromatic systems. The prochiral character of the C₃BN frame leads to interesting chiral consequences, if the rings are used in half sandwich or in sandwich complexes (see 3.17.4.4 and 3.17.5.3). 2*H*-1,2-Azoniaboratoles (12) formally derive from 1,2-azaboratoles (10) by additional hydrogenation of the boron atom, accompanied by a shift of the double bonds.

1,2-Oxaborolanes (13) contain saturated atoms only and are characterized by adjacent oxygen and boron atoms. The boron as well as the oxygen atom can be charged, as is realized in the 1,2-oxaboratolanes (14) and the 1,2-oxoniaboratolanes (15). 1,2-Oxaboroles (16) exist only as 2,3- and 2,5-dihydro derivatives (17, 18). The 1,2-oxoniaboratole (19) has been described as the 2,5-dihydro derivative (20).

Substitution of oxygen in 1,2-oxaborolanes by sulfur leads to the related 1,2-thiaborolanes (21). 1,2-Azaboroles, 1,2-oxaboroles, and 1,2-thiaboroles (22), respectively, also exist as benzo-derivatives.

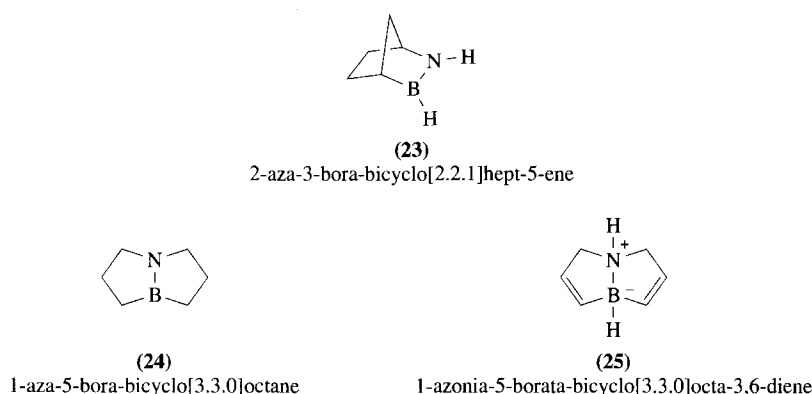
(5)
1,2-azaborole(6)
1H-2,3-dihydro-1,2-azaborole(7)
1H-2,5-dihydro-1,2-azaborole(8)
1H-1,2-azoniaboratole

exists as

(9)
1H-2,5-dihydro-1,2-azoniaboratole(10)
1,2-azaboratoleexists as conjugated
6π system(11)
trivial name:
1,2-azaborolyl(12)
2H-1,2-azoniaboratole(13)
1,2-oxaborolane(14)
1,2-oxaboratolane(15)
1,2-oxoniaboratolane(16)
1,2-oxaborole(17)
2,3-dihydro-1,2-oxaborole(18)
2,5-dihydro-1,2-oxaborole(19)
1,2-oxoniaboratole(20)
2,5-dihydro-1,2-oxoniaboratole



Some bicyclic BN heterocycles are mentioned to explain the rules of nomenclature. Owing to the lack of appropriate fundamental compounds with trivial names, the general heterocycle nomenclature is used ((23)–(25)).



3.17.2 THEORETICAL METHODS

Theoretical attempts to describe structure and bonding in five-membered rings containing one boron and one additional heteroatom are known in only one case. MNDO Calculations have been performed for the 1*H*-2,5-dihydro-1,2-azaborole and the anionic 1,2-azaborolyl ring system <82CB732>.

Considering that the calculated structures and the experimentally investigated compounds differ considerably, the agreement of the bonding increments is quite satisfying. Table 1 contains the calculated and the experimental data for the two pairs of compounds. As the 2,3-dihydro-2-methyl-1*H*-1,2-azaborole in Table 1 exists as a dimer in the solid state, BH₂ and NH₂ moieties have been used for the calculations to simulate the *sp*³-hybridization of the boron and nitrogen atoms in the existing derivative.

3.17.3 EXPERIMENTAL STRUCTURAL METHODS

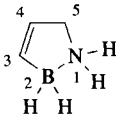
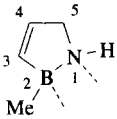
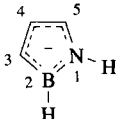
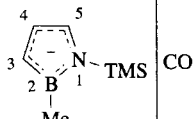
3.17.3.1 Single-crystal X-ray Analyses

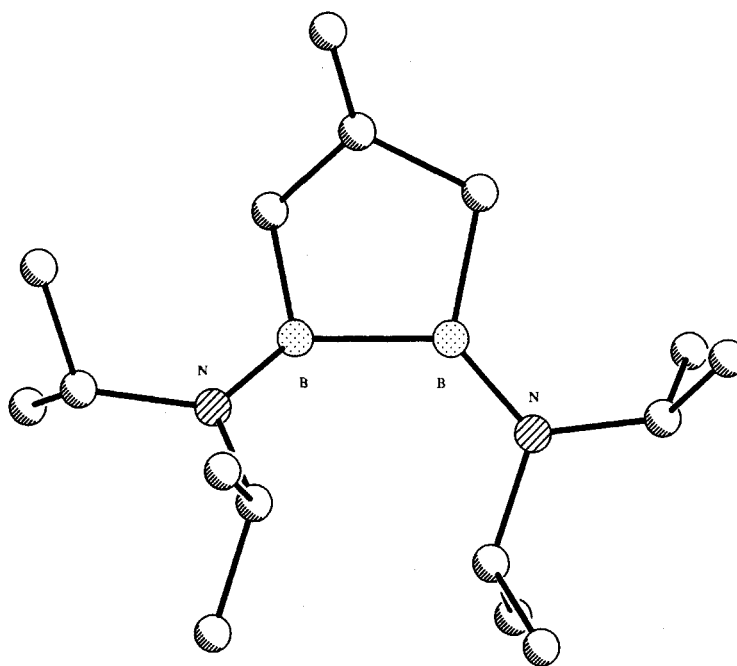
Single-crystal x-ray analyses require solid materials. However, small five-membered rings in most cases do not form crystals at normal temperatures. Techniques have been developed to investigate crystals at low temperatures, and even crystal growth of liquids on the goniometer of the four-cycle diffractometer is an established method <B-94MI 317-01>. The expense of such special methods explains the relatively small number of x-ray structure analyses performed on the compounds discussed in this chapter. The structure of a 1,2-diborolane derivate was described in 1990 by Herberich *et al.* <90AG(E)912>. It is characterized by a B—B single bond of 172.3 pm and two exocyclic B—N bonds showing considerable π interactions, as can be seen from the distances of 139–140 pm (Figure 1).

The 3-methylene derivate was described by Siebert and co-workers in 1992 <92AG(E)1603>. There is no significant difference between the two isomers, except the position of the methylene substituent.

The 4-methylene-1,2-diborolane of Figure 1 can be converted into the dianion by deprotonation. It crystallizes with lithium tetramethylethylenediamine as counterion (Figure 2) <92CB23>. This anion can be considered as a 2,3-diboratafulvene derivative. The B—C distances are remarkably shortened by 12 pm compared with the neutral compound of Figure 1, whereas the B—B bond length is increased from 172.3 to 179.9 pm.

Table 1 Experimental and MNDO-calculated structural parameters of 1*H*-2,5-dihydro-1,2-azaborole and the 1,2-azaborolyl anion.

			
Distance (pm)	Angle (deg)	Distance (pm)	Angle (deg)
B(2)—N(1) 162.5	B(2)—N(1)—C(5) 108.7	162.6	109.4
B(2)—C(3) 156.3	N(1)—C(5)—C(4) 104.7	159.3	105.9
C(3)—C(4) 135.3	C(5)—C(4)—C(3) 114.1	130.6	113.8
C(4)—C(5) 150.5	C(4)—C(3)—B(2) 112.1	146.8	113.1
C(5)—N(1) 151.9	C(3)—B(2)—N(1) 100.5	146.9	96.9
			
B(2)—N(1) 144.1	B(2)—N(1)—C(5) 109.8	143	108
B(2)—C(3) 146.5	N(1)—C(5)—C(4) 107.4	151	109
C(3)—C(4) 143.0	C(5)—C(4)—C(3) 110.5	136	110
C(4)—C(5) 139.4	C(4)—C(3)—B(2) 106.4	139	108

**Figure 1** Molecular structure of 1,2-bis(diisopropylamino)-4-methylene-1,2-diborolane at 120 K.

1,2-Azaboroles exist as manifold derivatives. The C_3BN framework is isoelectronic with the C_5 unit in cyclopentadiene and so attracts great interest as complex ligand, especially as the deprotonated version discussed below. 1,2-Azaboroles exist as 2,3- and 2,5-dihydro derivatives (Section 3.17.4.3). X-ray structure analyses have only been described of the 2,3-dihydro isomers. Two of them are mentioned here.

As one of a few examples, the 3-diphenylphosphanyl-3-trimethylsilyl derivative (Figure 3) crystallizes at room temperature and therefore could be used for a single-crystal x-ray structure analysis [94CB1891].

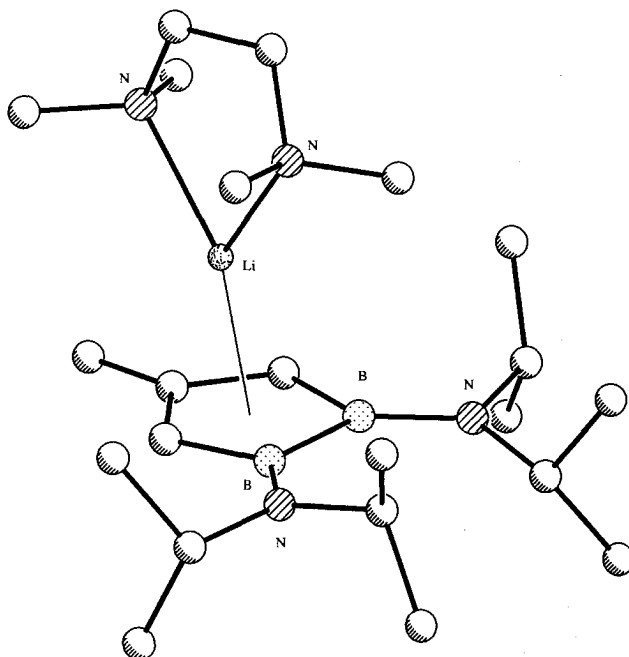


Figure 2 Structure of 2,3-bis(diisopropylamino)-2,3-diboratafulvene(tetramethylenediamine-*N,N'*)lithium.

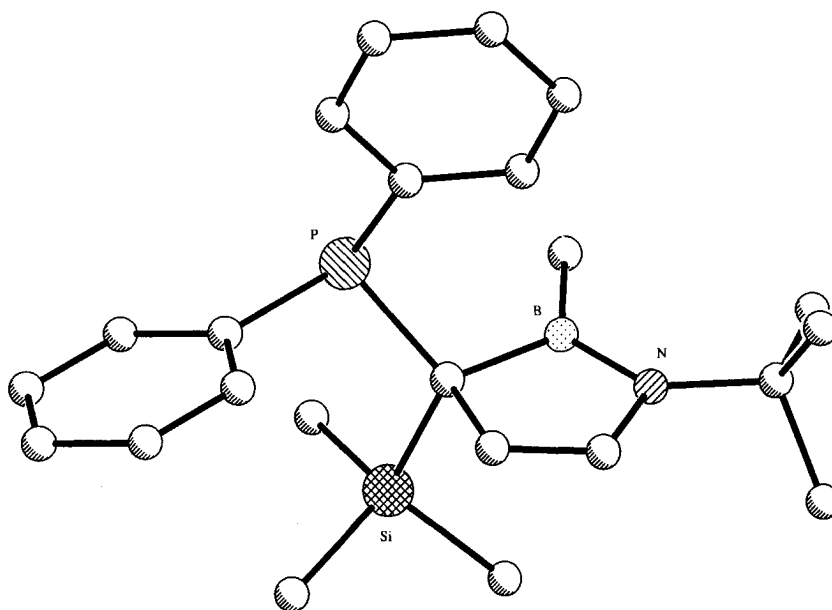


Figure 3 Molecular structure of 1-*t*-butyl-2,3-dihydro-3-diphenylphosphanyl-2-methyl-3-trimethylsilyl-1*H*-1,2-azaborole.

The B—N distance corresponds, as expected, to strong π -bond interactions. The existence of the C=C double bond is indicated by the C(4)—C(5) bond length of 133 pm.

Two 2,3-dihydro-1,2-azaboroles are linked via a silicon atom in the example shown in Figure 4 <88CB1873>. The structural data of the C₃BN ring framework are not significantly different from those of the example in Figure 3. However, there is one special property to be mentioned, namely the chirality of the C-3 atom. This can easily be seen from the structure in Figure 4 as, owing to the linkage between two molecules by the SiCl₂ group, they are oriented as mirror images. Chiral problems of azaborole rings will be discussed in more detail in Section 3.17.4.4.

An important structure to be mentioned is that of a 1*H*-1,2-azaboratole, the trivial name of which

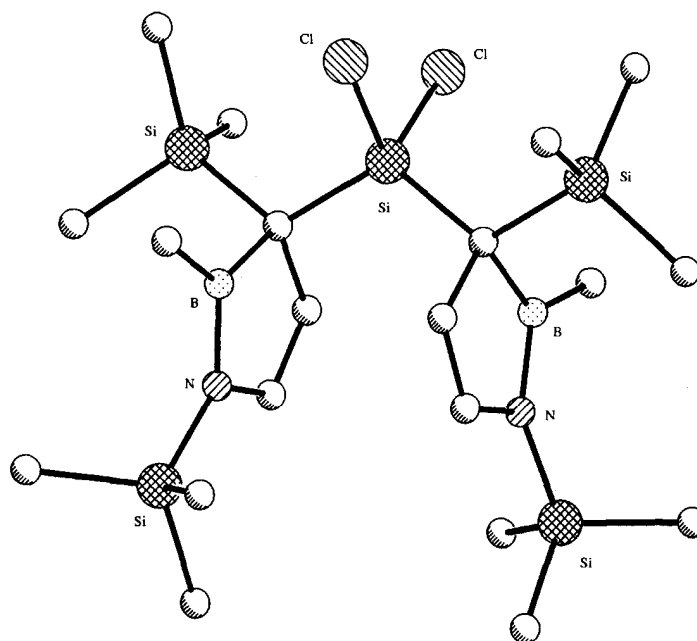


Figure 4 Molecular structure of dichlorobis[2,3-dihydro-2-methyl-1,3-bis(trimethylsilyl)-1*H*-1,2-azaborolyl] silane.

is 1,2-azaborolyl. This formal ion is isoelectronic with the cyclopentadienyl ring, the importance of which is seen in its extraordinary properties as complex ligand. In principle the 1*H*-1,2-azaborolyl ring can act in the same manner in complexation chemistry. However, owing to its prochiral character, in combination with a metal atom it forms chiral complex fragments. This special property will also be discussed in 3.17.4.4.

One of the numerous 1*H*-1,2-azaborolyl anions was analyzed structurally as its lithium salt (Figure 5) <88CB1873>. The C—C bond lengths are more or less completely averaged and the BN unit is also involved in the delocalization of π electrons.

This heteroaromatic character of 1,2-azaborolyl rings qualifies them to form numerous transition metal complexes. In contrast to the cyclopentadienyl ligand there is still a remarkable disturbance caused by the boron and nitrogen atoms. This becomes visible if those transition metals are used for complexation that cannot reach the 18-electron configuration in normal sandwich complexes. As a consequence, electron-rich metals tend to increase the distance to the electron-rich nitrogen atoms, whereas electron-poor metals tend to increase the distance to the boron atom. Three examples illustrate these structural features of 1,2-azaborolyl rings.

In Figure 6, an iron sandwich complex with η^5 -coordination of the azaborolyl rings is shown. The iron atom is located exactly above and below the centers of the rings, so reaching the ideal 18-electron configuration.

The example in Figure 7 shows a corresponding cobalt complex. The cobalt atom is shifted from the ring centers in such a way that the interaction with the N atom is reduced and so the electron density is decreased.

An increase of electron density is aimed at by the electron-poor vanadium atom (Figure 8) which as a maximum can reach 15 electrons in a normal cyclopentadienyl sandwich complex.

3.17.3.2 NMR Spectroscopy

NMR spectroscopy is probably the most important method for elucidating the structure and bonding of all compounds described in this chapter. As these compounds are often liquids or can easily be dissolved in organic solvents, the electronic behavior of single molecules can be studied in rather short times. Solid-state NMR techniques play a much less important role. However, NMR spectroscopy not only enables clarification of structural details but can also be used to follow the progress of reactions during the synthesis of known or unknown compounds. Furthermore, the

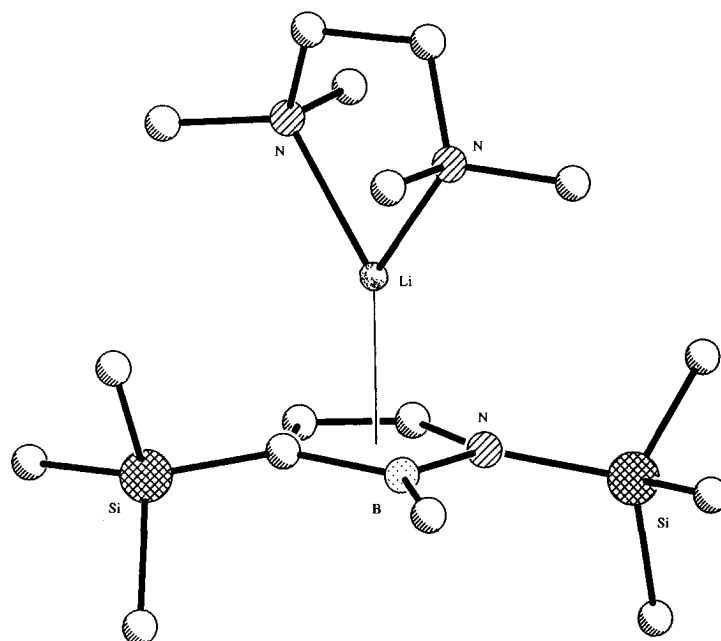


Figure 5 Structure of 2-methyl-1,3-bis(trimethylsilyl)-1*H*-1,2-azaborolyl(tetramethylethylenediamine-*N,N'*) lithium.

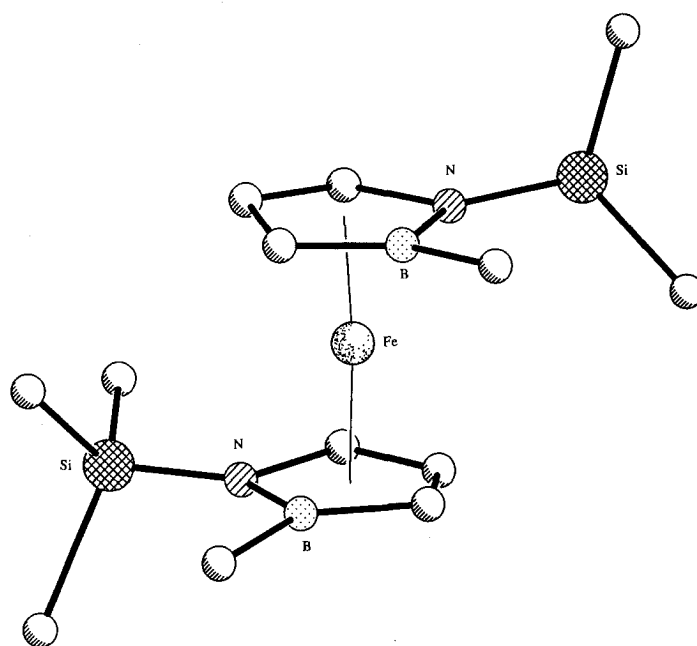


Figure 6 Molecular structure of bis(2-methyl-1-trimethylsilyl- η^5 -1,2-azaborolyl)iron (82CB3830).

study of dynamic processes in solution is a specific advantage of NMR spectroscopy. Among the various nuclei usable for NMR experiments, NMR of ^{11}B is the most important when boron-containing compounds are investigated. Many experiments can be followed through ^{11}B NMR spectra, as in most cases the chemical shift of the starting material is characteristically different from that in the expected compound. Also, the characterization and isolation of intermediates has become

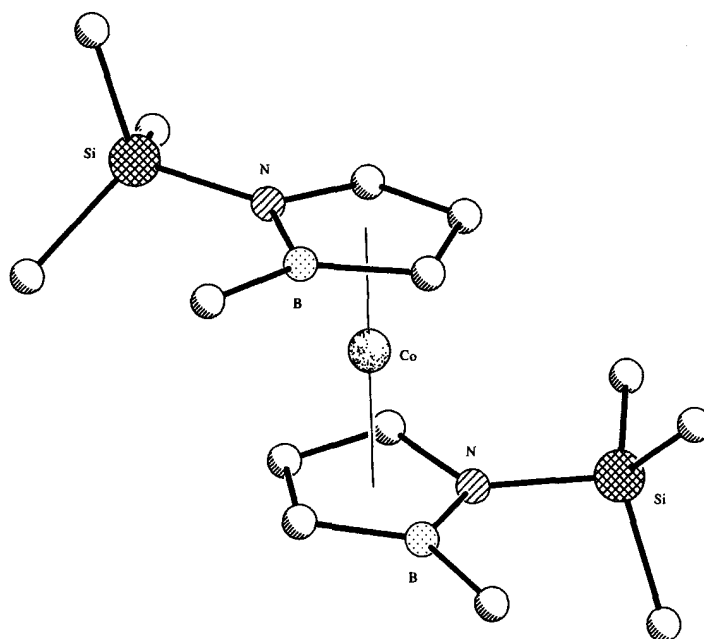


Figure 7 Molecular structure of bis(2-methyl-1-trimethylsilyl-1,2-azaborolyl)cobalt <82CB732>.

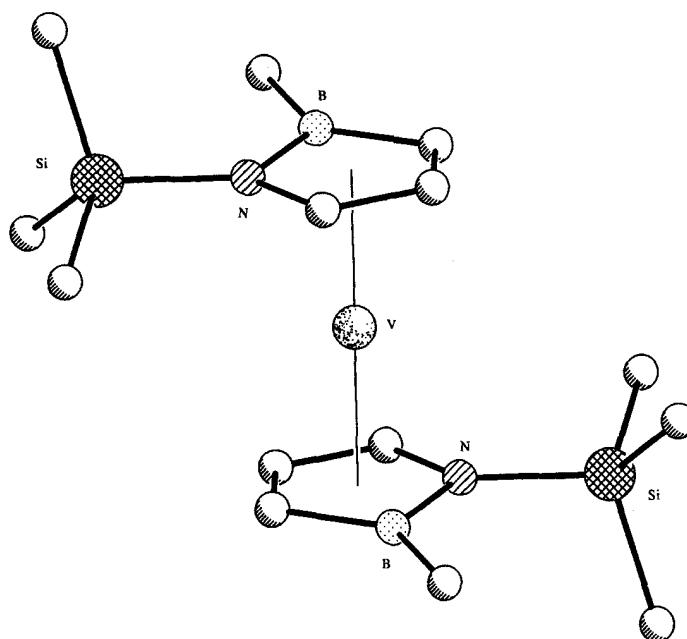


Figure 8 Molecular structure of bis(2-methyl-1-trimethylsilyl-1,2-azaborolyl)vanadium <82CB3830>.

possible using ^{11}B NMR spectroscopy. However, the most effective route is to combine as many of NMR parameters as possible— $\delta^1\text{H}$, $\delta^{11}\text{B}$, $\delta^{13}\text{C}$, $\delta^{14}\text{N}$, etc.

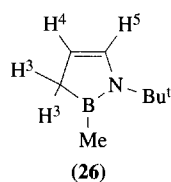
3.17.3.2.1 Proton NMR spectra

Proton NMR spectroscopy is preferred for identifying endocyclic and exocyclic organic groups of the heterocycles. The boron atom in organoboron compounds influences the chemical shift $\delta^1\text{H}$.

For saturated organic moieties, a high-field shift is often observed compared with related organic compounds. This is a consequence of the electropositive character of the boron atom <61JCP(35)722, 68JOM(12)23>. For instance, the ^1H NMR signal of the BMe_3 group in all known dihydro-1,2-azaboroles can be observed as a singlet between 0.5 and 1.0 ppm <88CB1873>. The nuclear magnetic properties of the boron isotopes (^{10}B , ^{11}B) usually cause a broadening of the ^1H NMR signals of organic groups directly bonded to the B atom, as a result of their quadrupole moment. Heteronuclear decoupling experiments $^1\text{H}(^{11}\text{B})$ help to solve such problems <74ZOB1882, 75CB3831>. Boron-bonded hydrogen atoms can normally only be registered with difficulty as broad signals of low intensity, except those of tetracoordinated boron atoms.

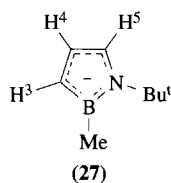
The ^1H NMR shift of unsaturated organic moieties in five-membered rings is influenced by several, sometimes opposed, effects and therefore trends can hardly be described.

An example showing the usefulness of a ^1H NMR spectrum is given by 1-*t*-butyl-2,3-dihydro-2-methyl-1*H*-1,2-azaborole and the corresponding 1,2-azaborolyl derivative (1*H*-1,2-azaboratol) (26).



$\delta^1\text{H}$:				
BCH_3	$\text{C}(\text{CH}_3)_3$	H-3	H-4	H-5
0.73	1.19	1.80	5.40	6.55
s (broad)	s	m	dd, $^3J_{\text{H-5}} = 4.2 \text{ Hz}$, $^3J_{\text{H-3}} = 2.6 \text{ Hz}$	dd, $^3J_{\text{H-4}} = 4.2 \text{ Hz}$, $^5J_{\text{H-3}} = 3.9 \text{ Hz}$

From simple decoupling experiments the signals of H-3 and H-4 can clearly be assigned. One of the two H-3 atoms can be removed as a proton by means of lithiumtetramethylpiperidide. The resulting anion (27) has three unsaturated CH units. Again, they can all be assigned by decoupling experiments or by 2D NMR techniques so that the characterization succeeds completely.

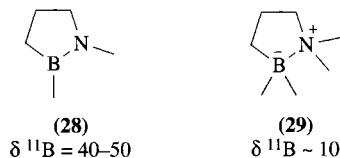


$\delta^1\text{H}$:				
BCH_3	$\text{C}(\text{CH}_3)_3$	H-3	H-4	H-5
0.53	1.39	3.81	5.61	5.91
s(9)	s(3)	dd, $^3J_{\text{H-4}} = 5 \text{ Hz}$, $^4J_{\text{H-5}} = 2.5 \text{ Hz}$	dd, $^3J_{\text{H-3}} = 5 \text{ Hz}$, $^3J_{\text{H-5}} = 2.5 \text{ Hz}$	dd, $^3J_{\text{H-4}} = 2.5 \text{ Hz}$, $^4J_{\text{H-3}} = 2.5 \text{ Hz}$

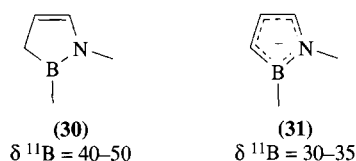
3.17.3.2.2 Boron-11 NMR spectra

As mentioned in 3.17.3.2, ^{11}B NMR spectroscopy is best suited to observing electronic changes in the neighborhood of the boron atom. The quadrupole moment of the boron atom normally causes broad signals. This disadvantage can be reduced by ^1H broadband decoupling or by an increase of temperature. The broadened signals may sometimes lead to some complications with signal overlapping. On the other hand, the region of the ^{11}B chemical shifts is of the order of 250 ppm <B-78MI 317-01, 79MI 317-01, 82MI 317-01> so that even small electronic changes at the boron atom lead to an observable shift. Boron-11 NMR spectroscopy is the most suitable method for distinguishing between three- and four-coordinated boron atoms. In boron–nitrogen and boron–oxygen compounds, the π -interaction between boron and nitrogen, and boron and oxygen, respectively, leads to a considerable increase of the electron density of the boron atom. Thus, ^{11}B NMR spectra give information about the strength of the B–N and the B–O bonds. Some examples of five-membered rings discussed in this chapter will elucidate these statements. Whereas in the satu-

rated 1,2-azaborolidines the ^{11}B NMR shift is observed typically in the region of 40–50 ppm, the transfer to the 1,2-azoniaboratolidines with sp^3 hybridized B atoms shifts $\delta^{11}\text{B}$ to around 10 ppm (28), (29) <B-78MI 317-01>.

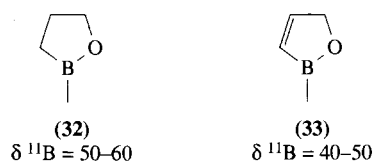


The transition of a 1*H*-2,3-dihydro-1,2-azaborole (30) to the deprotonated 1*H*-1,2-azaboratole (1,2-azaborolyl) (31) again shows the sensitivity of this tool <88CB1873>.

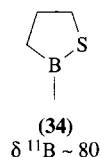


The delocalization of the π electrons in the anionic 1,2-azaborolyl system increases the electron density at the boron atom, manifested in a high-field shift. Oxygen is a less effective π donor for a Lewis acidic boron atom compared with nitrogen.

Oxaborolanes (32) show $\delta^{11}\text{B}$ values around 50–60 ppm. As in the boron nitrogen heterocycles, the transition to the unsaturated derivatives, the oxaboroles (33), results in a high-field shift.



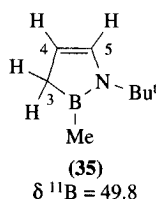
The decrease in π interaction on changing from B—O to B—S can also be followed by means of ^{11}B NMR. In 1,2-thiaborolanes (34) the ^{11}B NMR signal is observed around 80 ppm, indicating a more or less pure single bond between boron and sulfur atoms.



3.17.3.2.3 Carbon-13 NMR spectra

Carbon-13 NMR spectra of heterocycles provide an insight into the carbon part of the molecule and so can help to analyze structure and bonding in addition to ^1H and ^{11}B NMR information. As in ^1H NMR spectroscopy, the quadrupole nuclei ^{10}B and ^{11}B broaden the ^{13}C NMR signals of boron-neighbored carbon atoms. In some cases this may help to distinguish between carbon atoms linked with boron atoms or with other elements. Boron-11 decoupling experiments are best suited to suppressing CB coupling.

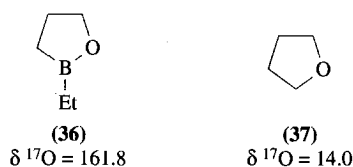
The ^{13}C NMR data of 1-*t*-butyl-2,3-dihydro-2-methyl-1*H*-1,2-azaborole (35) demonstrate the ability for characterization beyond doubt <88CB1873>.



$\delta^{13}\text{C}$:					
BCH_3	$\text{C}(\text{CH}_3)_3$	$\text{C}(\text{CH}_3)_3$	C-3	C-4	C-5
2.6(broad)	31.35	53.7	29.9	110.71	138.66

3.17.3.2.4 Oxygen-17 NMR spectra

Oxygen-17 NMR spectroscopy has led to important information about π -bonding between boron and oxygen atoms in general $\langle 80\text{CB}333, 82\text{CB}2022 \rangle$. However, information about boron- and oxygen-containing five-membered rings is rather rare. 2-Ethyl-1,2-oxaborolane (36) has been investigated by ^{17}O NMR spectroscopy $\langle 82\text{CB}2022 \rangle$. The value of $\delta^{17}\text{O} = 161.8$ can be compared with that of $\delta^{17}\text{O} = 14.0$ for the boron-free ring (37). It can be concluded that the low-field shift in the borolane is due to a considerable π back-bonding from oxygen to boron, compared with the carbon system.



To summarize the NMR characterization of boron-containing five-membered ring systems, the combination of ^1H , ^{11}B , and ^{13}C NMR spectra allows a perfect description of the molecules in liquid phase.

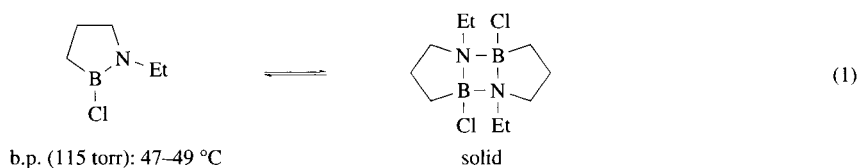
3.17.3.3 Infrared Spectroscopy

Compared with NMR spectroscopy, vibrational spectroscopy plays a much less decisive role in the characterization of boron-containing heterocycles because of the lack of vibrations which could give characteristic information about structure and bonding in most cases. Best suited for IR spectroscopic investigations are unsaturated rings with $\text{C}=\text{C}$ double bonds. For instance, 2,2,3-triethyl-1,1,4-trimethyl-1*H*-2,5-dihydro-1,2-azoniaboratole and 2,2,3,4-tetraethyl-1-methyl-2,5-dihydro-1,2-oxoniaboratole display easily determined $\nu(\text{C}=\text{C})$ vibrations at 1636 cm^{-1} $\langle 75\text{CB}395 \rangle$ and 1640 cm^{-1} $\langle 74\text{S}350 \rangle$, respectively.

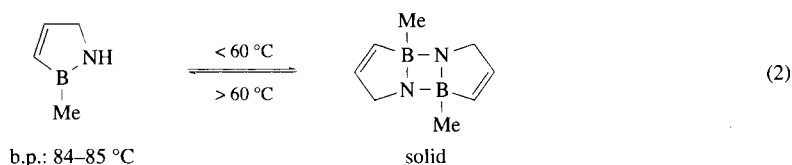
3.17.4 THERMODYNAMIC ASPECTS

3.17.4.1 Intermolecular Interactions

By far the majority of the derivatives of the compounds considered in this chapter are liquids under normal conditions with boiling points roughly corresponding to their molecular masses. This is especially the case for the oxygen-containing rings. However, nitrogen-containing rings can interact via $\text{B}-\text{N}$ acid-base forces to give dimers; whether this happens depends more or less exclusively upon steric considerations. Thus, small substituents enable dimerization, bulky ones prevent it. As an example, the 1,2-azaborolidines are mentioned. The liquid 1-alkyl-2-chloro-1,2-azaborolidines dimerize slowly at room temperature (Equation (1)) $\langle 70\text{ZOB}1817 \rangle$.

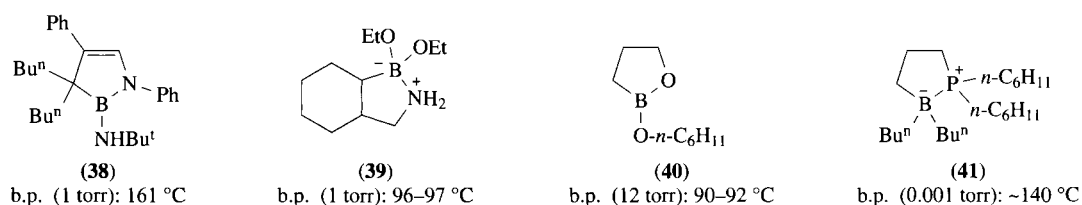


The intermolecular bond can easily be broken by heating to the boiling temperature of the monomer. Equivalent behavior is observed for 1,2-azaboroles if they bear small substituents, as in Equation (2), for example <81CB1297>.



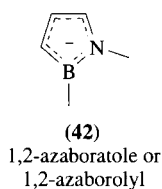
If the nitrogen atom is substituted, for instance by CMe_3 or TMS, dimerization is not observed. Another kind of intermolecular interaction is in principle possible but has so far never been observed, namely, Diels–Alder dimerization via the $\text{C}=\text{C}$ double bonds in 1,2-azaboroles.

As mentioned, the boiling points of the different B–O, B–N, B–S etc. rings depend on the molecular masses. The boiling points can thus reach remarkable temperatures, indicating that the compounds in general are thermodynamically very stable systems. Some such high-boiling rings are illustrated (38)–(41) <65IZV1618, 67CR(C)977, 70IZV1374, 81UP317-01>.



3.17.4.2 The Aromaticity Problem

Among the five-membered rings with boron and a second heteroatom, aromaticity is only relevant for anionic systems which are isoelectronic with C_5H_5^- . This is the case for only one type of compound, the 1,2-azaborolyl ring (1,2-azaboratole) (42). This anion derives from the neutral 1*H*-1,2-azaborole by abstraction of a proton, as when cyclopentadiene is transformed into the cyclopentadienide.



This system has already been discussed in Section 3.17.3 as a very interesting type of ligand. It exists as the lithium <88CB1873> or as thallium <94CB1891> salt with various substituents. Although there is an obvious relationship with C_5H_5^- , the presence of boron and nitrogen atoms disturbs the aromaticity considerably. The relationship with the cyclopentadienide anion is most pronounced in its behavior as a complex ligand. Numerous half-sandwich and sandwich complexes with transition and main-group metals have been synthesized and investigated by x-ray structure analysis; some of these have already been mentioned in Section 3.17.3. In spite of the structural similarities, the BN

disturbance of the aromaticity can best be explained by a simple MO diagram. Figure 9 elucidates the difference between the π -bond in a BN and in a C_2 moiety.

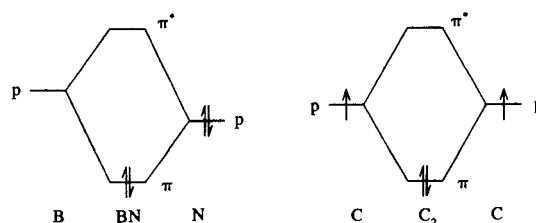
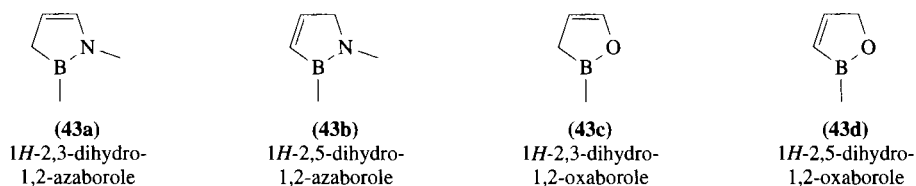


Figure 9 Comparison of the π -bond between B and N in an aminoborane and between two C atoms in a $C=C$ double bond.

Because of the electronegativity of nitrogen, the π -electron pair in the BN group is closely localized at the N atom, whereas the antibonding π^* -orbital is more related to the unoccupied p -orbital of the boron atom. In the C_2 case, there is no difference between the contributing orbitals, resulting in an ideal $C=C$ double bond. As a consequence, boron and nitrogen atoms in azaborolyl rings behave chemically quite differently. This is easily seen in reactions of 1,2-azaborolyl rings with Lewis acids and Lewis bases. Lewis acids such as BX_3 or AlX_3 , and also H^+ , attack the nitrogen atom. Owing to this behavior, 1,2-azaborolyl rings are easily attacked by various electrophiles and nucleophiles, not only in salts but even coordinated to transition metals.

3.17.4.3 Isomerism

Isomerism among five-membered rings with two adjacent heteroatoms is only possible in unsaturated molecules, owing to the different positions of the $C=C$ double bond relative to the heteroatoms. 1,2-Azaboroles (**43a,b**) and 1,2-oxaboroles (**43c,d**) in principle can each form two isomers. All four types of compounds have been realized by variously substituted derivatives. The formation of the 2,3- or 2,5-dihydro isomers depends on the synthetic conditions and will be discussed in Section 3.17.9.



3.17.4.4 Chirality Problems

Two kinds of chirality in five-membered rings with two adjacent heteroatoms are possible:

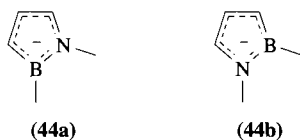
(i) The saturated carbon atom in 1,2-azaboroles and in 1,2-oxaboroles is substituted by two different substituents.

(ii) The 1,2-azaboratole (1,2-azaborolyl) ring itself is prochiral, owing to the lack of any symmetry element. Combination of such a prochiral ring with a metal atom gives a chiral complex fragment.

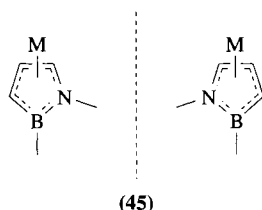
Both cases have been realized and are discussed briefly.

Type (i): If 1,2-azaborolyl salts react with various element halides, substitution in the 3-position usually occurs.

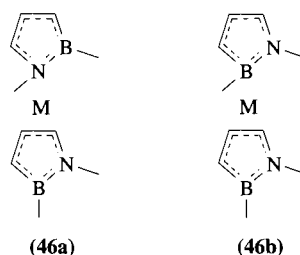
Type (ii): The C_3BN framework presents two different sites, owing to the lack of symmetry (**44a,b**).



Combination of the different faces with a transition metal atom gives pairs of enantiomers (45).

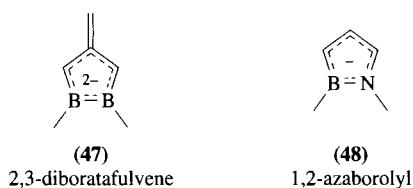


Combination with a second C_3BN ring leads to diastereoisomers which can be separated (46a,b). In the diastereoisomer (46a) the metal M uses the same ring sites, whereas in (46b) different sites are coordinated. Many examples have been described by Schmid where both isomers are formed and could be separated and characterized by single x-ray structure analysis [85MI 317-01]. This chiral property of 1,2-azaborolyl rings in combination with metal atoms has some interesting consequences with respect to stereoselective reactions.



3.17.5 REACTIVITY OF FULLY CONJUGATED RINGS

Among the five-membered rings with one boron atom and one additional adjacent heteroatom there are only two kinds of rings to be considered as fully conjugated: the anionic 2,3-diboratafulvene (47), mentioned already in Section 3.17.3.1, and the more frequently described and better investigated 1,2-azaboroles (48), normally called 1,2-azaborolyl rings, also mentioned previously (Section 3.17.4.4).

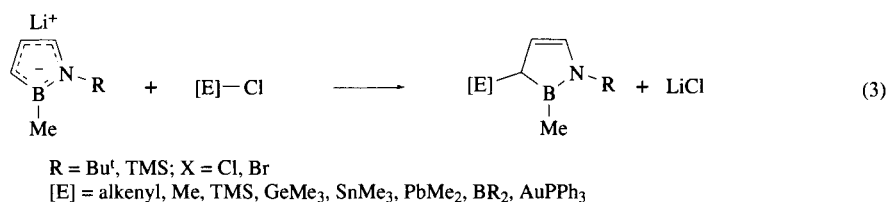


Both systems are anionic and so only exist in combination with various cations. In the simplest case this can be Li^+ , or, as frequently described for the 1,2-azaborolyl rings, other main-group or transition metals are used to synthesize half-sandwich and sandwich complexes. Some of the 1,2-azaborolyl compounds are selected for discussion here.

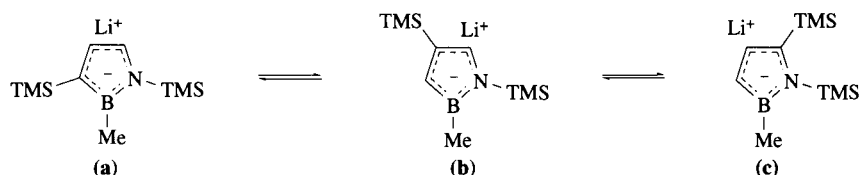
3.17.5.1 Electrophilic Attack at Carbon

The reactivity of the 1,2-azaborolyl rings is mainly influenced by the heteroatoms boron and nitrogen. Thus, if 1,2-azaborolyl lithium salts are reacted with element chlorides, the substitution

generally occurs at the boron-neighboring C-3 atom, leading to 1*H*-2,3-dihydro-1,2-azaboroles (Equation (3)) <88AG(E)952, 88CB1873>.

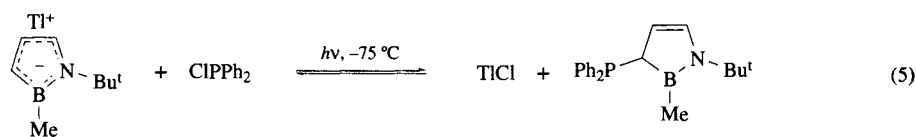
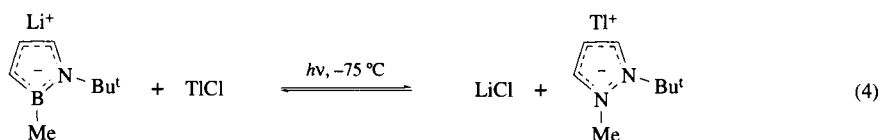


The electropositivity of the boron atom makes C-3 obviously the most nucleophilic atom. However, there is one example where the C-5 position takes part in dynamic processes. 2-Methyl-bis(triethylsilyl)-1,2-azaborolylithium shows temperature-dependent dynamic behavior in solution. At -100°C three different states can be trapped in which the carbon-bonded TMS group substitutes positions 3, 4, and 5 <88CB1873>. Compound (a) in Scheme 1 is the longest-lived one, as subsequent substitution reactions give products exclusively with the TMS group at C-3. Thus, with TMS-Cl the 1,3,3- and the 1,3,5-substituted tris(trimethylsilyl) derivatives are formed simultaneously. The 2,5-dihydro derivative, however, changes into the 2,3-dihydro isomer by a 5,3-TMS shift in the course of 24 hours.

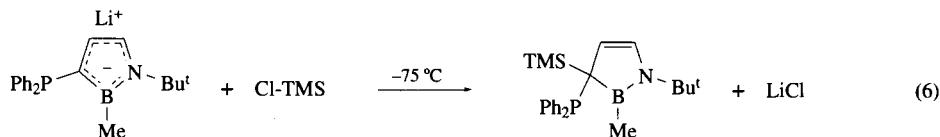


Scheme 1

The only PR₂ substituted 1*H*-2,5-dihydro-1,2-azaborole is formed via the thallium salt, which is generated from the Li salt with TlCl in a light-induced equilibrium at low temperatures (Equation (4)) <94CB1891>.



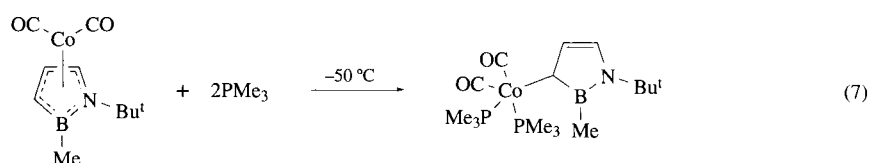
Equation (5) shows that the preferred substitution of C-3 does not depend upon the presence of Li⁺ as a cation. 1-*t*-Butyl-3-(diphenylphosphanyl)-2,3-dihydro-2-methyl-1*H*-1,2-azaborole can again be lithiated by Li(TMEDA). Subsequent reaction with TMS-Cl gives crystalline 1-*t*-butyl-3-(diphenylphosphanyl)-2,3-dihydro-2-methyl-3-(trimethylsilyl)-1*H*-1,2-azaborole (Equation (6)), which could be characterized by a single-crystal x-ray structure analysis.



3.17.5.2 Electrophilic Attack at Nitrogen and Nucleophilic Attack at Boron

Compared with the electrophilic attack at carbon, the heteroelements boron and nitrogen do not play a significant role in the chemistry of 1,2-azaborolyl systems, for two reasons. Firstly, electro-

philic attacks occur exclusively at the much more nucleophilic C-3 atom. In complexed form, for example, in transition metal sandwich complexes, where the C-3 atom is involved in the interaction with the transition metal, the nitrogen atom can be attacked, for instance, by protons. This, however, normally leads to the decomposition of the complex. Secondly, if lithium salts or metal complexes of 1,2-azaborolyl rings are attacked by nucleophiles, it is the more electropositive metal which reacts and not the boron atom. This behavior is best illustrated by the above discussed reaction of 1,2-azaborolyl lithium salts with [E]Cl (Equation (3)). The nucleophilic Cl^- in any case reacts with the Li^+ and not with the boron. Even if transition metal complexes are reacted with nucleophiles, it is again the metal which will be attacked. One example will elucidate this. The half-sandwich complex (η^5 -1-*t*-butyl-2-methyl-1,2-azaborolyl)dicarbonylcobalt reacts with two equivalents of the strong nucleophile PMe_3 with addition at the cobalt and with loss of contacts to the ring (Equation (7)).



At higher temperatures a CO and PMe_3 are removed to restore the η^5 coordination back. The boron atom is not involved in this procedure at all <92CB899>.

3.17.5.3 Complexation Reactions

Only two of the approximately 20 different types of five-membered rings containing one boron and one other adjacent heteroatom have been used successfully for complexation reactions. From these, only one formal 1,2-diborolane derivative has been described, but numerous examples including 1,2-azaborolyl rings as ligands exist. In Section 3.17.3.1 the anionic derivative of a 1,2-diborolane is mentioned, which can be considered as a diboratafulvene owing to its exocyclic $=\text{CH}_2$ substituent. Including this exocyclic π -moiety, the 1,2-bis(diethylamino)-1,2-dihydro-1,2-diboratafulvene can act as a 6 π electron ligand. In the only structurally investigated complex it plays the role of a bridging ligand (Figure 10).

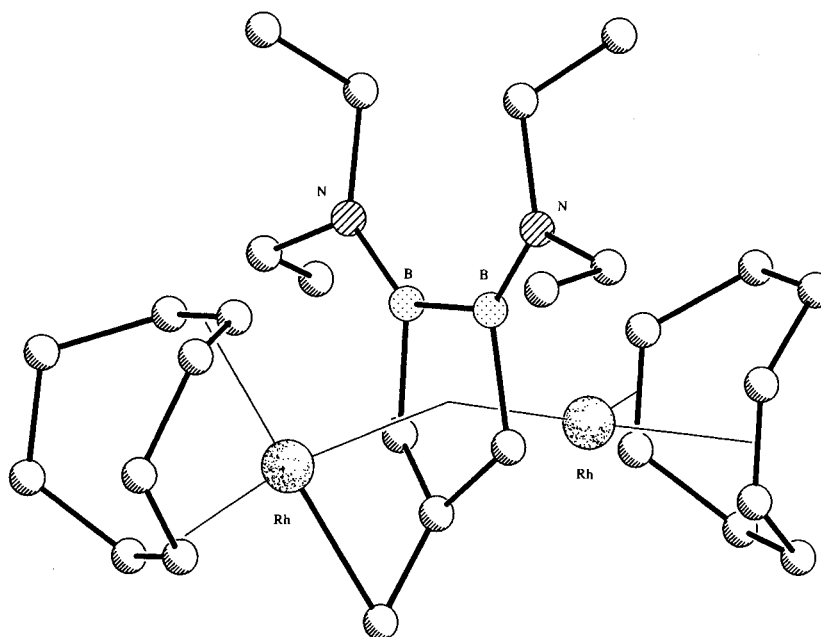
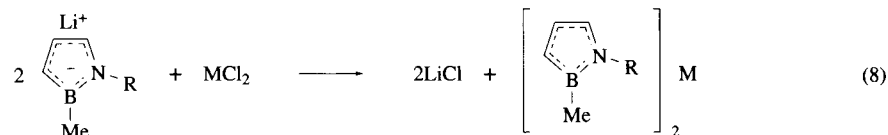


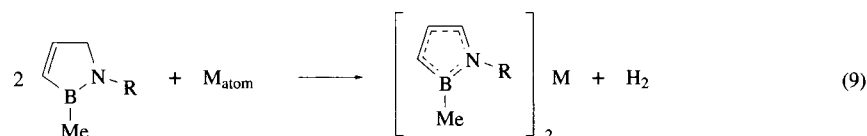
Figure 10 Molecular structure of bis(η^4 -cyclooctadiene)-[μ^2, η^5, η^4 -1,2-bis(diethylamino)-1,2-dihydro-1,2-diboratafulvene]dirhodium <90JOM(394)C1>.

From the numerous complexes of the 1,2-azaborolyl ligand type, only representatives of those compounds which have been investigated by x-ray structure analysis are mentioned.

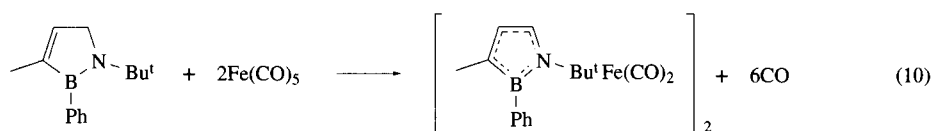
The most general method for synthesis of 1,2-azaborolyl sandwich complexes is the reaction between a lithium salt and the corresponding metal halides (Equation (8)).



Another route is metal vapor synthesis using neutral 2,5-dihydro-1*H*-1,2-azaboroles (Equation (9)).



Thermal reactions between some metal carbonyls and neutral 2,5-dihydro-1*H*-1,2-azaboroles in several cases yield half-sandwich complexes such as those shown in Equation (10) (80CB2348). This complex exists as *cis* and *trans* isomers.



Two main-group sandwich complexes deserve attention. Beryllium forms a complex with one η^5 - and one η^1 -coordinated 1,2-azaborolyl ligand (Figure 11) (87OM435). It was shown that in solution the ionically bonded η^5 -ring can dissociate partially. Thus, starting with a pure enantiomer, a racemate is formed after some time as both ring sites coordinate statistically in the ratio 1 : 1 (see Section 3.17.4).

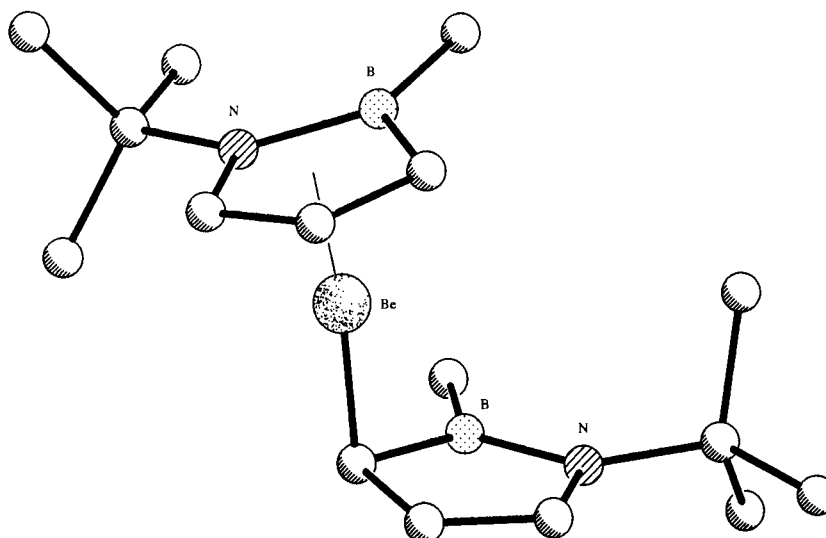


Figure 11 Molecular structure of (η^5 -1-*t*-butyl-2-methyl-1,2-azaborolyl)-(η^1 -1-*t*-butyl-2-methyl-1,2-azaborolyl)beryllium.

In the tin sandwich compound shown in Figure 12, both 1,2-azaborolyl rings are more or less η^3 -bonded as the Sn—N and Sn—B distances are found to be beyond binding interaction $\langle 85\text{AG(E)602} \rangle$. As in comparable cyclopentadienyltin sandwich complexes, the molecule has a bent structure as a result of the lone pair at the Sn atom.

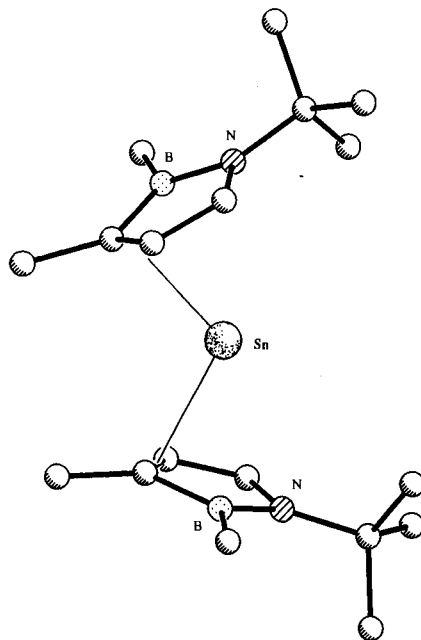


Figure 12 Molecular structure of bis(η^3 -1-*t*-butyl-2,3-dimethyl-1,2-azaborolyl)tin.

In contrast to main-group elements, transition metals usually try to reach high coordination numbers. Therefore, the 1,2-azaborolyl rings are normally η^5 -coordinated, offering 6π -electrons to the metal, if it is considered formally as an anion, except to the late and electron-rich representatives. Titanium and vanadium each form bent-type complexes as a result of the presence of two chloro ligands and one chloro ligand, respectively. Figures 13 and 14 show the structures.

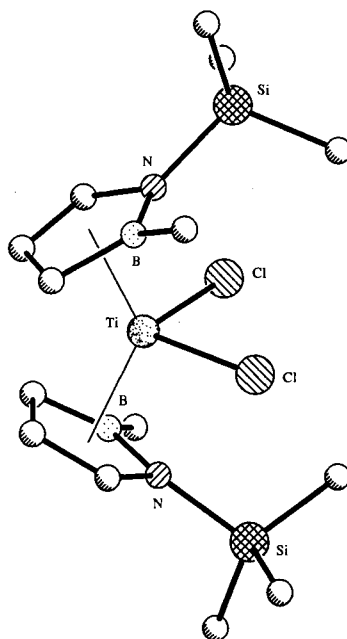


Figure 13 Molecular structure of dichloro-bis(η^5 -2-methyl-1-trimethylsilyl-1,2-azaborolyl)titanium $\langle 85\text{CB2418} \rangle$.

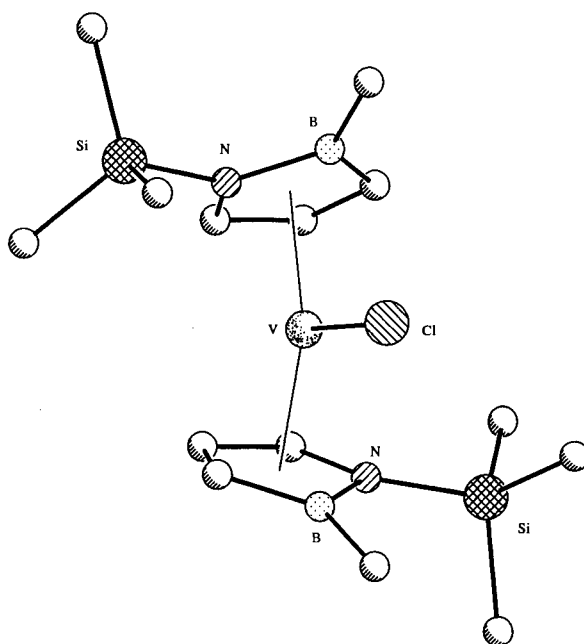


Figure 14 Molecular structure of chloro-bis(η^5 -2-methyl-1-trimethylsilyl-1,2-azaborolyl)vanadium <85CB2418>.

A mixed 1,2-azaborolylallyl complex is shown substitutionally for a metal of group 6 in Figure 15 <84CB672>. This is the first 18-electron complex on the way from left to right in the periodic table.

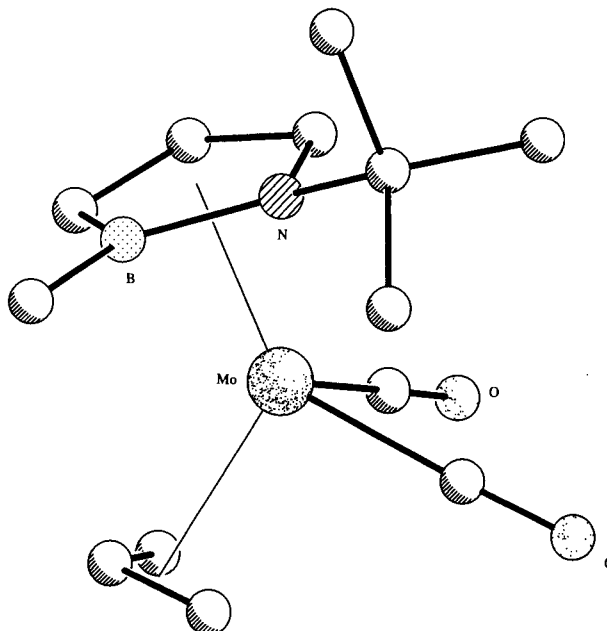


Figure 15 Molecular structure of (η^3 -allyl)-(η^5 -1-*t*-butyl-2-methyl-1,2-azaborolyl)dicarbonylmolybdenum.

A representative with a group 7 metal is still missing; however, numerous examples with elements of the iron group have been described. Bis(η^5 -2-methyl-1,2-azaborolyl)iron (Figure 16) is the only 1,2-azaborolyl sandwich complex with a nonsubstituted nitrogen atom <83CB951>.

Bis(1,2-azaborolyl)iron sandwich complexes, like the isoelectronic ferrocene compounds, are thermodynamically very stable, but, owing to the presence of the boron and nitrogen atoms, they are in any case sensitive to acids and bases.

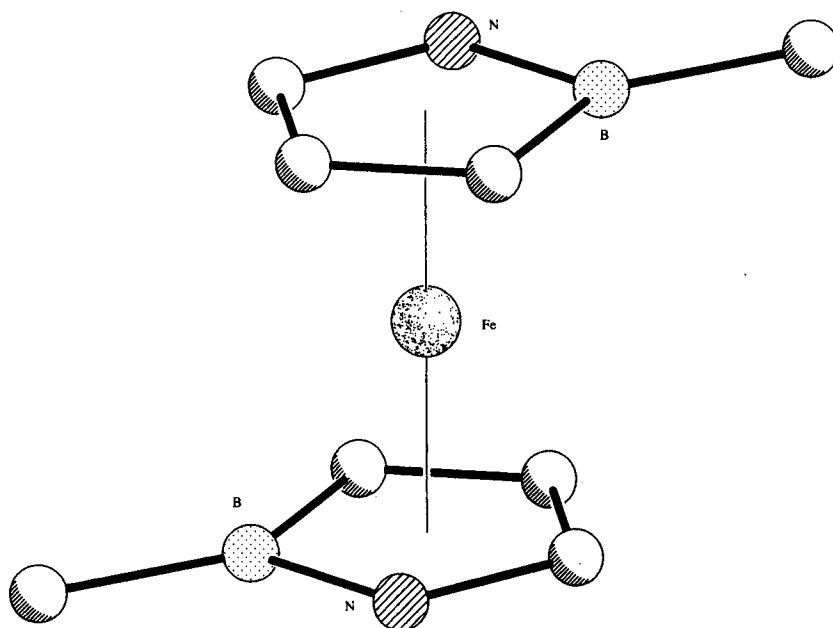


Figure 16 Molecular structure of bis(η^5 -2-methyl-1,2-azaborolyl)iron.

Several sandwich complexes with cobalt have been described $\langle 83CB951, 83ZN(B)485 \rangle$. Structurally they differ from the iron compounds only by a slight shift of the cobalt atoms from the ring centers $\langle 82AG(E)68, 82CB732, 82CB3830, 83JOM(256)252 \rangle$.

Bis(1,2-azaborolyl)nickel sandwich compounds play a special role structurally as the C_3BN framework is only used as an η^3 -allyl ligand. The tendency of nickel to form bis(η^3 -allyl) complexes is well known, and instead of forming a 20-electron complex, as is the case in nickelocene, the BN-disturbed cyclopentadienyl ring allows the nickel atom to select the C-3 unit only, instead of the unfavorable C_3BN ring (Figure 17) $\langle 84CB1052 \rangle$.

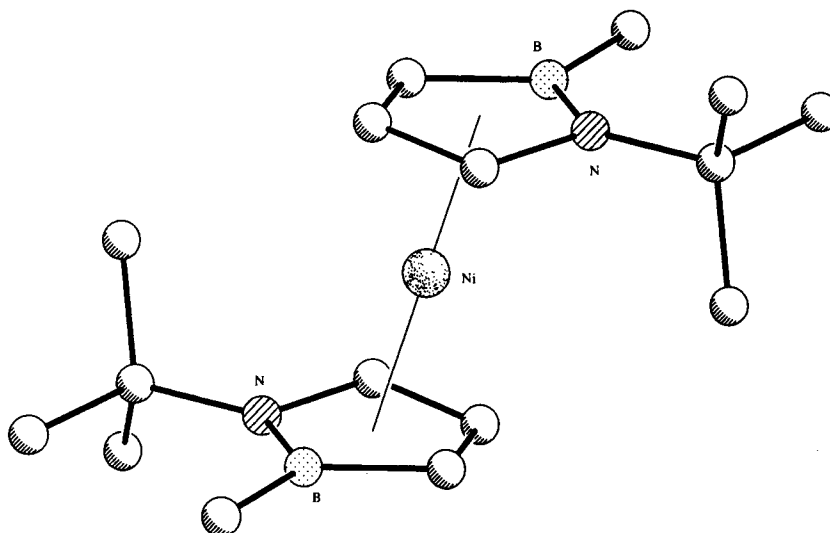


Figure 17 Molecular structure of bis(η^3 -1-*t*-butyl-2-methyl-1,2-azaborolyl)nickel.

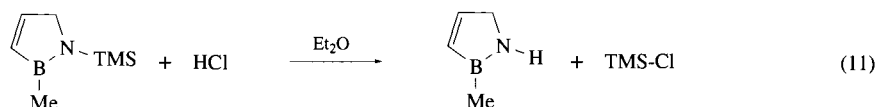
3.17.6 REACTIVITY OF NONCONJUGATED DIHYDRO RINGS

Relevant literature about the reactivity of nonconjugated oxygen-containing five-membered rings with an adjacent boron atom is common, but too old to be considered in CHEC-II. Most of the

literature considered again concentrates on the boron–nitrogen rings which have mostly been investigated after 1980.

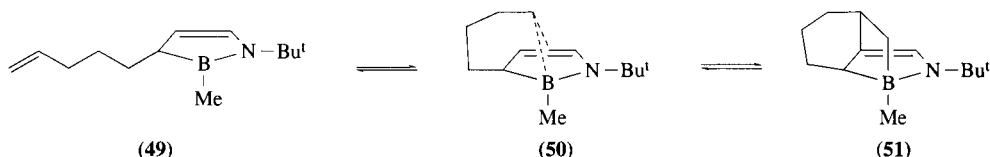
3.17.6.1 Electrophilic Attack at Nitrogen

Electrophilic attack at nitrogen is known from 1*H*-2,5-dihydro-1,2-azaboroles. Such a reaction is applied to protonate the nitrogen atom and to substitute, for example, TMS (Equation (11)) <82CB732>.



3.17.6.2 Nucleophilic Attack at Boron

Nucleophilic groups such as OH^- , OR^- , or R^- attack the boron atom, often followed by decomposition reactions. A very informative intramolecular nucleophilic attack has been observed with 1-*t*-butyl-2,3-dihydro-2-methyl-3-(4-pentenyl)-1*H*-1,2-azaborole (**49**) <88AG(E)952>. This compound rearranges slowly on cooling below 80°C to form a tricyclic crystalline product (Scheme 2).

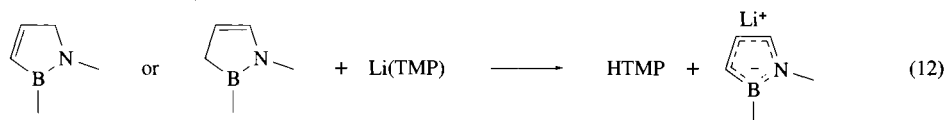


Scheme 2

This peculiar reaction is interpreted as a nucleophilic attack of the alkenic π -electron pair of the pentenyl group, finally leading to σ -bonds between boron and C-4 of the ring and the two carbon atoms of the $\text{C}=\text{C}$ double bond. The process is reversible at temperatures $>80^\circ\text{C}$. This rearrangement can be followed not only by ^{11}B NMR spectroscopy but also by single-crystal x-ray analysis. On the way from (**49**) to (**51**) a thermodynamically unstable intermediate (**50**) can be crystallized before the final situation is completed.

3.17.6.3 Deprotonation Reactions

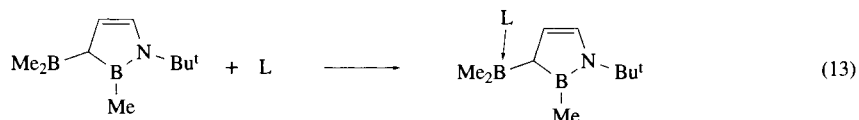
2,3- and 2,5-Dihydro-1,2-azaboroles can be deprotonated by strong and bulky bases. As mentioned above, others, such as OH^- , R^- , etc., attack the boron atom. Best suited for the deprotonation of sp^3 -hybridized carbon atoms is Li(TMP) with formation of HTMP and the corresponding 1,2-azaborollythium (Equation (12)).



3.17.7 REACTIVITY OF SUBSTITUENTS ATTACHED TO RING CARBON ATOMS

Again, the literature after 1980 covering the field of rings as defined in Section 3.17.1.2 is mainly restricted to BN-containing compounds. There is only one type of ring with chemically active substituents at a ring carbon atom, the 1*H*-dihydro-1,2-azaboroles. Among these (see Section 3.17.5.1) again only one is relevant here. It is the boryl-substituted derivative in which the boron atom behaves as a typical Lewis acid. As the ring-boron atom is a second potential Lewis acid, it is

a matter of interest which is the more reactive. As could be expected, it is the exocyclic boron atom which behaves as the stronger Lewis acid. Amines and phosphines have been investigated as Lewis bases (Equation (13)) <93MI 317-01>. Chinuclidine forms a crystalline adduct which could be analyzed structurally.



3.17.8 REACTIVITY OF SUBSTITUENTS ATTACHED TO RING HETEROATOMS

The situation in literature is comparable to that outlined in Section 3.17.7. Only the nitrogen-attached TMS group in 1*H*-dihydro-1,2-azaboroles shows some chemical activity. However, this activity is restricted to the substitution by a hydrogen atom, initiated by the attack of HCl. This reaction can be understood as an electrophilic attack of H⁺ at the nitrogen atom, as in Section 3.17.6.1, or, very formally, as an attack of Cl⁻ at the silicon atom. In either case the end result is the loss of the TMS group.

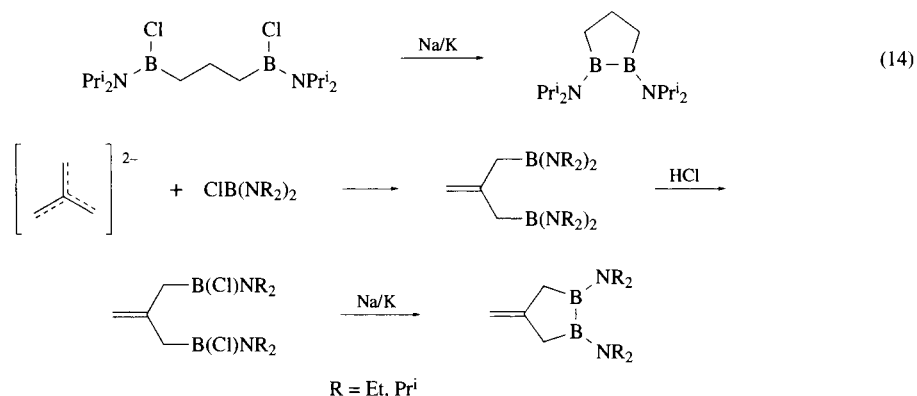
3.17.9 RING SYNTHESSES CLASSIFIED BY NUMBER OF RING ATOMS IN EACH COMPONENT

As variously mentioned, considerable parts of the subject described in this chapter, especially concerning boron-oxygen compounds, have been treated in the literature before 1980. However, as some important aspects, particularly those concerning syntheses, were not considered in CHEC-I, synthetic principles, describing the route to the various types of rings, will be taken into consideration.

3.17.9.1 Formation of One Bond

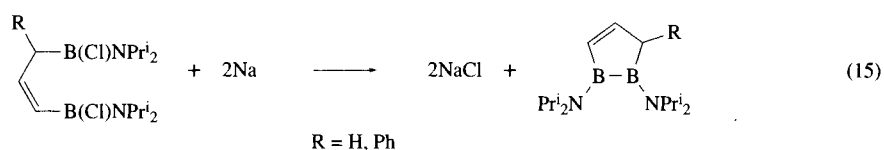
3.17.9.1.1 Formation of a B—B bond

1,2-Diborolanes and 1,2-diboroles are available by the formation of one B—B bond in appropriate diboryl components. Some novel syntheses of 1,2-diborolanes have been described since 1980 (Equation (14), Scheme 3) <90AG(E)912, 90ZN(B)1136, 92CB23>.



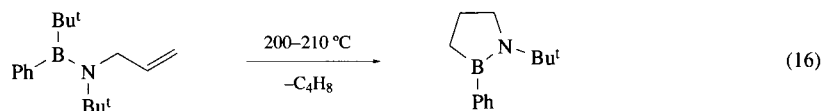
Scheme 3

The only representative of 1,2-diboroles has been described (Equation (15)) <94CB1363>.

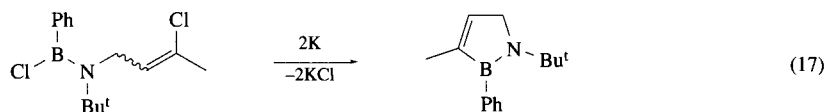


3.17.9.1.2 Formation of a B—C bond

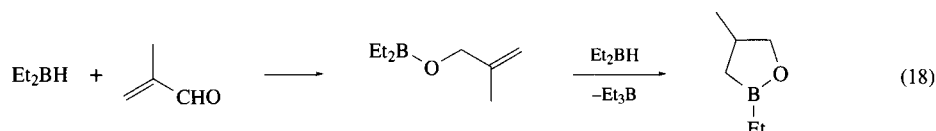
Starting with borylated allylamines, ring formation can be reached by thermolysis with B—C linkage. Thus, the thermolysis of allyl-*t*-butylaminobutylphenylborane at 200–210 °C with loss of butene is a route to 1,2-azaborolidines (Equation (16)) <80AG(E)54>.



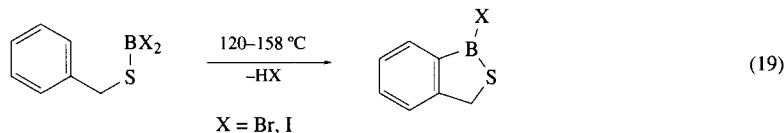
Equation (17) shows an example using intramolecular ring formation by dehalogenation <80AG(E)54>.



Synthetic routes to 1,2-oxaborolanes are rather old. In 1964–1966 Mikhailov *et al.* described several synthetic procedures to this class of BO heterocycles <64IZV887, 65ZOB228>. Later, in the mid-1970s, Köster *et al.* developed other syntheses which yield 1,2-oxaborolanes in relatively high yields (e.g., Equation (18)) <76MI 317-01>.

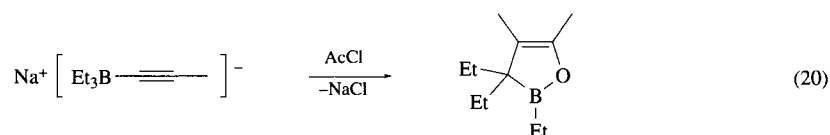


1,2-Thiaboroles have been known since 1976 as benzo-derivatives (Equation (19)) <76CB823>.

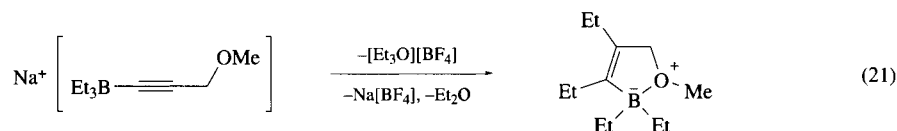


3.17.9.1.3 Formation of a B—O bond

Like most of the BO five-membered rings, 1,2-oxaboroles have existed since the early 1970s. They will therefore be mentioned only briefly. 2,3-Dihydro examples were described in 1969 by Binger (Equation (20)) <69AG56>.



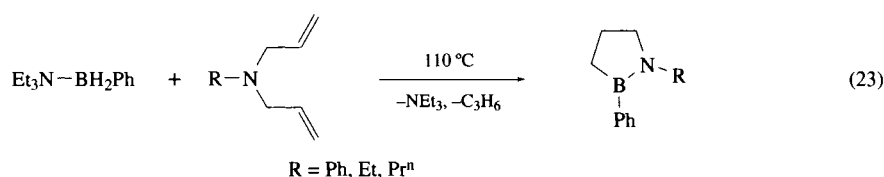
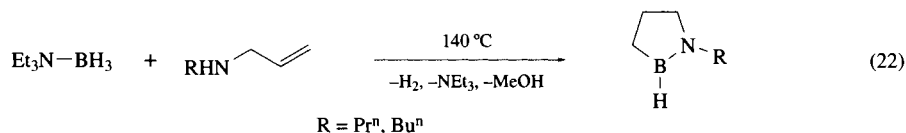
A similar reaction, using $\text{Na}^+[\text{Et}_3\text{B}-\text{C}\equiv\text{C}-\text{TMS}]$ leads to the 2,3,3-triethyl-5-methyl-4-trimethylsilyl-2,3-dihydro-1,2-oxaborole <77SRI53>. 2,5-Dihydro derivatives are formed from $\text{Na}^+[\text{Et}_3\text{B}-\text{C}\equiv\text{C}-\text{C}(\text{R}^1\text{R}^2)-\text{O}-\text{BEt}_2]^-$ and R^3X (e.g. $[\text{Et}_3\text{O}^+][\text{BF}_4^-]$) <82HOU(13)568>. 2,5-Dihydro-1,2-oxoniaboratolanes are formed under similar conditions to the 1,2-oxaboroles (Equation (21)) <74S350>.



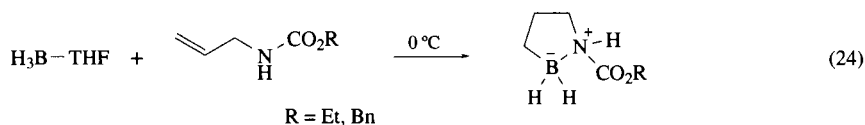
3.17.9.2 Formation of Two Bonds

3.17.9.2.1 From [1 + 4] atom fragments

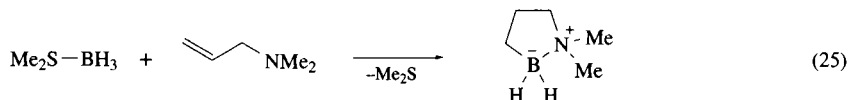
As 4-atom fragments, allylamines are often used for the synthesis of 1,2-azaborolidines, 1,2-azoniaboratolidines, 1,2-azaboroles, and 1,2-azoniaboratoles. 1,2-Azaborolidines are generally formed if borane-amine adducts are thermally burdened in the presence of alkyl-, allyl-, and diallyl amines. These reactions can also be described as hydroborations of diallyl compounds (Equations (22) and (23)) <70ZOB1528, 76JOC2803>.



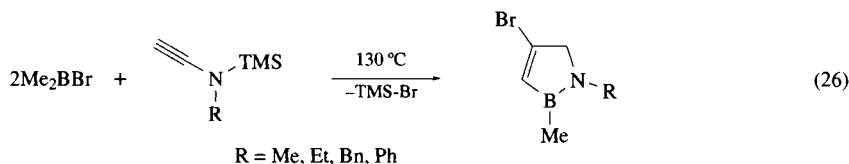
A direct route to 1,2-azoniaboratolidines is possible by using BH_3 -adducts and *N*-allylcarbonates (Equation (24)) <66JA484>.



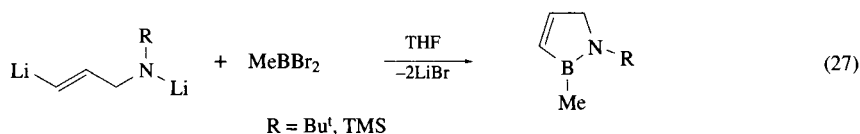
A 1990 paper describes a novel reaction (Equation (25)) <90JCS(P2)1663>.



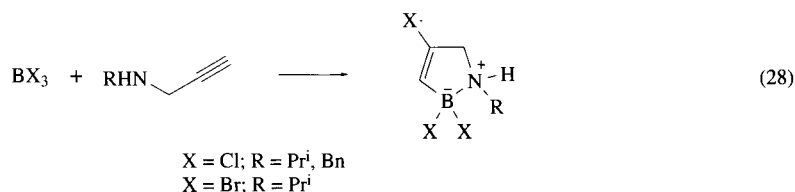
Fully substituted 2,3-dihydro-1,2-azaboroles were described in 1976 <76IZV1374>. They have been generated in a complicated manner via the 1,2-azoniaboratoles. A more convenient method was found in 1981 by the reaction between bromodimethylborane and organo-2-propenyltrimethylsilylamines to give 2,5-dihydro derivatives (Equation (26)) <81CB2519>.



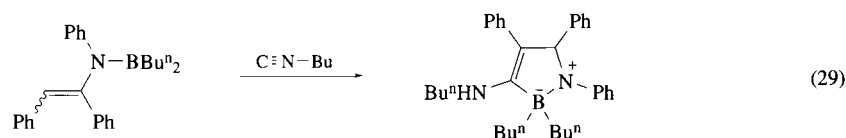
Probably the most generalized and most convenient route to 2,5-dihydro-1,2-azaboroles uses the reaction of (Equation (27)) <80JOM(193)83>.



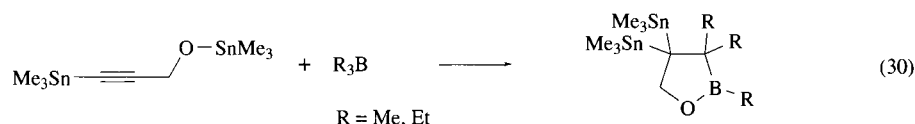
1,2-Azoniaboratoles exist as 1*H*- and 2*H*-derivatives. 1*H*-1,2-Azoniaboratoles are available by haloboration of $\text{C}\equiv\text{C}$ triple bonds (Equation (28)) <81CB2519>.



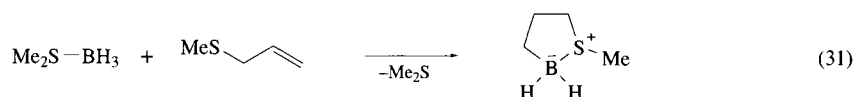
A 2*H*-1,2-azoniaboratole has been described starting with a vinylaminoborane and an isonitrile (Equation (29)) <81CB2519>.



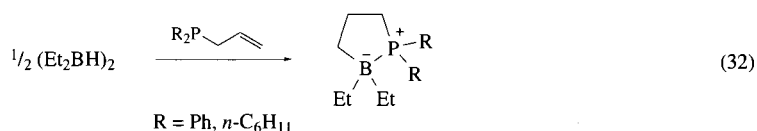
Several novel routes to 1,2-oxaborolanes have been described since 1980, one of which is mentioned here (Equation (30)) <89T1119>.



The sulfur homologues of the above discussed oxoniaboratolanes are equally old and therefore will be mentioned only incidentally. 1,2-Thioniaboratolanes can be generated from sulfane–borane adducts and allylmethylsulfanes (Equation (31)) <71JOC2388>.



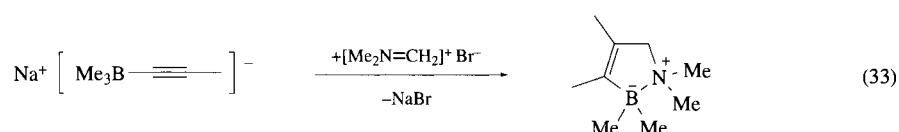
The first derivative of a 1,2-phosphoniaboratolane was described in 1972 <73MI 317-01> by reacting diethyldiborane with allyldiphenyl- or allyldicyclohexylphosphane (Equation (32)).



Ligand exchange reactions from the same period gave various derivatives.

3.17.9.2.2 From [2 + 3] atom fragments

A 1,2-azoniaboratole results if in a [2 + 3] atom fragment reaction sodium 1-propynyl-trimethylborate and dimethylmethyleneammonium bromide are combined (Equation (33)) <75CB395>.

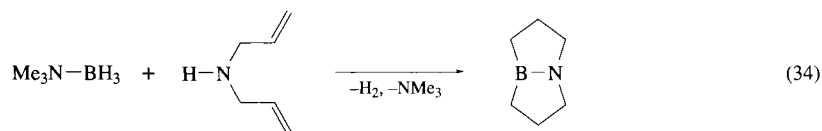


The product (35%) is the pure (*E*)-isomer.

3.17.9.3 Formation of Three Bonds

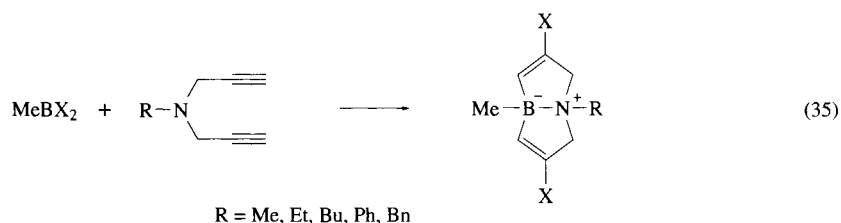
The simultaneous formation of three bonds to generate five-membered heterocycles only became known when bicyclic systems were synthesized.

1-Aza-5-bora-bicyclo[3.3.0]octanes were discovered in 1971 by the reaction of triethylborane with diallylamine (Equation (34)) <71CB1687>. No considerable development followed.



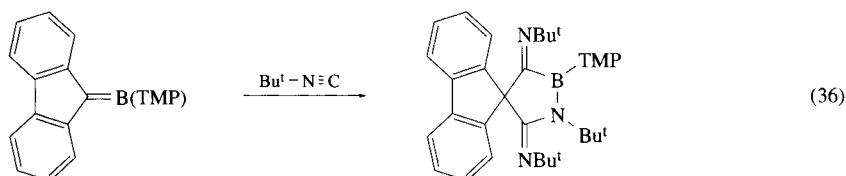
The 1-azonia-5-borata-derivatives with sp^3 -hybridized nitrogen and boron atoms have been found to be generated together with 1,2-azaborolidines (see Section 3.17.9.2):

1-Azonia-5-borata-bicyclo[3.3.0]octa-3,6-diene was described for the first time in 1981 (Equation (35)) <81CB2519>.



3.17.9.4 Formation of Five Bonds

A very special route to a 1,2-azaborolidine was described by Nöth and co-workers (Equation (36)) <93CB1551>.

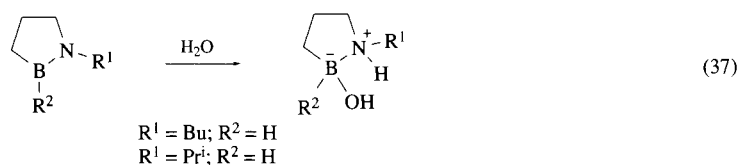


The $\text{C}=\text{B}$ double bond in the starting compound is used for the insertion of two $\text{Bu}^t\text{N}\equiv\text{C}$ molecules, each forming two new bonds. Additionally a Bu^tN fragment completes the five-membered ring with formation of a $\text{B}-\text{N}$ bond.

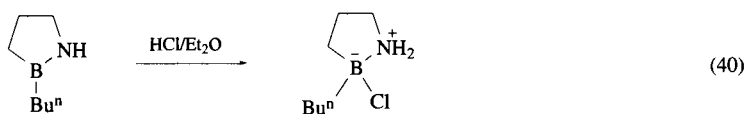
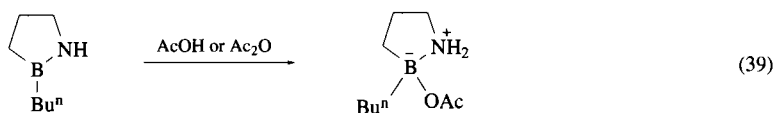
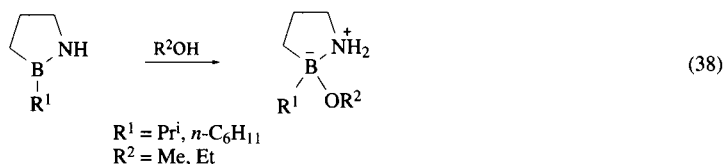
3.17.10 RING SYNTHESSES BY TRANSFORMATION OF ANOTHER RING

3.17.10.1 From Other Five-membered Rings

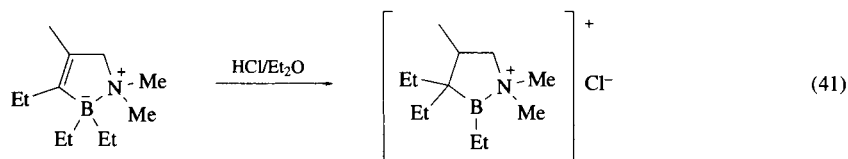
A very common route to 1,2-azoniaboratolindines uses the quaternization of boron and nitrogen in 1,2-azaborolidines. The most simple reaction is that with water (Equation (37)) <65MI 317-01>.



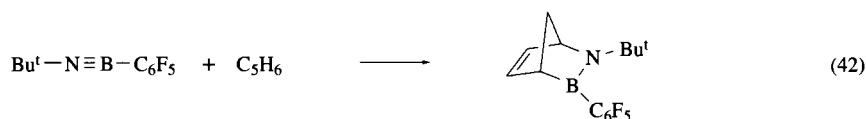
Alcohols (Equation (38)), carbonic acids and anhydrides (Equation (39)), and HCl (Equation (40)) among others can transform azaborolidines into azoniaboratolidines <65IZV1698, 65MI 317-01, 66IZV90>.



1,2-Azoniaborolidines belong to an old but very rare class of compounds and have been generated from 1,2-azoniaboratolidines by the shift of a boron substituent to the neighboring carbon atom with a change of sp^3 to sp^2 hybridized boron and from sp^2 to sp^3 hybridized carbon (Equation (41)) <65IZV714>.



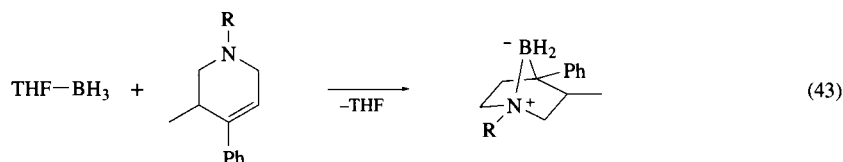
A 2-aza-3-bora-bicyclo[2.2.1]hept-5-ene derivative has been known since 1979 (Equation (42)) <79CB3811>.



A $\text{B}\equiv\text{N}$ triple bond is used to add to a cyclopentadiene, bridging two of its carbon atoms.

3.17.10.2 From Six-membered Rings

The hydroboration of a $\text{C}=\text{C}$ double bond in a tetrahydropyridine ultimately gives the formation of 1-azonia-7-borata-bicyclo[2.2.1]heptane, by an additional N-B coordination (Equation (43)) <75T1959>.



3.18

Two Nonadjacent Heteroatoms with at least One Boron

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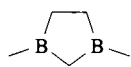
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3.18.1 INTRODUCTION

3.18.1.1 Types of Rings, Nomenclature

Five-membered rings with two nonadjacent heteroatoms and at least one boron atom were in principle not considered in the first edition of *Comprehensive Heterocyclic Chemistry* (CHEC-I). In 1995 there only existed a relatively small number of types of compounds belonging to this class of rings: 1,3-diborolanes (**1**) and 2,3-dihydro-1,3-diboroles (**2**). The 2,3-dihydro-1,3-diboroles also exist as dehydrogenated radicals (**3**) in various transition metal complexes, acting as 3-electron

donors. Their special importance results from their preferred function as bridging ligands in triple- and tetradecar complexes.



1,3-diborolane

(1)



2,3-dihydro-1,3-diborole

(2)



1,3-diboroly radical

(3)

A few examples of five-membered rings belonging to this chapter have become known, where silicon, tin, and phosphorus atoms substitute the second boron atom.

3.18.2 THEORETICAL METHODS

Theoretical methods for describing the electronic specialities of heterocycles belonging to this chapter have been applied only sparsely. More interest has been shown in the theoretical treatment of transition metal complexes having such heterocycles as ligands. *Ab initio* calculations have been performed for the 2,3-dihydro-1,3-diborole (4) <80JA939, 94CB1363>. Compared with the 1,2-diborole isomer the 1,3-derivative is more stable by about 85 kJ mol⁻¹.



(4)

MNDO calculations on various five-membered rings suggested their use as bridging ligands in polydecker sandwich complexes <84ZN(A)223>. These predictions led to preparative efforts that resulted in considerable success <85AG(E)943, 88PAC1345>. The energy and the electronic structure of the one-dimensional polydecker compound [Ni(H₅C₃B₂)]_∞ have been calculated by a semiempirical crystal orbital formalism based on INDO Hamiltonian <93CPH85>. This system was taken to represent the polydecked compounds [Ni(R₄HC₃B₂)]_∞ with 1,3-diborol rings <86AG(E)105>. As a result two different mechanisms for the Peierls distortion have been found, which are due to covalent bonding and to electrostatic interactions, with the covalent contribution dominating the electrostatic one. The Peierls distortion also changes the energetic ordering of the electronic states, leading to a destabilization of the electronic configuration deriving from the ground state of the Ni(H₅C₃B₂) stacking unit.

3.18.3 EXPERIMENTAL STRUCTURAL METHODS

3.18.3.1 Single-crystal X-ray Analysis

The importance of this method with respect to the available knowledge of molecular structures and bonding situations has been emphasized in Chapter 3.17. The application of single-crystal x-ray analysis to five-membered rings with two nonadjacent heteroatoms is less frequent owing to the paucity of compounds. However, the 1,3-diboroly fragment, frequently used as ligand in transition metal complexes, has been studied very often by x-ray structural analyses; several of them are discussed. First some molecular structures of free 2,3-dihydro-1,3-diborole derivatives are mentioned. Figure 1 shows the molecular structure of a representative of the 2,3-dihydro-1,3-diboroles with two C—C-interlinked rings having the envelope conformation <93CB1291>.

As expected, the B—C bond lengths of 157–158 pm correspond with single bonds, whereas the nature of the C=C double bond is demonstrated by a distance of 135 pm. Both rings are slightly folded along the B—B line by an angle of 30°.

In Figure 2 the molecular structure of another, but planar, 2,3-dihydro-1,3-diborole derivative is shown which is linked with a borole ring via a spiro carbon atom <90CC741>.

A benzo derivative of the 2,3-dihydro-1,3-diboroles is illustrated in Figure 3 <90CB2273>.

Owing to the C=C double bond between C-2 and the exocyclic CMe₂ group, this molecule can also be considered as a diborafulvene derivative. The bond lengths in the almost planar ring agree

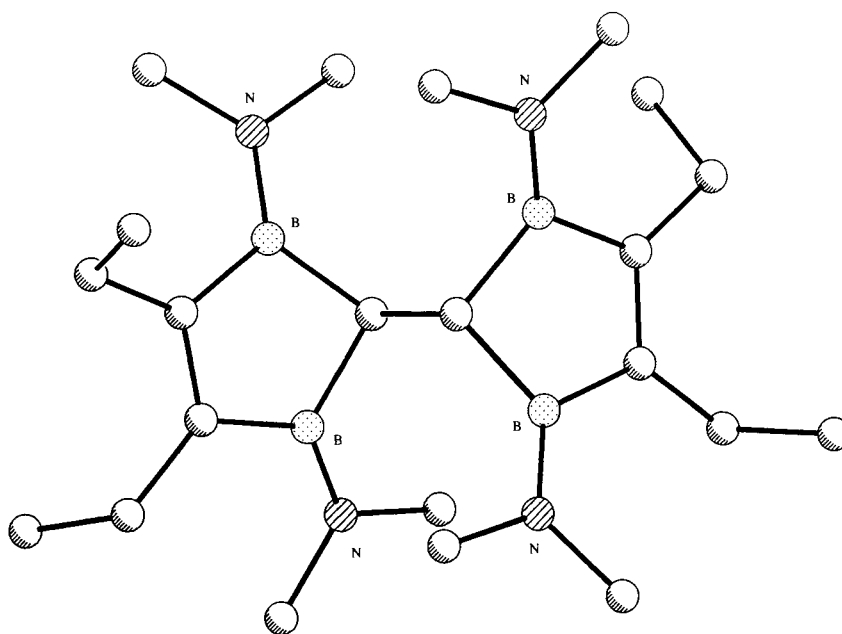


Figure 1 Molecular structure of 2,2'-bis(1,3-dimethylamino-4,5-diethyl-2,3-dihydro-1H-1,3-diborole).

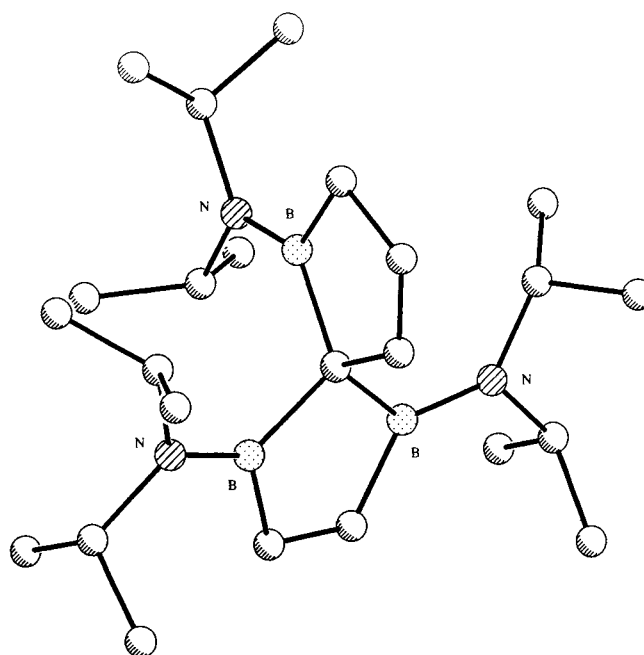


Figure 2 Molecular structure of 1,4,6-tris(diisopropylamino)-1,4,6-triborasp[4.4]nona-2,8-diene.

with those in the former 1,3-diboroles. Silicon is the second heteroelement in a saturated ring in the derivative shown in Figure 4 (91ZN(B)1127). This 1-bora-3-silacyclopentane derivative has a half-chair conformation, also known from other five-membered heterocycles with exocyclic methylene groups (91AG(E)84, 96UP 318-01). The observed twisting is probably caused by steric interactions between the substituents of the methylene groups and those of the dimethylamino groups.

In contrast to the relatively small number of x-ray structural investigations of free rings, numerous examples of 1,3-diborolyl complexes have become known since 1980. The 1,3-diborolyl radical is obviously an excellent system to form oligodecked complexes. A few examples will elucidate the

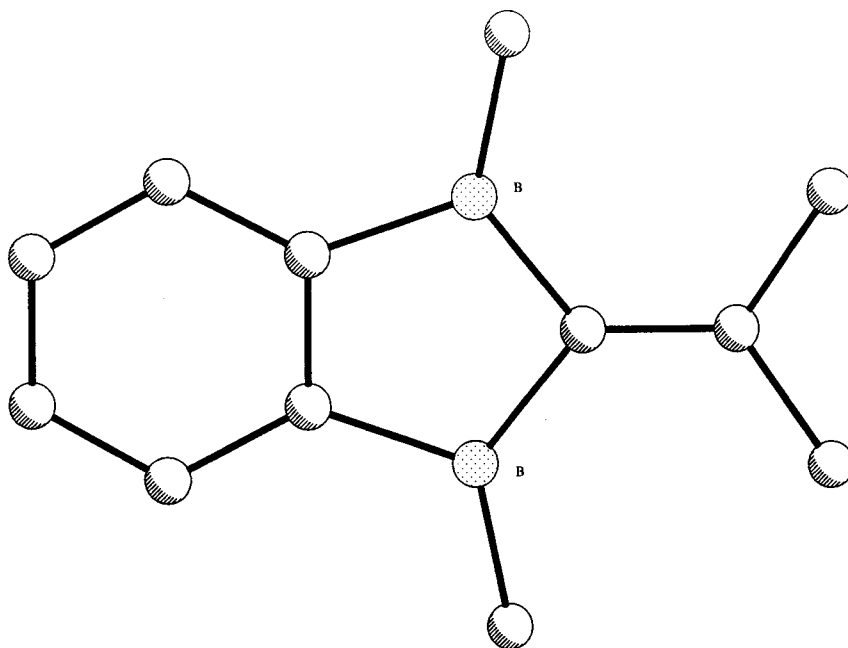


Figure 3 Molecular structure of 2,3-benzo-1,4-dihydro-1,4,6,6-tetramethyl-1,4-diborafulvene.

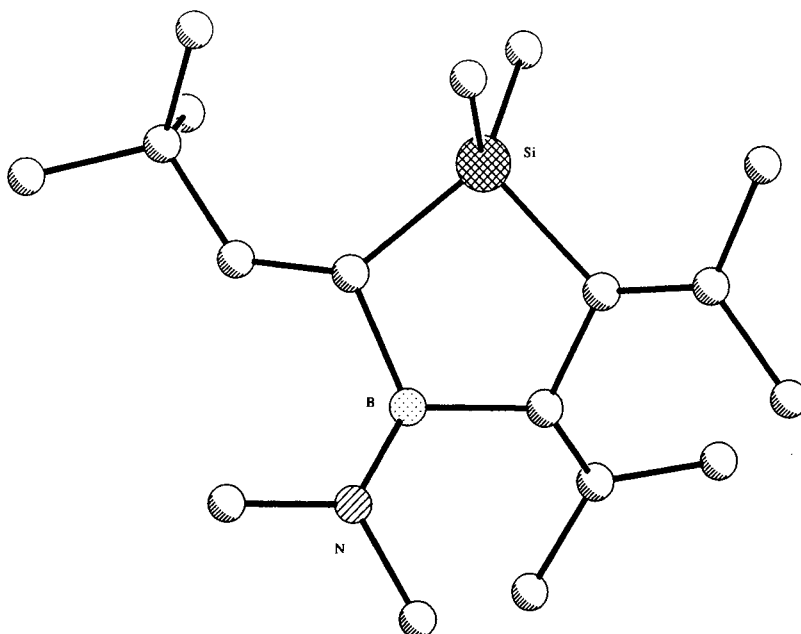


Figure 4 Molecular structure of 2-(*t*-butylmethylene)-4,5-bis(dimethylmethylene)-1-dimethylamino-3-dimethyl-1-bora-3-silacyclopentane.

significance of the x-ray single-crystal structure analysis. Compounds of the complexity of triple-, tetra-, or pentadecked systems would never have been understood without this decisive method.

A simple sandwich complex with only one 1,3-diborolyl ligand is shown in Figure 5 <78ZN(B)1410>.

A triple-decked mixed-metal compound is shown in Figure 6 <83JA2582>. In such mixed cyclopentadienyl/1,3-diborolyl oligodecked complexes the diborolyl rings always function as bridging but not as terminal ligands. A mixed Pt/Fe system representative of numerous other tetradecded complexes containing 1,3-diborolyl rings as ligands is shown in Figure 7 <85AG(E)943>.

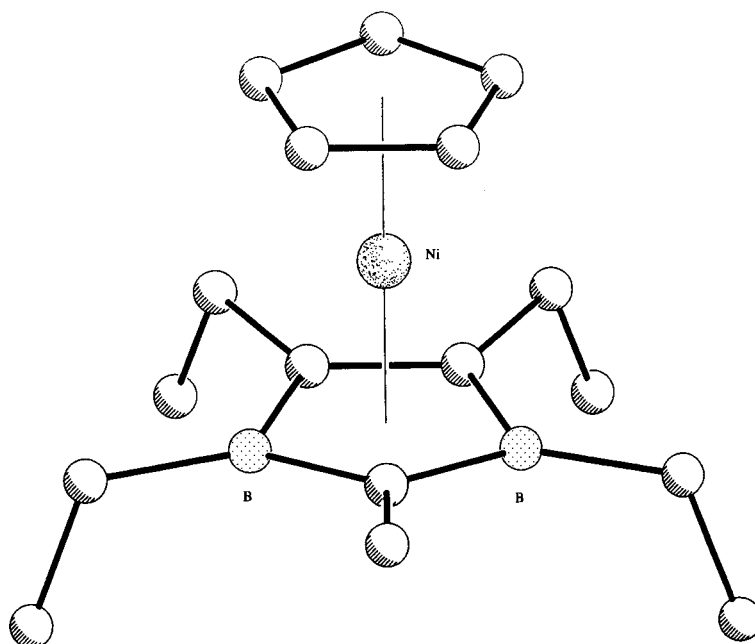


Figure 5 Molecular structure of $(\eta^5\text{-cyclopentadienyl})(\eta^5\text{-1,3,4,5-tetraethyl-2-methyl-1,3-diborolyl})\text{nickel}$.

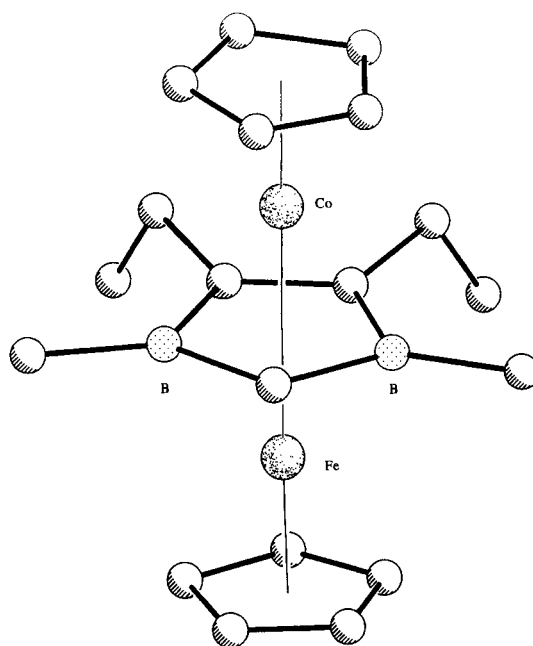


Figure 6 Molecular structure of $(\eta^5\text{-cyclopentadienyl})\text{cobalt-}(\mu\text{-4,5-diethyl-1,3-dimethyl-1,3-diborolyl})(\eta^5\text{-cyclopentadienyl})\text{iron}$.

3.18.3.2 NMR Spectroscopy

NMR spectroscopy as a method for the study of the structure and bonding of the five-membered heterocycles of this chapter is as important as for the compounds described in Chapter 3.17. It is unnecessary to enter into a general discussion; a few characteristic examples are mentioned to underline the different NMR techniques.

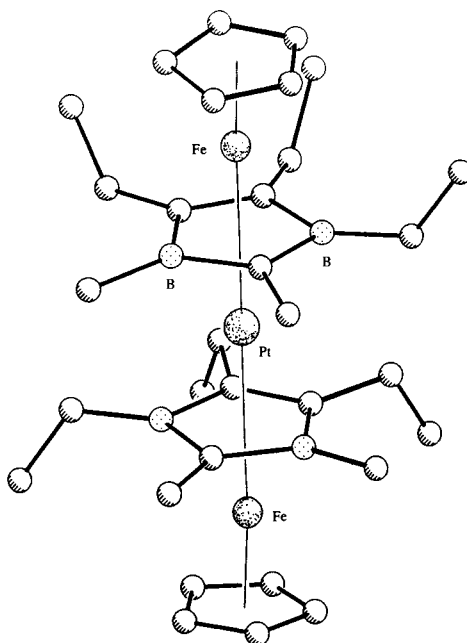
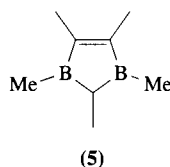


Figure 7 Molecular structure of $(\eta^5\text{-cyclopentadienyl})\text{iron-}(\mu\text{-1,4,5-triethyl-2,3-dimethyl-1,3-diborolyl})$ platinum- $(\mu\text{-1,4,5-triethyl-2,3-dimethyl-1,3-diborolyl})$ -($\eta^5\text{-cyclopentadienyl})\text{iron}$.

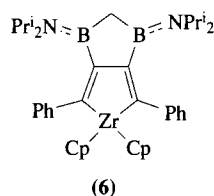
3.18.3.2.1 Proton NMR spectra

Modern NMR techniques such as 1D and 2D double-resonance experiments help to clarify coupling processes in some cases, as for 1,2,3,4,5-pentamethyl-2,3-dihydro-1,3-diborole (**5**).



Here, the coupling between the methyl protons at C-4 and C-5, and the H atom at C-2 ($^5J_{\text{HH}} = 0.7$ Hz) is unusual because such couplings are not observed if C-3 is unsubstituted or C-1 and C-2 have ethyl substituents $\langle 88\text{ZN}(\text{B})306 \rangle$. The formation of this 2,3-dihydro-1,3-diborole from 1,2,3,4-tetramethyl-1,4-diboracyclohexene-2 could also be followed in detail by ^1H NMR spectroscopy. A first-order rate law has been observed and a free activation energy $\Delta G^\ddagger = 139.7 \pm 0.5 \text{ kJ mol}^{-1}$ was found $\langle 88\text{ZN}(\text{B})306 \rangle$.

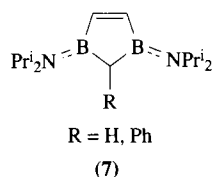
Hindered rotation at the exocyclic B—N bond in a 1,3-diborolane (**6**) could be shown by ^1H and ^{13}C NMR spectra, using the 2D-NOESY techniques $\langle 93\text{OM}2433 \rangle$.



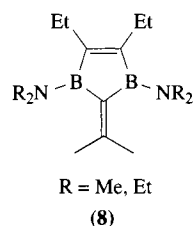
One cross-peak between the methine proton of one Pr^i group and the CH_2 group of the 1,3-diborolane ring and another cross-peak between the $m\text{-H}$ atoms of the phenyl rings and the CH group of the other Pr^i group indicate fixed B— NPr^i_2 moieties.

Inequivalence of two B-bonded Pr^i_2N groups in a 2,3-dihydro-1,3-diborole (**7**) has been shown

by ^1H NMR spectroscopy <94CB1363>. This effect is also caused by the $\text{B}=\text{N}$ π -bonding and the magnetic inequivalence of the isopropyl substituents.



From ^1H NMR data, a deshielding of the CH_2 protons in 1,3-diiodo derivatives of 2,3-dihydro-1,3-diboroles compared with alkyl could be recognized <85ZN(B)326>. The nonplanarity of a 1,3-dihydro-1,3-diborapentafulvene is indicated by ^1H NMR spectra, if the boron atoms are substituted by NMe_2 and NEt_2 groups instead of Me (**8**) <89CB401>.

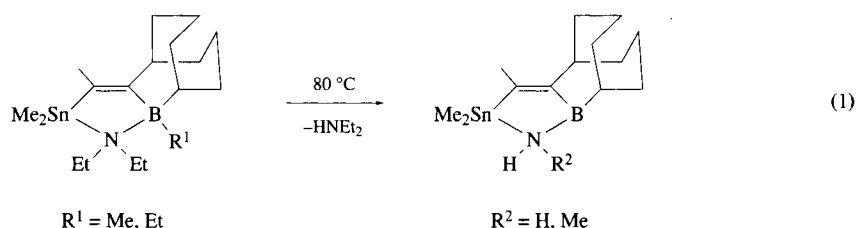


These selected examples show impressively the significance of ^1H NMR investigations of five-membered boron-containing heterocycles. Not only can structural details be deduced, but rotation barriers and rearrangement processes are also rendered observable.

3.18.3.2.2 Boron-11 NMR spectra

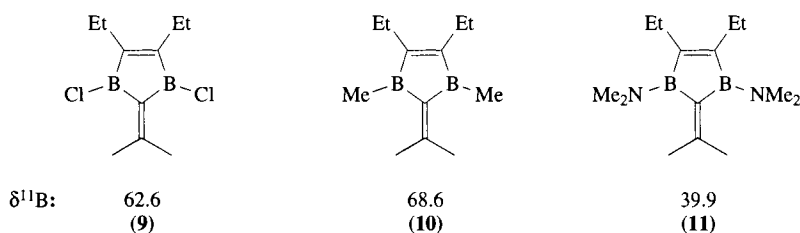
As already emphasized in Chapter 3.17.3.2.2, ^{11}B NMR spectroscopy is an essential tool in understanding the electronic environment in boron compounds. Again, some compounds of five-membered rings with an additional nonadjacent heteroatom is mentioned as representative of many other examples.

The formation of a 2,3-dihydro-1*H*-1,3-stannaborole from a 3-azonia precursor can be followed easily by ^{11}B NMR spectroscopy (Equation (1)) <88CB1451>.

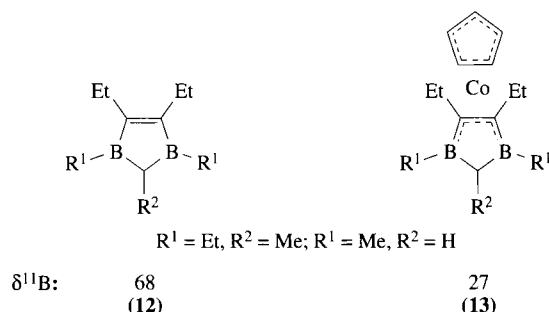


The difference in the $\delta^{11}\text{B}$ values is more than 70 ppm owing to the rehybridization of the boron atom from sp^3 to sp^2 .

Substitutions at the B atoms in 1,3-dihydro-1,3-diborapentafulvenes are accompanied by characteristic $\delta^{11}\text{B}$ values (**9**)–(**11**) <89CB401>.



The complexation of B-containing compounds is normally accompanied by dramatic electronic changes at the B atom. This is impressively demonstrated if neutral 2,3-dihydro-1,3-diboroles are coordinated to transition metals (**12**) and (**13**) <82AG(E)148>.



This effect is due to strong metal–boron interactions leading to an increased coordination number of the B atoms and, additionally, to a much better electronic shielding of the B nuclei.

If the tetramethyl-1,3-dihydro-1,3-diborapentafulvene (**10**) is coordinated to the $\text{Mo}(\text{CO})_4$ moiety, the ^{11}B NMR signal is shifted to 37.2 ppm owing to effects corresponding to those mentioned above <89CB401>.

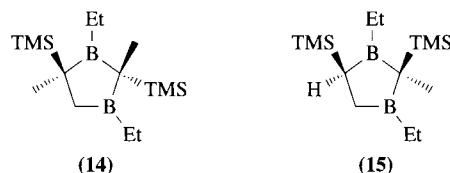
3.18.3.2.3 Carbon-13 NMR spectra

As already explained in Chapter 3.17 Section 3.2.3, ^{13}C NMR data provides information on the electronic environment of C atoms in the ring framework in particular, but also of course on exocyclic substituents. Detailed statements can often be made about ring conformation, couplings, and deshielding processes, for example. In noncyclic BMe compounds a more or less linear relationship between ^{11}B and ^{13}C NMR shifts is observed <75CB3831>. However, in OEt- and SMe-substituted 2,3-dihydro-1,3-diboroles this trend cannot be confirmed <85ZN(B)326>.

3.18.3.2.4 NMR spectra of other nuclei

Occasionally nuclei other than ^1H , ^{11}B , and ^{13}C can be used to provide information about the electronic and structural properties of the five-membered rings of the types discussed in this chapter, provided such an element is part of the ring itself or of a substituent.

Silicon-29 NMR spectra can be used to identify isomers of trimethylsilylated 1,3-diborolanes (**14**) and (**15**) <94CB813>.



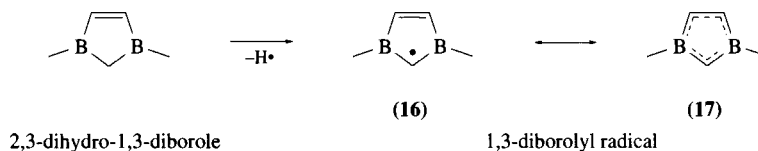
Compound (**14**) can easily be identified by $^{29}\text{Si}/^1\text{H}$ HETCOR experiments indicating the couplings of ^{29}Si nuclei over two or three bonds to the BCH and BCH_2 protons, respectively ($\delta^{29}\text{Si} = 3.0$), and over three bonds to the C-2 Me_3 protons ($\delta^{29}\text{Si} = -7.0$). The ^{29}Si NMR spectrum also allows the observation of ^{13}C satellite signals. The relatively small coupling constant $^1J(^{29}\text{Si}-^{13}\text{C}(2)) = 18.2$ Hz is typical for the accumulation of electropositive substituents at carbon <79ZN(B)1270, 91SA(A)849>.

The structural analysis of 2,3-dihydro-1H-1,3-stannaboroles has been performed using ^{119}Sn NMR spectroscopy in addition to ^1H , ^{11}B , and ^{13}C <88CB1451>.

3.18.4 REACTIVITY OF FULLY CONJUGATED RINGS

3.18.4.1 The 1,3-Diborolyl System

2,3-Dihydro-1,3-diboroles are transformed into the 1,3-diborolyl radicals (**16**) by the loss of a hydrogen atom (Scheme 1). They can act as 3-electron donors in many transition metal complexes.

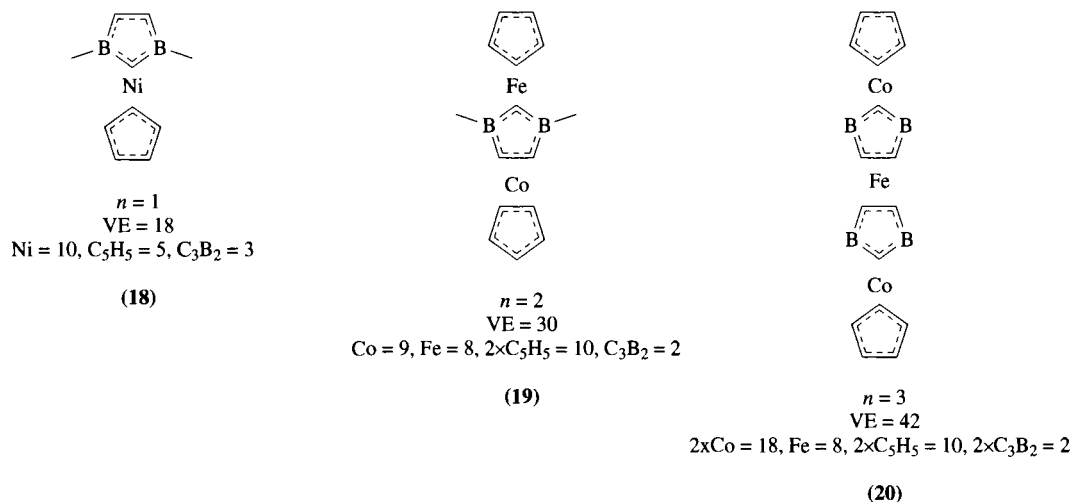


Scheme 1

The delocalization of the three π -electrons is indicated in the mesomeric formula (**17**) which exists in simple sandwich compounds but also in a bifacial arrangement in numerous oligonuclear complexes. Numerous x-ray structure analyses show the two B atoms to be involved in the ring-metal interactions leading to an η^5 -coordination of the 1,3-diborolyl rings. <87PAC947, 88PAC1345, 93AOC(35)187>.

3.18.4.2 1,3-Diborolyl Complexes

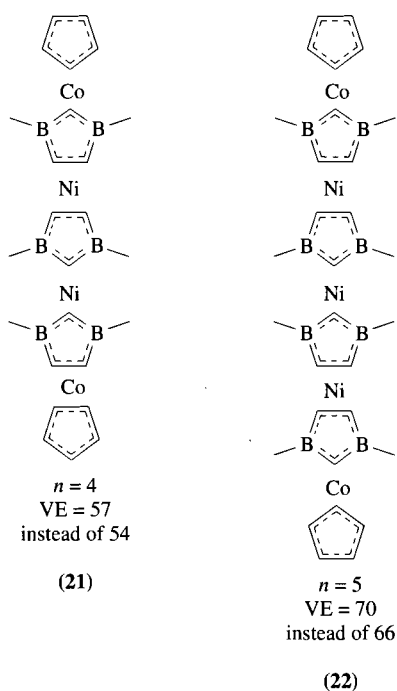
As a radical, the 1,3-diborolyl ring system cannot exist independently but only in combination with one or two transition metal atoms. It can offer three electrons to metal atoms by the C π -electrons, whereas the two B atoms act as acceptor centers towards the metals. In formulas (**18**)–(**20**) a mononuclear and several oligonuclear 1,3-diborolyl complexes are shown representatively. The ideal number of valence electrons (VE) in such a complex is $12n + 6$, where n is the number of stacks <88PAC1345>.



Oligo- and polydecker complexes can still exist, however, even if the optimum number of valence electrons is not reached. In (**21**) a pentadecked complex with 57 instead of 54 VE and in (**22**) a hexadecked compound with 70 instead of 66 VE are shown <85AG(E)943>.

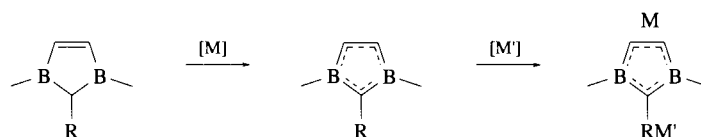
3.18.5 REACTIVITY OF NONCONJUGATED RINGS

The only nonconjugated ring system of relevance belonging to this chapter is that of the 2,3-dihydro-1,3-diboroles. They are of importance due to their ability to lose a hydrogen atom in the 2-position and so form the 1,3-diborolyl-radical (see Section 3.18.4), and in addition to act as complex ligands not only using the C=C π -bond, but also the C-2 H moiety for the interaction with transition metal atoms.



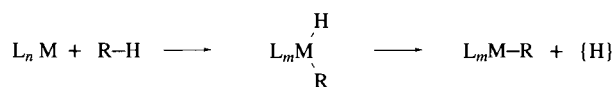
3.18.5.1 Dehydrogenation of 2,3-Dihydro-1,3-diboroles

As already shown by Scheme 1, a hydrogen atom in the 2-position can be removed to form the 3-electron-donating 1,3-diborolyl radical. The dehydrogenation occurs by metal complex fragments which then coordinate to the 1,3-diborolyl ring generated. In general this behavior can be formulated as in Scheme 2 <85AG(E)943>.



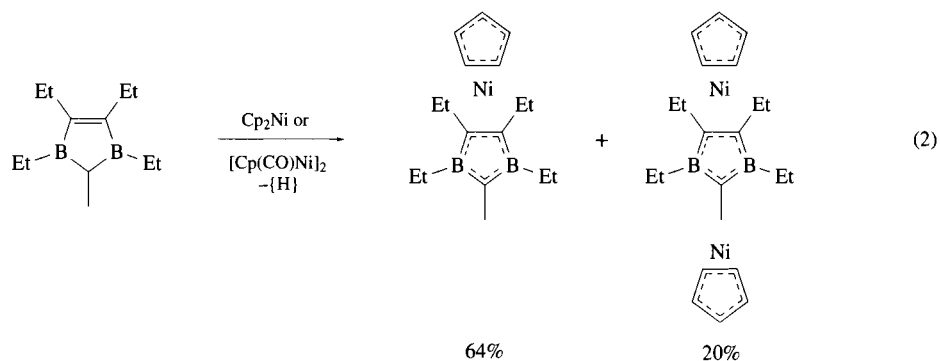
Scheme 2

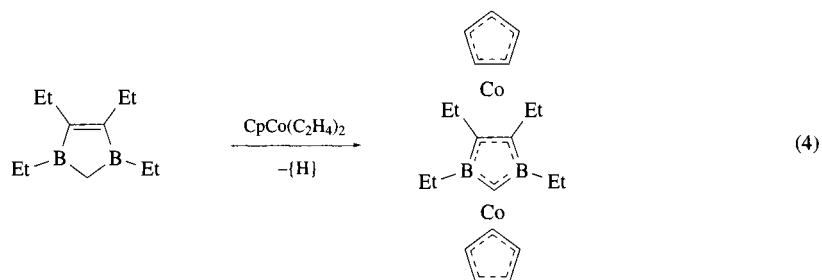
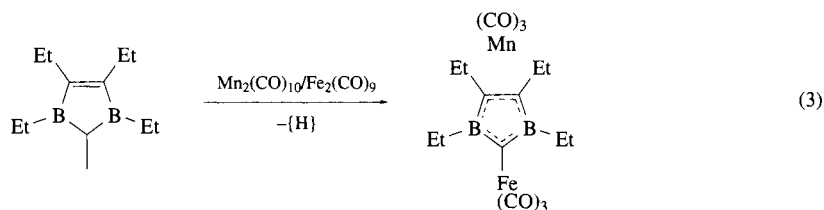
The formation of the 1,3-diborolyl radical and its interaction with a metal center can be understood as an oxidative addition reaction with elimination of hydrogen (Scheme 3) <B-91MI 318-01>.



Scheme 3

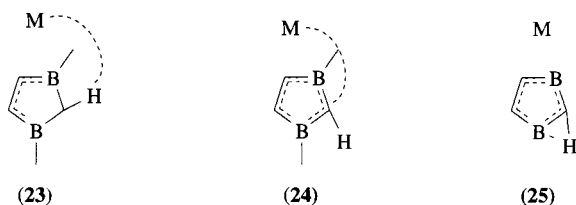
Some examples elucidate this principle (Equations (2)–(4)) <77AG(E)468, 80AOC(18)332, 82AG(E)148>.





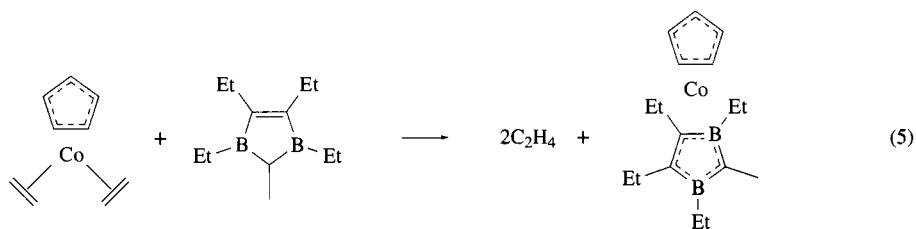
3.18.5.2 Complexation of 2,3-Dihydro-1,3-diboroles

1,3-Dialkyl-2,3-dihydro-1,3-diboroles attract attention because of their unusual ligand properties. If an H atom is not removed as discussed in the preceding Section the C-2 H moiety can be used in addition to the C=C double bond for a special kind of metal coordination (<83OM1666, 85AG(E)943, 87ZN(B)186>). As indicated in structures (23)–(25) different 3-center–2-electron bonds can in principle be realized.

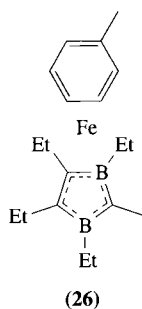


Type (23) represents an agostic $\text{M} \leftarrow \text{H}$ interaction, whereas (24) describes an $\text{M} \leftarrow \text{C} \cdots \text{H}$ bonding situation using the axial C—H moiety. In (25) a part of a 4-center–4-electron bond is shown, consisting of the 3-center–2-electron bonds $\text{B} \leftarrow \text{H} \cdots \text{C}$ and $\text{B} \cdots \text{M} \cdots \text{C}$, comparable to the bonding situation in B_2H_6 . Some representative examples are mentioned in the following.

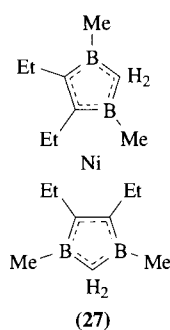
The four π -electrons of the ethene ligands in $\text{CpCo}(\text{C}_2\text{H}_4)_2$ are substituted by a 2,3-dihydro-1,3-diborole molecule, acting as 4-electron donor (Equation (5)) (<85AG(E)943>).



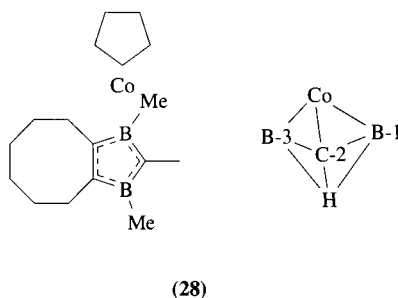
One toluene ligand in bis(toluene)iron can be substituted by the same 2,3-dihydro-1,3-diborole (26) (<85AG(E)943>).



A bis(2,3-dihydro-1,3-diborole)nickel sandwich complex (27) is formed when $\text{Ni}(\text{C}_3\text{H}_5)_2$ or $\text{Ni}(\text{C}_2\text{H}_4)_3$ react with the corresponding 1,3-diborole $\langle 85\text{AG}(\text{E})943 \rangle$.



The single-crystal x-ray structural analysis of a Co-coordinated 4,5-cycloocta-2,3-dihydro-1,3-diborole (28) elucidates structural details with respect to the C-2 H-metal interactions $\langle 94\text{ZN}(\text{B})315 \rangle$.

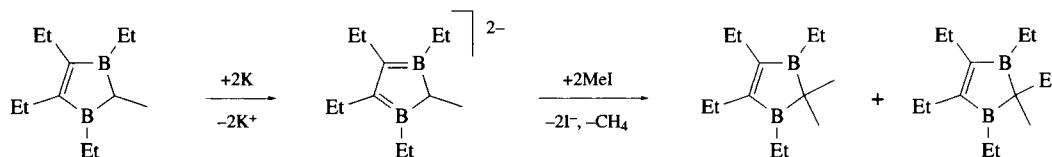


As can be seen from (28) a hydrogen bridge between B-1 and C-2 is formed. It can be described as a 3-center-2-electron bond or, including the Co atom, as a 4-center-4-electron bond, leading to an elongation of the B-1—C-2 bond distance compared with B-3—C-2 and simultaneously to a shortening of the B-1—Co distance.

3.18.6 REACTIVITY OF SUBSTITUENTS ATTACHED TO RING CARBON ATOMS

The reactivity of the carbon atoms in the heterocycles relevant to this chapter can be exclusively restricted to the class of 2,3-dihydro-1,3-diboroles. Here the only atom of interest is C-2. Its tendency to lose a hydrogen atom and to form the 1,3-diborolyl radical is described in detail in Sections 3.18.4 and 3.18.5. Here only one reaction is mentioned, which has been described for an unlabeled ring (Scheme 4) $\langle 87\text{ZN}(\text{B})186 \rangle$.

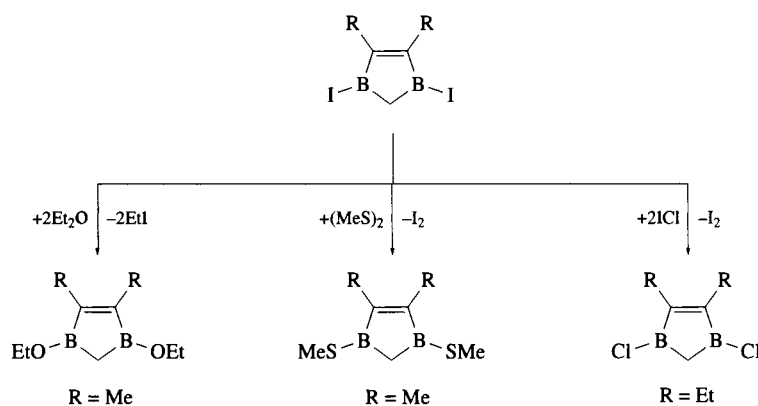
Methylation of the dianion by MeI leads to the substitution of the hydrogen atom by a methyl group and in addition to the formation of an ethyl-substituted derivative, probably generated by methylation of a methyl group at C-2.



Scheme 4

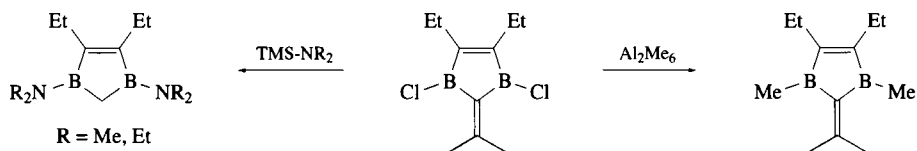
3.18.7 REACTIVITY OF SUBSTITUENTS ATTACHED TO RING HETEROATOMS

The reactivity of B-substituents in 2,3-dihydro-1,3-diboroles can be studied by means of a few examples. 1,3-Diodo-1,3-diboroles can be transformed into the alkoxy, thioalkyl, and chloro derivatives (Scheme 5) <85ZN(B)326>.



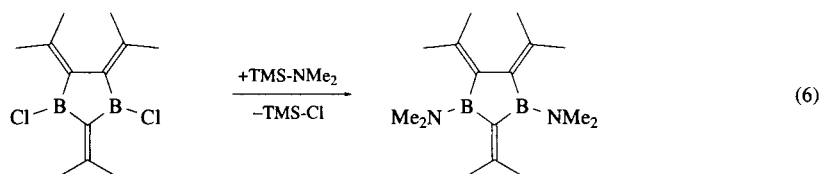
Scheme 5

1,3-Dihydro-1,3-diborapentafulvenes can also be used for substitution reactions at the boron atoms (Scheme 6) <89CB401>.

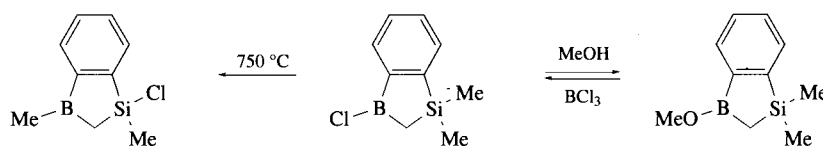


Scheme 6

A 1,3-dibora[5]radialene has been known to enable substitutions at the boron atoms (Equation (6)) <91AG(E)84>.



As a representative of the 1,3-borasilaindanes, the 1,1-dimethyl-3-chloro-1-sila-3-boraindane is mentioned to illustrate a very special kind of reactivity at the heteroatoms (Scheme 7) <87JOM(331)139>. At temperatures of 750°C an Me-Cl exchange between boron and silicon atoms is observed. Methanolysis gives the BMe derivative which, however, can easily be transformed back to the starting compound by means of BCl₃.



Scheme 7

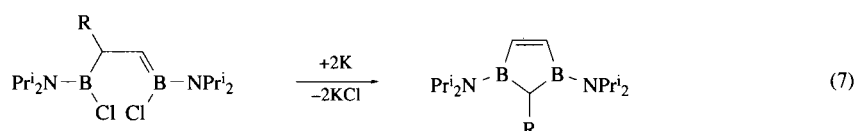
3.18.8 RING SYNTHESIS CLASSIFIED BY NUMBER OF RING ATOMS IN EACH COMPONENT

Among the compounds containing a nonadjacent heteroatom in addition to a boron atom, only the 2,3-dihydro-1,3-diboroles are really important and therefore these are mainly considered here. Only a few examples of 1,3-diborolanes and rings with a nonboron atom as a second heteroatom have been synthesized and these are also mentioned.

The first synthesis of 2,3-dihydro-1,3-diboroles was accomplished in the 1960s. Binger described the thermolysis of diborylalkynes at 150–180 °C with formation of pentaalkyl-2,3-dihydro-1,3-diboroles <75TL2675>. Meanwhile a series of methods has been developed to generate variously substituted diboroles; most of them have been synthesized by Siebert and co-workers <89CB401, 90CB2273, 90ZN(B)15, 91ZN(B)1127, 93ZN(B)68, 94CB1363, 94ZN(B)315>.

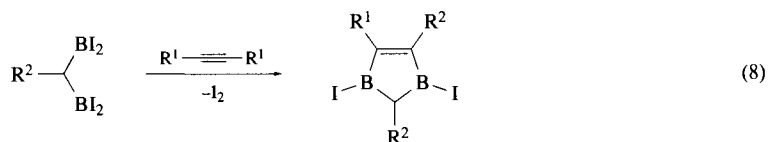
3.18.8.1 Formation of One Bond

The formation of a B—B bond, accompanied by a rearrangement, leads to 1,3-bis(diisopropylamino)-2,3-dihydro-1,3-diboroles (Equation (7)) <94CB1363>. The yields are 39% (R = H) and 37% (R = Ph), respectively. If sodium is used instead of potassium for the dehalogenation, 1,2-diboroles are formed, as expected.

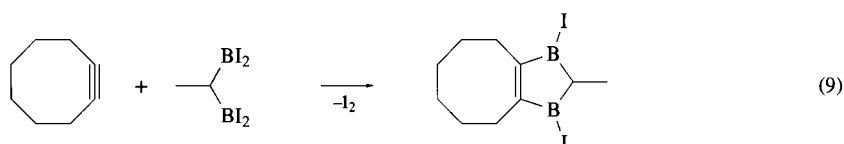


3.18.8.2 Formation of Two Bonds

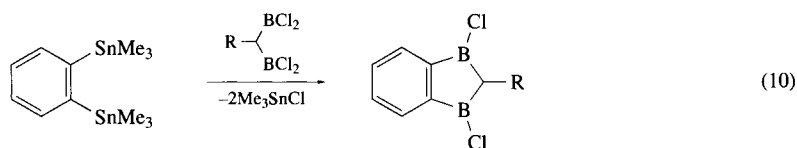
Several syntheses have become known in which the formation of two bonds leads to 2,3-dihydro-1,3-diboroles. 1,1-Bis(diiodoboryl)alkanes are reacted with alkynes with elimination of I₂ and formation of two B—C bonds to give 2,3-dihydro-1,3-diiodo-2,4,5-trialkyl-1,3-diboroles in high yields (70–90%) (Equation (8)) <90ZN(B)15>.



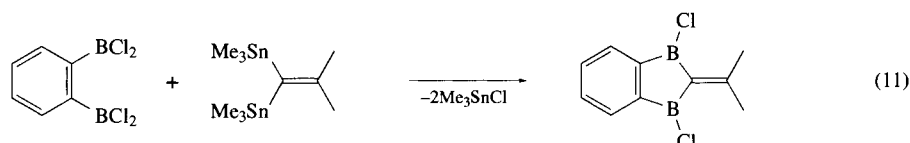
The 1,3-diiodo compounds can be transformed into 1,3-dialkyl derivatives by alkylations using AlR₃. In a corresponding reaction with cyclooctyne instead of the alkynes mentioned above, a bicyclic system is generated in 84% yield (Equation (9)) <94ZN(B)315>.



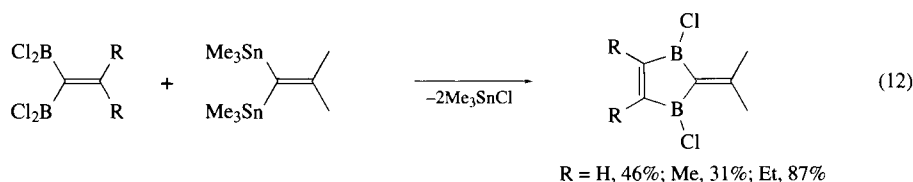
A benzo-derivative is available via the substitution of SnMe_3 by boryl moieties in 1,2-bis(trimethylstannyl)benzene (Equation (10)) <93ZN(B)68>.



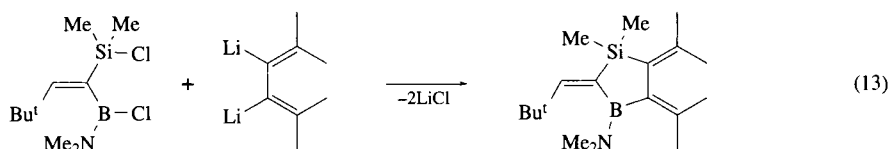
The opposite route uses 1,2-bis(dichloroboryl)benzene to react with a distannylhydrocarbon. In Equation (11) it is 1,1-bis(trimethylstannyl)-2-methyl-1-propene, leading to a diborafulvalene (80%), which can formally be considered as a special 1,3-diborole <90CB2273>.



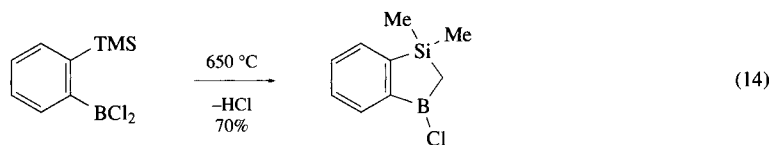
AlMe_3 is used to methylate the boron atoms; using TMSNMe_2 they can be aminated. Instead of diborylated benzene, diborylated alkenes can also be used (Equation (12)) <89CB401>.



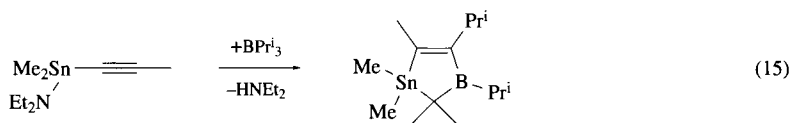
Two bonds also have to be formed to generate 1-bora-3-disilacyclopentanes in 41% yield (Equation (13)), which can be described as radialene derivatives <91ZN(B)1127>.



Two bonds are also created formally during the flash vacuum pyrolysis (FVP) of *o*-(dichloroboryl)phenyltrimethylsilane at 650°C (Equation (14)) <87JOM(331)139>.

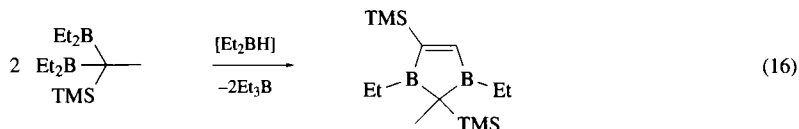


The elimination of HCl is due to the reaction of B-Cl with Si-CH_3 moieties. A last example of five-ring formation by generation of two bonds leads to a 1,2-dihydro-1,3-stannaborole (Equation (15)) <85CC1199, 88CB1451>.



One of the Pr^i substituents of BPr_3 reacts with the SnNEt_2 group to give HNEt_2 and an Sn-C bond. The ring formation is completed by the borylation of the $\text{C}\equiv\text{C}$ triple bond, accompanied by a methyl shift.

A 1,3-diborolane is formed in very low yield ($\approx 5\%$) during a complicated reaction between 1,1-bis(diethylboryl)-1-trimethylsilylthane molecules in the presence of excessive Et_2BH <94CB813>. The exchange of the Et substituents between the B atoms leads to the elimination of BEt_3 . Ring formation finally occurs by two new B—C linkages (Equation (16)).

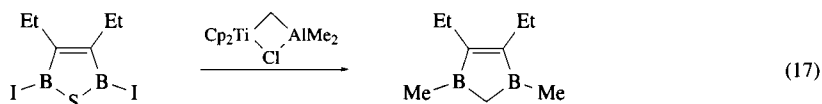


3.18.9 RING SYNTHESIS BY TRANSFORMATION OF ANOTHER RING

The synthesis of five-membered boron heterocycles with one nonadjacent heteroelement from another ring is exceptional. Only two examples are discussed here, one starting from another five-membered ring, a second from a six-membered heterocycle.

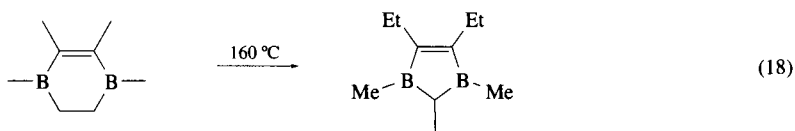
3.18.9.1 From Other Five-membered Heterocycles

A thiadiborole can be used for a desulfurization reaction by means of the Tebbe reagent (Equation (17)) <83JA2582, 85ZN(B)326>. The yield of the diborole ring is about 35%.



3.18.9.2 From Six-membered Heterocycles

A ring contraction occurs if the six-membered tetramethyl-1,4-diboracyclohexene is thermally treated at 160°C (Equation (18)) <88ZN(B)306>.



3.19

Two Adjacent Heteroatoms with at least One Other Element

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3.19.1 INTRODUCTION

Ring systems with two adjacent heteroatoms and at least one other element were reviewed in the first edition of *Comprehensive Heterocyclic Chemistry* (CHEC-I) <84CHEC-I(1)665, 84CHEC-I(5)692>, which covers literature up to 1982. However, CHEC-I did not cover this subject systematically in one place. This chapter will cover reports up to early 1994. The literature was searched by groups within the periodic table.

3.19.1.1 Scope

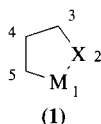
Syntheses of complexes that have one or more weak bonds in the intended five-membered ring will not be covered here, as the cyclic complex is in equilibrium with open-chain forms, and polymeric forms. Chemistry and physical properties of such compounds may not be indicative of the "heterocycle" ring at all. Most literature reports will identify these compounds as "complexes," "chelates," "coordination compounds," or structures having "ligands" and have cyclic structures drawn with a dotted line or arrow for the heteroatom-metal bond. Some authors do not follow these conventions, unfortunately, and show a metallaheterocycle with heteroatoms having more valences than can be supported without formal charge, but with no such charge being indicated. In almost all cases, these authors really mean *complexation* although indicating a heteroatom-metal sigma bond in the drawn structure. In many cases, the carbon-metal bond is labile and subject to facile reactions such as insertion, protonation, or substitution.

The chemistry of these intramolecular complexes has been reviewed <90CRV403, 95ACR406> and previously <79CRV287, 86CRV451>. Hypervalent silicon heterocycles have been reviewed <90JOM(400)81>. Palladium-induced carbocyclization of aryl rings <92T2427> and cyclopalladated complexes in general <85S233> were reviewed.

However, only heterocycles with stable cyclic structures will be reviewed in this chapter. Since some pertinent material overlaps with the previous review <84CHEC-I(1)665, 84CHEC-I(5)692>, published material from there is repeated when it is appropriate to discussions.

3.19.1.2 Nomenclature

IUPAC nomenclature <B-79MI 319-01> is generally followed using numbering shown in (1). The cyclic structure, when X is a non-metallic heteroatom and M is a metal, is called a metallaheterocycle or a cyclometallic compound. In general, there are no aromatic compounds with this structure except when X = NR, O, S, or Se, and when M is capable of forming a double bond with carbon. These give heterocycles with furan-like, thiophene-like, and pyrrole-like aromaticity where the lone pair of *p*-electrons on the heteroatom participates in aromaticity.



Most metallaheterocyclopentanes will have a stabilizing aromatic ring fused to the five-membered ring. However, a few cases of unfused, stable metallaheterocyclopentanes are known.

3.19.2 THEORETICAL METHODS

There are no reports of *ab initio* or semi-empirical methods being used on five-membered ring heterocycles of this class.

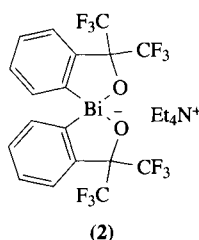
3.19.3 EXPERIMENTAL STRUCTURAL METHODS

Most studies (x-ray diffraction and NMR) have focused on determining conformation of the five-membered ring or substituents, or geometry about the metal atom. NMR studies have addressed rate of lone-pair inversion of some heteroatoms, such as nitrogen or phosphorus. Occasionally, NMR has been used for structure determination.

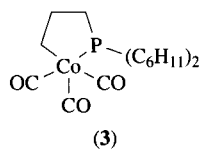
3.19.3.1 X-ray Diffraction Studies

Diffraction data give information about solid-state structures and conformations, which may be significantly different from solution conformations. On occasion, diffraction studies are used to support one possible structure from two or more possibilities.

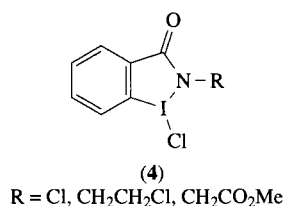
The anionic 10-Bi-4 species, (2), has distorted pseudotrigonal bipyramidal geometry about the bismuth atom <92TL6653>. The corresponding iodonium triflate, where tetracoordinate, cationic iodine replaces the bismuth atom, assumes similar geometry <82JA902, 93JA2488>.



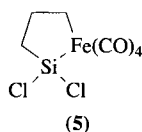
Phosphacobaltacyclopentane (3) also has distorted trigonal bipyramid geometry around the cobalt atom <86OM2030>.



Structure of benziodazoles (4) was determined by diffraction studies to be tricoordinate about the iodine atom <75JOC2129, 79JOC1447>.

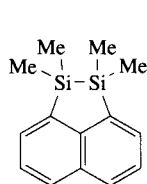


Silaferrocyclopentane (5) has distorted octahedral geometry about iron atom, and has chair conformation of the ring <79JOM(166)323>.

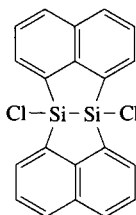


X-ray diffraction studies on disilacyclopentanes (6) and (7) show constriction of the C—Si—Si bond angles (93°) <74IZV2156, 75MI 319-01, 76MI 319-01>. The Si—Si bond distances (2.34 Å and

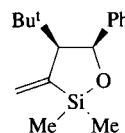
2.31 Å, respectively) do not differ significantly from acyclic compounds. Oxasilacyclopentane (**8**) x-ray diffraction has also been reported <86TL5625>.



(6)

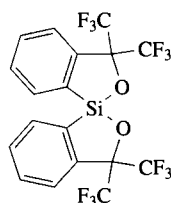


(7)



(8)

Oxasilacyclopentane (**9**) exhibits an analogous distorted tetrahedral geometry at silicon <85JA6340>. A report of the crystal structure of (**9**) has also appeared which lacks structural parameters <86TL5625>.

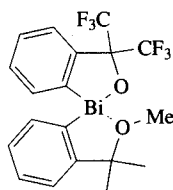


(9)

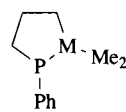
3.19.3.2 NMR Studies

Dynamic NMR is used to assess conformations and symmetry present in solution. It can reveal differences in conformation due to solvent effects, and activation energy for interconversion of conformers can be determined. This area was reviewed in <84CHEC-I(5)692> and will not be repeated here.

Variable-temperature ^{19}F NMR indicated the activation energy for inversion about the bismuth atom of organobismuth (**10**) was $15.4 \text{ kcal mol}^{-1}$ at 55°C and $21.2 \text{ kcal mol}^{-1}$ at 175°C in DMSO-d_6 <92JA7906>. Intramolecular coordination of the heteroatom (oxygen in (**10**)) stabilizes the transition state of inversion at the bismuth atom. The inversion barrier around phosphorus was studied by ^1H NMR in (**10**), and was found to be proportional to the electronegativity of "M" <76AG445>.



(10)



(11)

M = Si, Ge, Sn

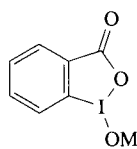
^{13}C NMR studies confirmed cyclic structure of iodoxybenzoate anions (**12**) and corresponding protonated forms <89MRC1007, 90JCS(P2)1657>.

3.19.3.3 UV and IR Spectroscopy

There are no studies of stable metallaheterocycles.

3.19.4 THERMODYNAMIC ASPECTS

Because of the wide range of atoms that can occupy sites in the heterocycle ring, it is not possible to make too many generalizations about the physical and thermodynamic properties. However, it



(12)
M = Na, H

is possible to conclude that many metal–carbon bonds are weak or subject to facile reactions such as protonation, insertion, or redox reactions. Many metal bonds to nitrogen, oxygen, sulfur, silicon, and phosphorus are also labile. Particular attention should be paid to the valence states of heteroatoms. Those heteroatoms whose normal valence state is satisfied without closure of the ring, or those whose normal valence is exceeded on ring closure, are generally in equilibrium with open-chain or polymeric structures. These compounds are not true heterocycles and their physical and spectral properties may not be indicative of the cyclic structure.

3.19.4.1 Physical Properties

A common feature of many metallaheterocyclopentanes is their sensitivity to hydrolysis, insertion of carbon monoxide, or oxidation on exposure to air. Many are subject to dimerization reactions that are thermally induced or thermally reversed.

3.19.4.2 Conformational Studies

Conformational studies were first reviewed in CHEC-I <84CHEC-I(1)665>. There have been no further studies other than those referenced in Sections 3.19.3.1 and 3.19.3.2.

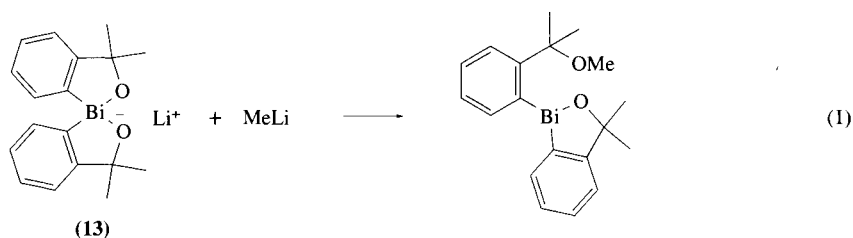
3.19.5 REACTIVITY OF FULLY CONJUGATED RINGS

Metallaheterocycles with the metal atom capable of supporting a carbon–metal double bond, and with oxygen, nitrogen, sulfur, or selenium as the second heteroatom are the only structures capable of full conjugation. These compounds show furan-like aromaticity with the heteroatom *p*-electrons participating. Obviously, very few reported metallaheterocycles fill these criteria, and the only report which documents aromaticity is one for a rhenium oxametallacyclic <93JA9986>. This report did not describe the chemistry of the aromatic compound, only its synthesis and characterization.

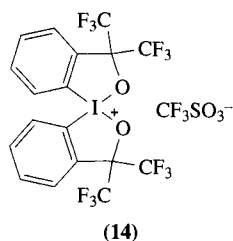
3.19.6 REACTIVITY OF NONCONJUGATED RINGS

This section considers both reduced or partially reduced metallaheterocycles. For five-membered rings, this means metallaheterocycles with one or no double bonds.

Spiro oxametallacyclic (13), analogous to (2), reacted with methyl lithium preferentially at oxygen rather than at bismuth (Equation (1)) <92TL6653>.



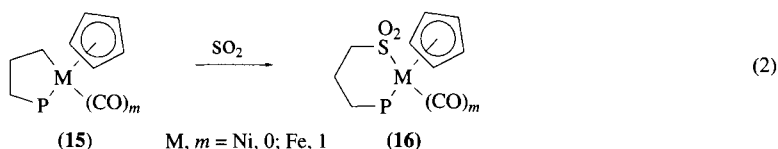
The analogous periodinium ion, (14), reacts with strong nucleophiles at iodine rather than at oxygen <82JA902, 93JA2488>.



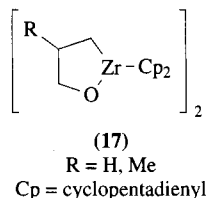
The analogous silicon compound (9) reacts reversibly at silicon with strong and weak nucleophiles <81JOC1049, 85JA6340, 90JA5342>. Hypervalent silicon compounds such as these have been reviewed <B-91MI 319-01>.

Iodosonaphthalates, similar in structure to anionic form of (12), with the phenyl ring replaced with a naphthyl ring, are good catalysts for hydrolysis of reactive phosphates <93TL1729>. Iodoso- and iodoxybenzoic acids also perform similarly as catalysts <86JOC4303, 88JOC3972>.

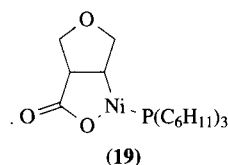
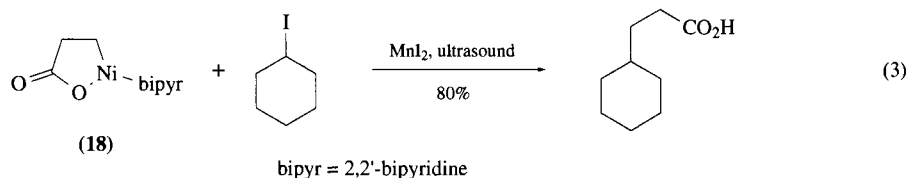
Metallacyclopentanes (15) underwent insertion of sulfur dioxide into the metal-carbon bond to give metallacyclohexanes (16) (Equation (2)) <79AG569, 81CB2653>.



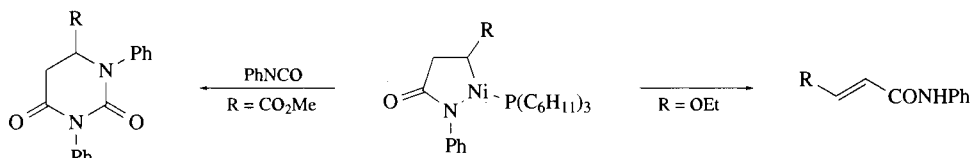
Thermal reactions of dimeric oxazirconacyclopentanes (17) have been studied <91JCS(D)2851>.



Interest in the oxanickelacyclopentanone system ("nickelalactones") and azanickelacyclopentanone ("nickelalactams") are high due to their ease of preparation and their ability to participate in elimination and coupling reactions. For instance, nickelalactone (18) cross-couples with alkyl iodides (Equation (3)) <90TL1257, 92JOM(427)395>. These heterocycles can be made to undergo only H-abstraction, in preference to carbon-carbon coupling, when they are part of a tricyclic or bicyclic system, such as (19) <90JOM(382)C6, 91JOM(412)225>. Reaction of nickelalactones and nickelalactams with alkenes has been studied <85JOM(288)237, 87AG799>.



Furthermore, β -elimination can be favored over carbon–carbon coupling reaction by varying substituent on carbon bonded to nickel in nickelalactams (Scheme 1) <85AG987, 86JOM(315)245, 89JOM(375)245>.



Scheme 1

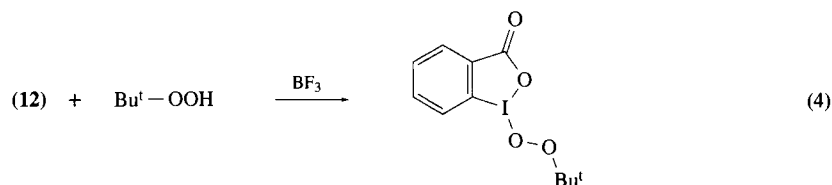
Palladium and platinum analogues of nickelalactones and nickelalactams have been prepared <90OM2396>.

3.19.7 REACTIVITY OF SUBSTITUENTS ATTACHED TO RING CARBON ATOMS

Substituent chemistry is that expected from analogous reactions of those substituents on saturated cyclic hydrocarbons or on aromatic heterocycles.

3.19.8 REACTIVITY OF SUBSTITUENTS ATTACHED TO RING HETEROATOMS

Stable alkylperoxyiodinanes can be prepared from the corresponding cyclic iodoxybenzoic acids, (12) where M = H (Equation (4)) <92JA6269>.



3.19.9 RING SYNTHESSES

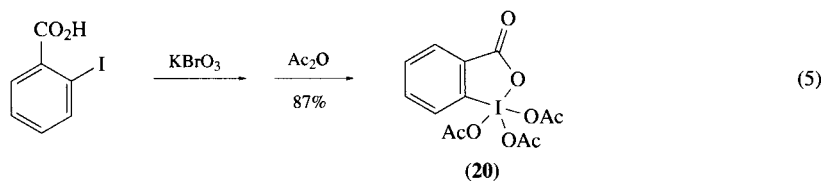
In general, ring-forming reactions which result in hypervalent heteroatoms give complexes, where one of the ring bonds is much weaker than the other ring bonds. That is, the intended ring bond, between the metal atom and the heteroatom, generates formal charge on one or more atomic centers. As such, these complexes are in equilibrium with open-chain and polymeric structures. In this section, only rings which have relatively strong σ -bonds between adjacent atoms are reviewed.

3.19.9.1 Fully Conjugated Rings

It is rare to find a metallaheterocycle which is aromatic. There are no reports of such ring syntheses from acyclic materials, but ring transformations are known (see Section 3.19.10).

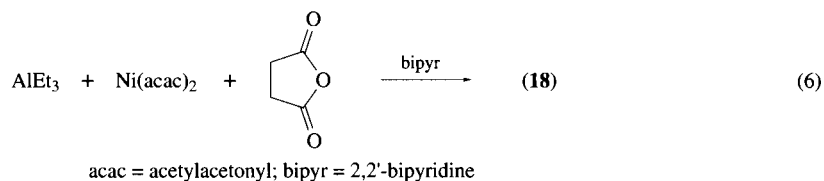
3.19.9.2 Fully Saturated or Partially Saturated Derivatives

The Dess–Martin periodinane reagent (20) is prepared by oxidation of *ortho*-iodobenzoic acids, followed by acetylation (Equation (5)) <83JOC4155>.

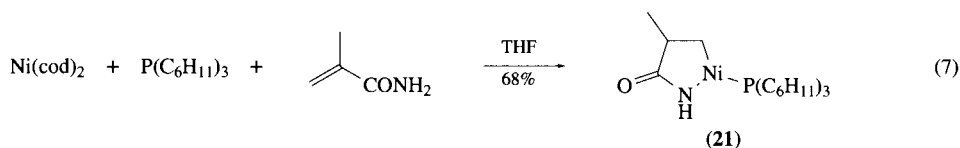


Related spiro compounds, **(13)** and **(9)**, are made differently from bis(trifluoromethyl)chloroiodinane or silicon tetrafluoride, respectively, and dilithiated hexfluorocumyl alcohol <81JOC1049, 82JA902>.

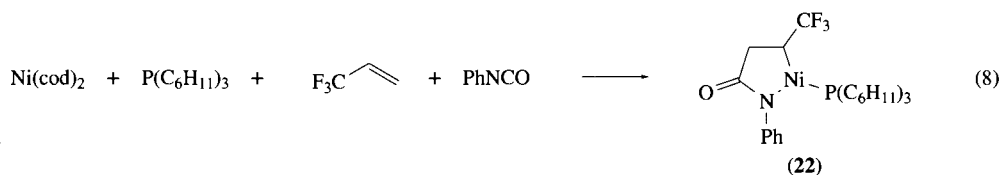
Nickelalactone **(18)** is prepared in a single step from a Ni(0) complex, ligand, alkylaluminum, and cyclic anhydride (Equation (6)) <92JOM(427)395>, although it may also be made from an appropriate alkene, CO₂, a ligand, and nickel metal or Ni(0) complex <87AG799, 91JOM(407)C23>.



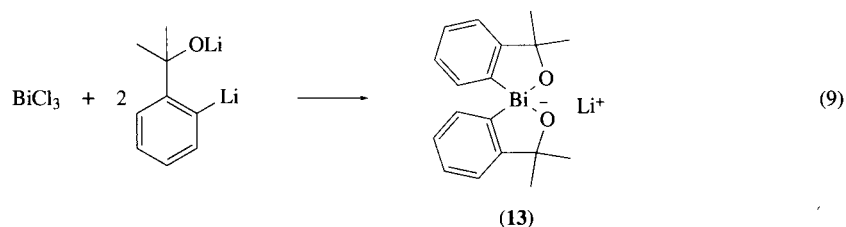
Nickelalactams are prepared from a Ni(0) complex (usually Ni(1,5-cyclooctadiene)₂), ligand (usually P(C₆H₁₁)₃), and an acrylamide derivative (see preparation of **(21)** in Equation (7)) <89IS204>.



Replacing acrylamide derivatives with alkenes and an isocyanate allows an alternative, flexible synthesis of nickelalactams (see preparation of **(22)** in Equation (8)) <85AG987, 85JOM(288)237, 86JOM(315)245, 87JOM(328)403, 89JOM(375)245, 89JOM(378)279>. This scheme works well for cyclic and heterocyclic alkenes <91JOM(412)225>.

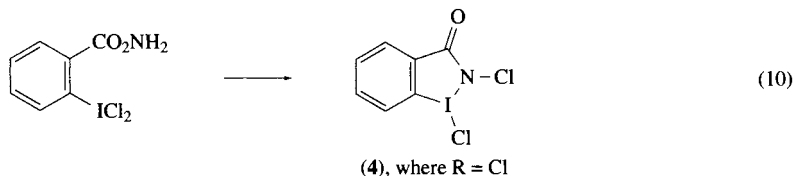


Organobismuth **(13)** was synthesized directly from BiCl₃ and a dilithiated benzyl alcohol (Equation (9)) <92TL6653>. Similar schemes have been used to prepare **(9)** and **(13)**.

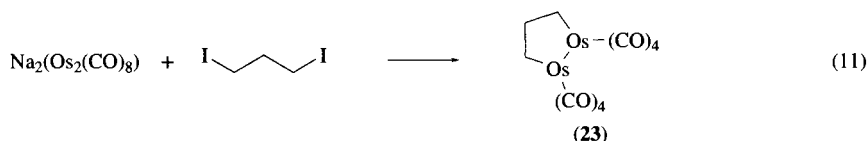


Metallacyclopentane **(15)** was prepared from the metal halide and Ph₂P(CH₂)₃Cl in 18–40% yield <79AG569, 81CB2653>. Other phosphacobaltacyclopentanes, phosphaplatinacyclopentanes, and phospharhodacyclopentanes can be prepared in a similar way <82JOM(235)345, 86OM2030, 90JOM(385)C13>.

Chlorinated azabenzoxidoles are made by disproportionation, to give (**4**; R = Cl) (Equation (10)) <75JOC2129>, or by chlorination/dehydrochlorination of *N*-substituted-*o*-iodobenzamides to give (**4**; R = Prⁱ, Buⁱ, benzyl, cyclohexyl) <81PHA535> and (**4**; R = CH₂CH₂Cl, CH₂CO₂Me) <79JOC1447>.

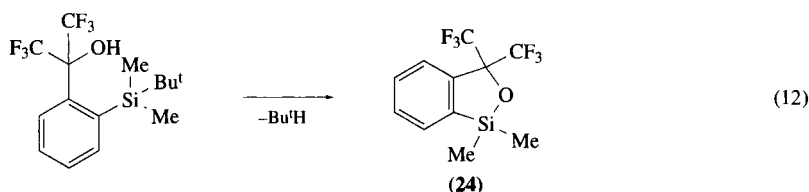


Diosmacyclopentane (**23**) can be synthesized from propylene diiodide and Na₂(Os₂(CO)₈) (Equation (11)) <82JA7325>.

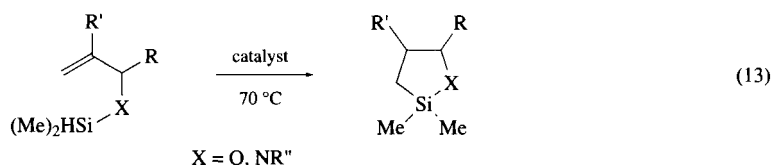


γ -Hydroxymetal hydrides, where the metal was silicon, germanium, or tin, were condensed intramolecularly to form the corresponding oxametallacyclopentane <74JOM(80)47>.

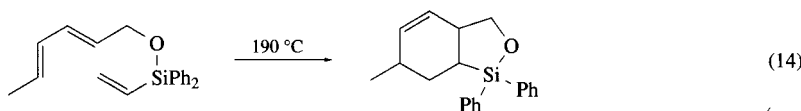
Oxasilacyclopentanes ("cyclic siloxanes"), (**24**), are formed from alkane elimination from *o*-silylbenzyl alcohols (Equation (12)) <89TL725>.



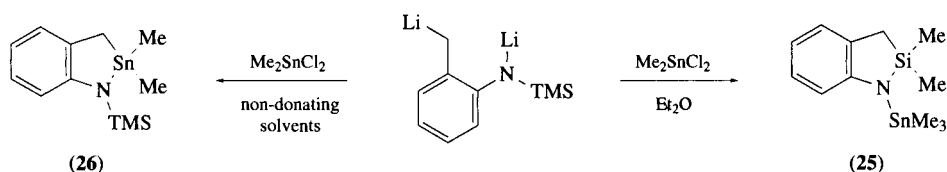
Cyclic siloxanes and their aza analogues, azasilacyclopentanes, can be prepared from appropriate unsaturated, acyclic silane or aza analogue (Equation (13)) <90JOC3438, 93OM2297>.



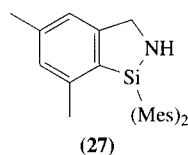
Intramolecular Diels–Alder reactions have been used to make bicyclic siloxanes (Equation (14)) <92JOC5279>.



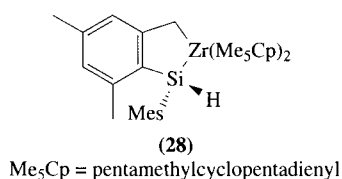
A unique control over product distribution was noted in the preparation of benzofused azametallacyclopentanes (**25**) and (**26**) by use of donating solvents (Scheme 2) <89JOM(375)1>.



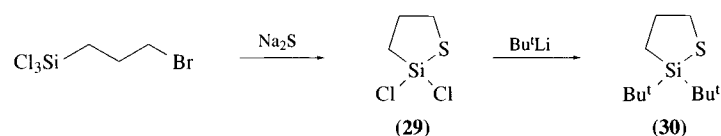
Azasilacyclopentane (**27**) can be prepared from the corresponding silylazide <86CL1025, 88JOM(341)187>.



Silazirconacyclopentane (**28**) has been prepared from $(\text{Me}_5\text{Cp})_2\text{ZrCl}_2$ and excess dimesitylsilyl-lithium <89OM324>. The ring is probably formed from a benzylic anion intermediate.

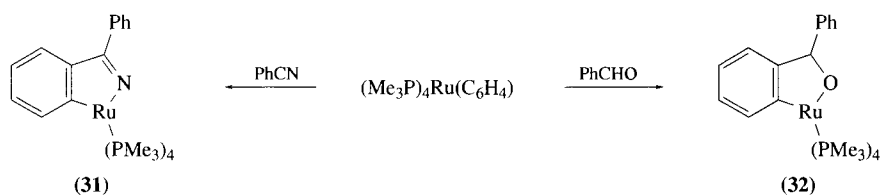


Silathiacyclopentane (**29**) was prepared by treatment of a halosilane with sulfide. Compound (**29**) was converted to (**30**) by reaction with *t*-butyllithium (Scheme 3) <80JOM(195)171>.



Scheme 3

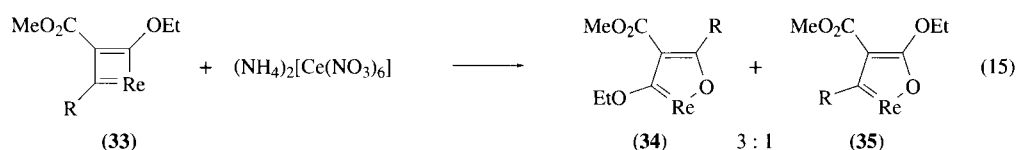
Azaruthenacyclopentane (**31**) and oxaruthenacyclopentane (**32**) were prepared by insertion into a ruthenium benzyne complex (Scheme 4) <91JA3404>.



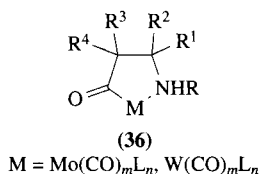
Scheme 4

3.19.10 RING SYNTHESIS BY TRANSFORMATION OF ANOTHER RING

Rhenacyclobutadiene (**33**) serves as precursor to oxarhenacyclopentanes (**34**) and (**35**) by oxygen atom insertion (Equation (15)) <93JA9986>.

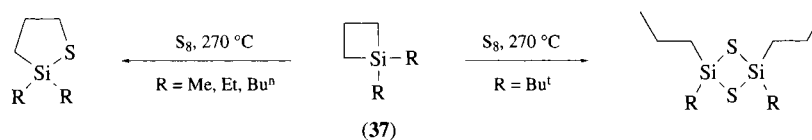


Aziridines can be opened regiospecifically to azametallacyclopentanes (**36**) using metal carbonyl hydrides <73AG87, 84ZN(B)167>.

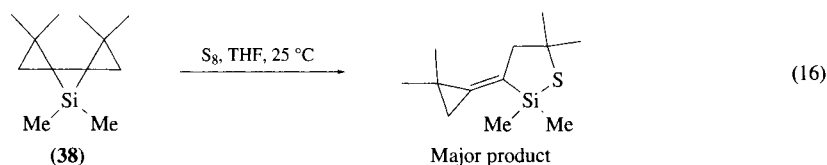


Exchange reactions on existing oxastannacyclopentanes or oxastannacyclopentenenes afforded the germana- and silaheterocycles <74JOM(71)C45>. Ring contraction of nickelalactones from six-membered rings to five-membered rings was favored when bulky ligands surrounded the nickel atom <87JA1092>. Diosmacyclopropanes can be converted to diosmacyclopentane (**23**) by reaction with ethylene <82JA7325>.

Silacyclobutane (**37**), when $R = Me, Et, Bu^n$, can be ring expanded with elemental sulfur (Scheme 5) in contrast to reports which indicate the reaction does not proceed <84CHEC-I(5)594>. Bulky substituents, such as Bu^t , inhibit ring expansion. The expansion strategy works for silacyclopropane (**38**) also (Equation (16)) <79JOM(164)305, 80JOM(195)171>.



Scheme 5



3.19.11 SYNTHESIS OF PARTICULAR CLASSES OF COMPOUNDS AND CRITICAL COMPARISON OF THE VARIOUS ROUTES AVAILABLE

The most important compounds that fall into this class of heterocycle are the Dess–Martin reagents, such as (**20**), the nickelalactones and nickelalactams (**18**) and (**21**), and the cyclic siloxanes and aza analogues (Equation (13)). There are few redundant methods of preparation for each heterocycle. The type of heterocycle and the substitution pattern will dictate which particular synthetic method is used.

3.19.12 IMPORTANT COMPOUNDS AND APPLICATIONS

Dess–Martin reagents, such as (**20**), are used for oxidations, such as a general oxidation method for α -hydroxyesters to give α -ketoesters <88TL3433>. 2-Iodoxy- and iodosobenzoic acids and their anions, which partly or fully exist in cyclic form, are catalysts for the hydrolysis of phosphate esters <86JOC4303, 88JOC3972, 89JA250>.

Nickelalactones are used as propionic acid equivalents in carbon–carbon bond forming reactions (Equation (3)) <90TL1257>.

Oxasilacyclopentane intermediates have been used to achieve stereocontrol of an acyclic chain <88S417, 92JOC1643>. Normally bimolecular Diels–Alder reactions can be made unimolecular by

uniting enophile and dienophile into the same molecule using a silane ether linkage (see Equation (14)) <92JOC5279>. Oxasilacyclopentane (**9**), in combination with its hydride adduct, rapidly reduce carbonyl compounds. The hydride adduct alone is a selective reagent for the conjugate reduction of enones <90JA5342>.

3.20

Two Nonadjacent Heteroatoms with at least One Other Element

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3.20.1 INTRODUCTION

No systematic coverage of nonadjacent heteroatoms with at least one other element was made in the first edition of *Comprehensive Heterocyclic Chemistry* (CHEC-I), which covered the literature up to 1982, though scattered examples of some of these ring systems were reported. In this chapter, the literature up to January 1994 is covered comprehensively, with more sparse inclusion of reports from the rest of 1994 and 1995.

3.20.1.1 Scope

Only heterocycles with stable, cyclic structures, where this can be ascertained, are discussed in this chapter. In addition, certain heterocycles have been reported only as mechanistic intermediates or sparsely and, rather than devote separate sections to them, they are shown in Figure 1 <82JOM(236)281, 83CC276, 84JOM(269)21, 84OM1917, 85JOM(297)C30, 86CB535, 86JA40, 86JOM(308)263, 88JOM(358)245, 93OM3890>.

No aromatic compounds with appropriate orientation have been uncovered. Furthermore, the majority of the heterocycles which fall under the auspice of this chapter contain silicon and where this is the case, it has been elected to group them together instead of using the general section headings employed in other chapters. Accordingly, to simplify access for the reader, it has proven easier to present other heterocycles in order of the position of their key heteroatom in the periodic table, for example group 1 then group 2, etc.

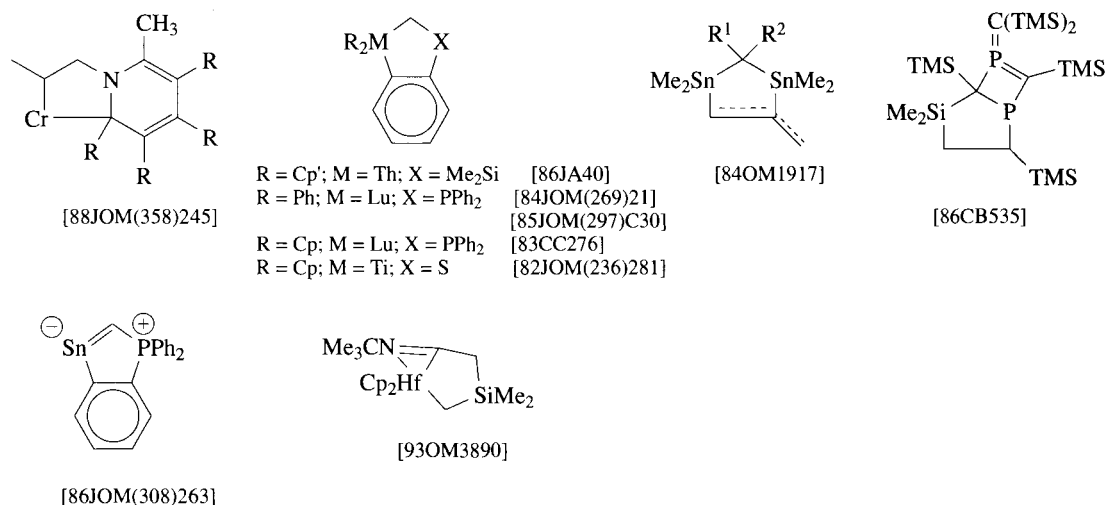


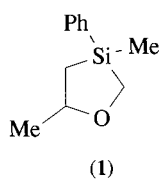
Figure 1 Miscellaneous heterocycles not specifically addressed in this chapter.

3.20.1.2 Nomenclature

IUPAC nomenclature <B-79MI 320-01> has generally been followed. The cyclic species, where M is a metal (or metalloid) and X is a non-metallic heteroatom, is called a metallaheterocycle or a cyclometallic compound.

3.20.2 THEORETICAL METHODS

An MM2 study of the two stereoisomers from (1) showed that the Si—C—O—C torsion angles were very similar <90JA1962>. Molecular orbital calculations using the CNDO/2 method have been performed for cyclic silanes. Additionally, net atomic charges, bond orders and other quantum mechanical parameters for disilacyclopentanes were obtained using SP- and SPD- basis set computations <80JOM(190)9>. The hypothesis that the photochemical [2 + 3] cycloaddition of C₆₀ with disiliranes gives a 6,6-ring junction in the adduct was supported by AM1 and *ab initio* 3-21G molecular orbital calculations <93JA10366>.



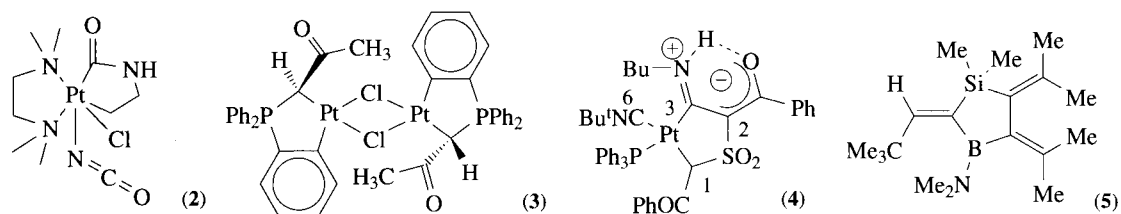
3.20.3 EXPERIMENTAL STRUCTURAL METHODS

3.20.3.1 X-ray Diffraction Studies

X-ray structural assignments have been reported for a number of the molecules reported in this chapter, and mention of this usually is made in the appropriate section dealing with the synthesis of the heterocycle. This section includes examples where some discussion of the shape of, or nature of the bonding in, the molecule was discussed.

Several platinum-containing heterocycles have been examined by x-ray crystallography. The unusual platinaazacycle (**2**) was shown to have octahedral coordination around platinum. The Pt–N–ethylenecarbamoyl ring is puckered; however, the Pt, N and carbonyl C atoms are strictly coplanar <82JA7661>. In contrast, the platinaphosphacycle (**3**) has square planar geometry around each Pt atom with some puckering of the five-membered rings. The two platinum and chlorine atoms are in the same plane, with a non-bonding distance between platinum atoms of 3.599 Å. Similarly, the metallaheterocycle (**4**) exhibits square planar coordination around Pt with a small twist angle of 8.78(53)° between the P–Pt–C(6) and C(1)–Pt–C(3) planes <90JCS(D)781>.

The borasilacyclopentane (**5**) has a half chair conformation, wherein the strong steric interactions between the substituents on the exocyclic methylene groups, as well as those with the dimethylamino, cannot be reduced by rotation of the C=C and B=N bonds <91ZN(B)1127>.



3.20.3.2 NMR Studies

No comprehensive NMR spectral study has been reported for any of the heterocycles discussed in this chapter. However, structural characterization by NMR methods is routine and, in general, mention of the results has been deferred to the sections dealing with the synthesis of particular heterocycles. This section includes results where sufficient work has been performed to suggest patterns and where more unusual techniques or results have been discussed.

The addition of a SiH₂ into a cyclopentane or cyclopentene ring causes the methylene protons adjacent to the SiH₂ to be shifted by -0.6 ± 0.4 ppm whereas those β to the silicon are shifted by $+0.3 \pm 0.1$ ppm. The alkene hydrogen atoms adjacent or β to a SiH₂ have chemical shifts 0.2 ± 0.1 ppm greater than those for cyclopentene. However, in the disilyl species where silicon is adjacent to the double bond (see (7)), the alkene hydrogen atoms show an increase of 1.3 ± 0.1 ppm, indicative of considerable interaction between the silicon atom and the π -system. The chlorosilanes display similar effects except that all of their chemical shifts tend to be higher because of the electronegativity of the chlorine atoms <91JPC6494>. These trends can be seen in Figure 2. An extensive tabulation of the ¹H NMR shifts for a variety of disilacyclopentanes and disilacyclopentenenes has been collated by Fritz and Schober <70ZAAC(372)21>. Additionally, the ¹H NMR shifts for the photochlorination products of (**8**) and some of their dimethyl derivatives have been reported. Interestingly, in the photochlorination reaction, it is the CH group with the lowest ¹H NMR shift which is chlorinated preferentially <79ZAAC(458)37>. ²⁹Si and ¹³C NMR results for some related compounds have been published <80JOM(190)9, 91OM1457>.

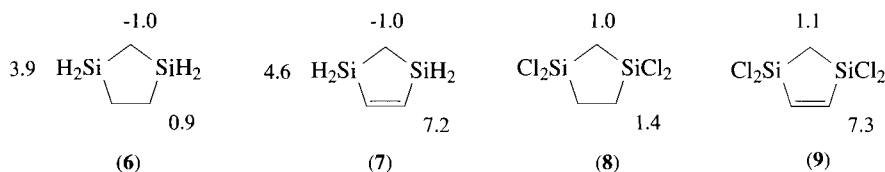


Figure 2 Proton NMR chemical shifts.

The ^{13}C and ^{11}B NMR (in brackets, relative to $\text{BF}_3 \cdot \text{Et}_2\text{O}$) signals for (10) and (11) in C_6D_6 are shown in Figure 3. The peaks in parentheses are broad signals owing to a directly bound boron atom $\langle 84\text{JOC}2565 \rangle$. The ^{11}B and ^{29}Si NMR shifts in related silaboraindanes are at higher field than those for the parent bora- and silaindanes, which may indicate a through-bond interaction between the heteroatoms $\langle 87\text{JOM}(331)139 \rangle$. Proton and ^{11}B NMR shifts for some vinylborasilacyclopentanes also have been reported $\langle 91\text{ZN}(\text{B})1127 \rangle$, as have the ^1H NMR spectra of Ge-Ge $\langle 87\text{OM}659 \rangle$ and Ge-N $\langle 88\text{JOM}(339)259 \rangle$ heterocycles.

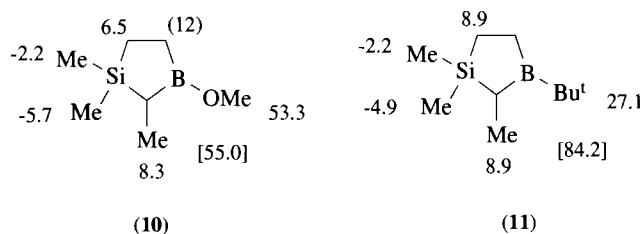
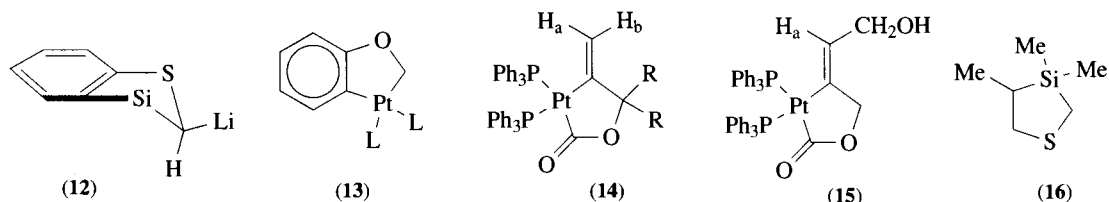


Figure 3 ^{13}C and ^{11}B NMR signals in C_6D_6 (^{11}B values are relative to $\text{BF}_3 \cdot \text{Et}_2\text{O}$).

A low-temperature ^{13}C , ^7Li , ^{31}P , and ^{29}Si NMR study of the 2-lithio species (12) has been used to assess whether or not a planar or pyramidal carbanion is present under different conditions $\langle 93\text{JA}7041 \rangle$. The ^1H NMR spectra for the platinacycles (13; L = various ligands) have been recorded and, in general, the PtCH_2 signal falls in the range 5.41–6 ppm with a $^2J_{(\text{Pt-CH})}$ of 51–70 Hz $\langle 81\text{JCS}(\text{D})933 \rangle$. In the vinyl platinacycle (14), the assignment of H_a and H_b was made on the basis that $^3J_{(\text{Pt-H})}$ (*trans*) was considered to be greater than $^3J_{(\text{Pt-H})}$ (*cis*). For (15), the configuration was assigned from the fact that $^3J_{(\text{Pt-H})}$ was 62 Hz, indicating that the platinum and hydrogen were mutually *cis* $\langle 76\text{JCS}(\text{D})185 \rangle$.



3.20.3.3 Ultraviolet and Infrared Spectroscopy

There have been no comprehensive studies reported on the UV and IR spectra of stable 1,3-metallaheterocycles. However, the far infrared, mid infrared and Raman spectra for 1,3-disilacyclopent-4-ene have been analyzed $\langle 91\text{JPC}6494 \rangle$. From this data, the ring puckering potential energy surface was determined. The molecule is planar but not nearly as rigid as silacyclopent-2-ene. The electron donor ability of the sulfur atom in the thiosilacycloalkane (16) has been assessed by comparison of its UV spectra with those of its charge transfer complexes with tetracyanoethylene and linear analogs $\langle 86\text{ZOB}2095 \rangle$.

3.20.4 THERMODYNAMIC ASPECTS

Because of the wide ranging nature of the atoms which can occupy positions in the heterocyclic ring it is impossible to draw many general conclusions regarding the thermodynamic properties of such species. As mentioned in Chapter 3.19, many metal-carbon and metal heteroatom bonds are sufficiently labile to facilitate a variety of reactions, and the heterocyclic nature of such species is often questionable.

A kinetic study was performed and thermodynamic factors were estimated for the activation energy of abstraction of hydrogen atoms from a disilacyclopentane $\langle 74\text{IZV}61 \rangle$. In addition, a thermochemical study of the dissociative ionization of 2,3,3-trimethyl-1-thia-3-silacyclopentane has been reported $\langle 85\text{JOM}(288)27 \rangle$.

3.20.4.1 Physical Properties

Many of the metallaheterocyclopentanes and congeners mentioned in this chapter are unstable and are subject to hydrolysis or oxidation on exposure to air.

3.20.4.2 Conformational Studies

Reports dealing with the conformations of appropriate heterocycles have been sparse (see Section 3.20.3.1 for further discussion). The conformation of 3,3-dimethyl-3-silathiophane was studied by electron diffraction <91ZSK148>.

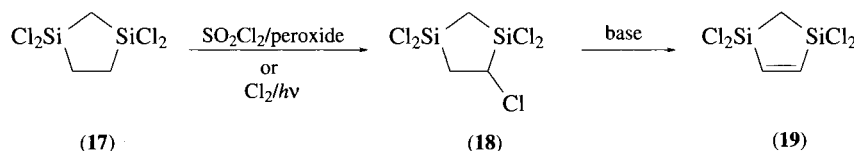
3.20.5 REACTIVITY OF FULLY CONJUGATED RINGS

No examples of this type of ring system were uncovered, undoubtedly due to the instability of the metalla-carbon double bonds required for their formation.

3.20.6 REACTIVITY OF NONCONJUGATED RINGS

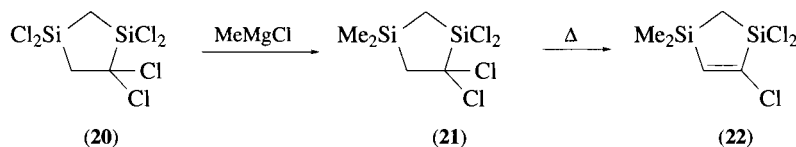
Most of the reports appropriate to this chapter deal with the preparation and characterization of the appropriate metallacycles, and, accordingly, there has been little data on their reactions. The largest body of work has been for silicon-containing heterocycles, and this has been included here. The scattered data for other systems has been incorporated into the appropriate sections on synthesis.

1,1,3,3-Tetrachloro-1,3-disilacyclopentane (**17**) undergoes chlorination at a carbon adjacent to one of the silicon atoms either photochemically <79ZAAC(458)37> or using sulfuryl chloride in the presence of benzoyl peroxide <70ZAAC(372)21, 91JPC6494>. Base-catalyzed dehydrohalogenation of (**18**) constitutes a reliable route to the corresponding disilacyclopentene (**19**) (Scheme 1), which in turn can be functionalized further by substitution of the chlorines on silicon by either Grignard reagents or hydride.



Scheme 1

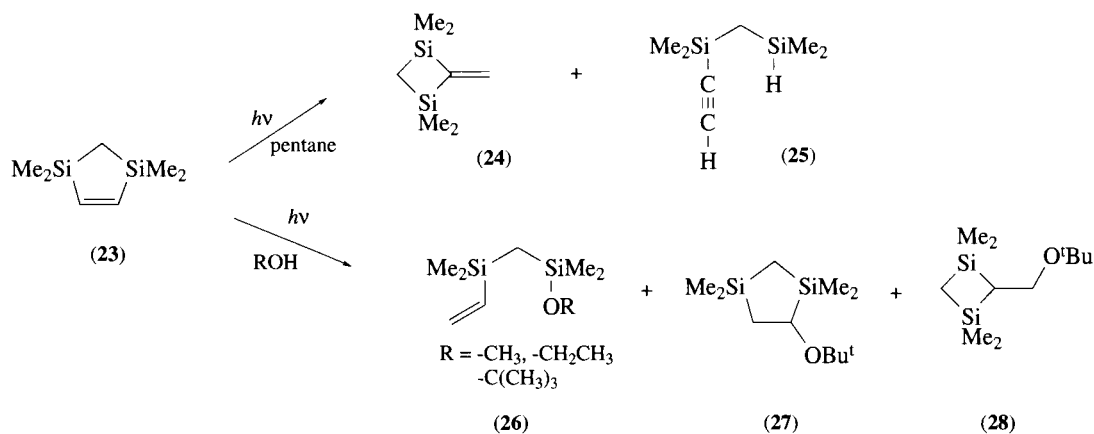
Polychlorination of (**17**) is possible (Scheme 1), especially under photochemical conditions, in which case substitution occurs preferentially at the C—H group with the most deshielded ^1H NMR shift <79ZAAC(458)37>. Thus, formation of the dichloro species (**20**) is followed by consecutive formation of the tri-, tetra-, and hexachloro derivatives. It is interesting to note that methylation of the dichloro derivative (**20**) with MeMgCl (2 equivalents) occurs regioselectively at the silicon atom not adjacent to the CCl_2 group, to afford (**21**) (Scheme 2). Upon heating, (**21**) undergoes elimination of HCl to afford the disilacyclopentene (**22**) as well as β -elimination to $\text{Me}_2\text{SiCH}_2\text{CH}_2\text{SiCl}_2\text{CCl}=\text{CH}_2$.



Scheme 2

Direct photolysis of 1,1,3,3-tetramethyl-1,3-disilacyclopentene (**23**) at 185 nm and 254 nm in deoxygenated pentane produces a ring contraction product 1,1,3,3-tetramethyl-2-methylene-1,3-disilacyclobutane (**24**) and a cleavage product, 2,4,4-trimethyl-2,4-disilahept-5-yne (**25**) in absolute

yields of 5–9% and 12%, respectively (Scheme 3) <86JOC5051>. When the photolysis of (23) was conducted in alcohol solvents (methanol, 2,2,2-trifluoroethanol and *tert*-butyl alcohol), along with minor amounts of (24) and (25), solvent addition with concomitant cleavage of the vinyl Si—C bond was observed, affording the 5-alkoxy-3,5-disila-1-hexenes (26) in 24–30% yield. Moreover, in the case of *tert*-butyl alcohol, the oxygenated disilacyclopentane (27) and disilacyclobutane (28) were obtained in 5% and 10% yield, respectively.



Scheme 3

3.20.7 REACTIVITY OF SUBSTITUENTS ATTACHED TO RING CARBON ATOMS

Since no reactivity unique to these heterocyclic systems was uncovered, this topic has been included in Section 3.20.6 and sparsely in the individual synthesis sections.

3.20.8 REACTIVITY OF SUBSTITUENTS ATTACHED TO RING HETEROATOMS

Some examples of halide displacement from disilacyclopentanes have been reported and they will be discussed in more detail in Section 3.20.9.6.1.i.

3.20.9 RING SYNTHESSES—FULLY SATURATED OR PARTIALLY SATURATED DERIVATIVES

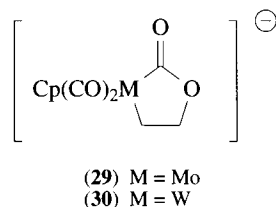
(There are no reports of syntheses of fully conjugated rings.)

No examples were found of suitable heterocycles containing elements from groups 1–3, 5, 11–13, and 15–18.

3.20.9.1 Group 6: Chromium, Molybdenum, and Tungsten

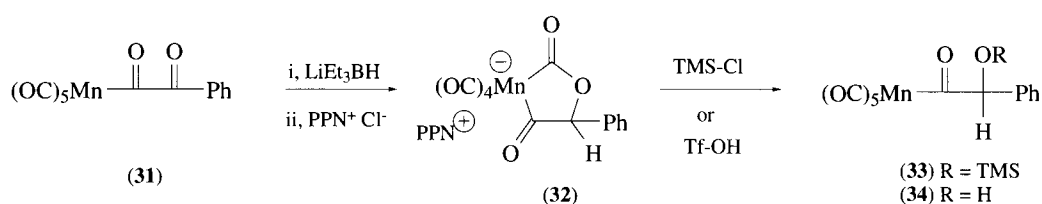
Not much is known about such systems and the heterocyclic nature of these metallacycles is questionable. The few reports concerning this area have involved the postulation of 1,3-thia-tungstacycles as intermediates during thermolysis of their 1,2-congeners <84CC964, 86JCS(D)1577>

and the suggestion that CpMo(CO)_3^- and CpW(CO)_3^- react with ethylene oxide to form 1,3-oxametallacycles (29) and (30) <75IC1566>, the infrared spectra of which exhibit $\text{C}=\text{O}$ stretching absorptions at 1580 cm^{-1} and 1550 cm^{-1} , respectively.



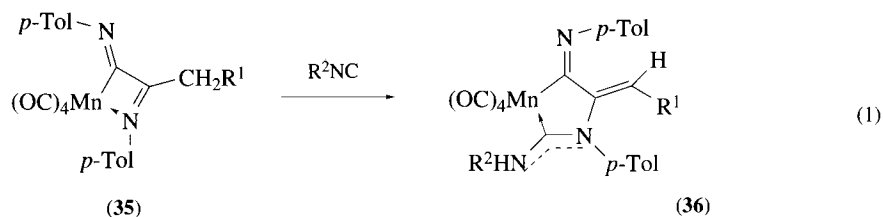
3.20.9.2 Group 7: Manganese, Technetium, and Rhenium

As for the group 6 elements, very few examples of such systems have been reported and, once again, their heterocyclic nature is questionable. However, treatment of benzoylformylmanganese pentacarbonyl (31) with lithium triethylborohydride followed by $\text{PPN}^+ \text{Cl}^-$ gave a 48% yield of a stable, gold powder identified as (32) by its spectral and x-ray characteristics <78JA6766, 86JA1455>. Ring opening of (32) occurred with trimethylsilyl chloride or triflic anhydride to form (33) or (34), respectively (Scheme 4).



Scheme 4

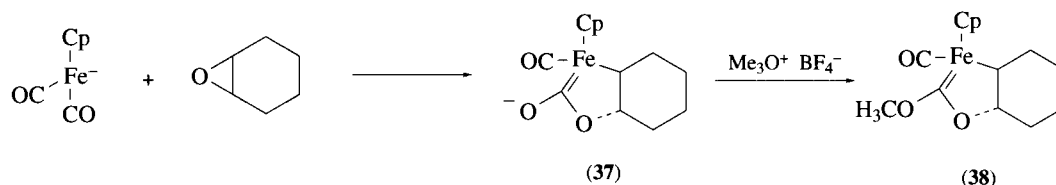
Insertion of isocyanides into the $\text{Mn}-\text{N}$ bond of bis(iminoacyl) complexes (35) gave the azamanganacycles (36) as major products (Equation (1)) <89OM2589>. X-ray studies suggest that these species are carbene complexes (as shown in (36)) rather than true heterocycles. Analogous insertion of isocyanides into the $\text{Pt}-\text{C}$ bond has led to $\text{Pt}-\text{S}$ metallacycles <90JCS(D)781> (see Section 3.20.9.5) and into the $\text{Ir}-\text{N}$ or $\text{Ir}-\text{O}$ bonds has afforded $\text{Ir}-\text{N}$ or $\text{Ir}-\text{O}$ heterocycles <88JA3704> (see Section 3.20.9.4).



3.20.9.3 Group 8: Iron, Ruthenium, and Osmium

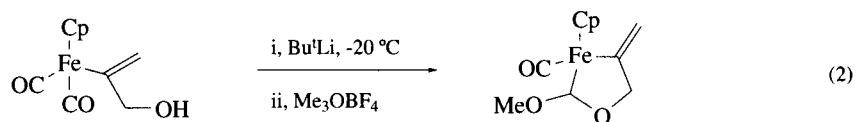
Only iron-containing heterocycles were found, again with the proviso that their heterocyclic nature is suspect. Reaction of the $(\eta^5\text{-C}_5\text{H}_5)\text{Fe(CO)}_2$ anion with cyclohexene oxide afforded an anion formulated as (37) in which the metal-carbene bond is part of the ring <77JOM(139)C25>. The structural assignment as (37) was based on the observation that this molecule displayed a single metal carbonyl absorption in the IR spectrum at 1880 cm^{-1} and an absorption at 1530 cm^{-1} assigned to the lactone function. Additionally, ^{13}C NMR analysis indicated it to be a single diastereomer <77JOM(139)C29>. While the addition of some electrophilic reagents to (37) resulted in either addition

to the cyclopentadienyl ring or cleavage of the Fe—C single bond, quenching this anion with $\text{Me}_3\text{O}^+ \text{BF}_4^-$ at 0°C gave (38) in 40% yield (Scheme 5).



Scheme 5

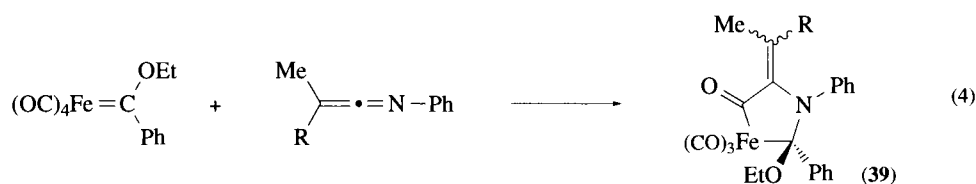
A second series of similar metallacycle carbene complexes was obtained from treatment of an iron allyl alcohol complex with BuLi at -20°C , followed by methylation of the anion with $\text{Me}_3\text{O}^+ \text{BF}_4^-$, as shown in Equation (2).



π -Allyltricarbonyl iron lactone complexes, precursors for the preparation of lactones and lactams, can be obtained by the light-induced reaction of vinyloxiranes with Fe(CO)_5 <79CB3644>, as shown in Equation (3), or from butene-1,4-diols and Fe(CO)_9 in benzene under ultrasonic conditions <90T4063>. While such species are not of the appropriate nature for this chapter, iron heterocycles often have been suggested as intermediates in their reactions. The structures of the former have been studied crystallographically <79CB3644> and the area has been reviewed <96CRV423>.

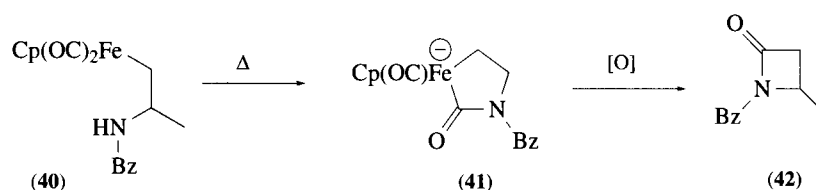


N-Vinylaminocarbene complexes (e.g., (39)) can be prepared from the reaction of ketene imines with the carbene iron complex $(\text{CO})_4\text{Fe}=\text{C}(\text{OEt})\text{Ph}$ (Equation (4)) and the structures of such complexes have been determined by x-ray <91CB1795>.



Electrochemical studies have demonstrated that formation of the β -lactam (42) from the β -aminoacyl iron complex (40) proceeds via initial formation of the anion (41) followed by sequential one-electron oxidations to give a transient iron(IV) complex which then collapses to (42) (Scheme 6) <84OM1927>.

Reaction of $[\text{CpFe(CO)}_2]$ with phosphonium salts $(\text{Ph}_3\text{PCH}_2\text{R})^+\text{Br}^-$ in the presence of excess



Scheme 6

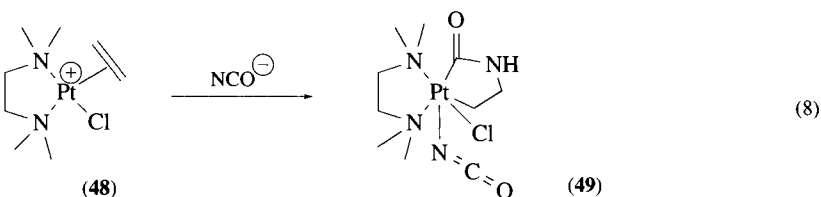
$$[\text{CpFe}(\text{CO})_2] + (\text{PH}_3\text{PCH}_2\text{R})\text{Br} \xrightarrow{\text{Bu}^n\text{Li (excess)}} \text{Cp-Fe}(\text{CO})\text{P}(\text{Ph})_2\text{CH}_2\text{R} \quad (5)$$

The only examples from this group are the iridium–nitrogen, –oxygen and –phosphorus heterocycles. Iridium–nitrogen heterocycles have been prepared by isocyanide insertion into an Ir–N bond $\langle 88JA3704 \rangle$, by treatment of *trans*-Ir(CO)(NHAr)(PPh₃)₂ with carbon monoxide $\langle 93OM2401 \rangle$ and from the reactions of *mer*-(Me₃P)₃Ir(H)(H)(Cl) and 2-ethynylpyridine in water or *mer*-(Me₃P)₃Ir(H)(Ph)(Cl) and 2-ethynylpyridine / TIPF₆ in dichloromethane $\langle 94JOM(468)257 \rangle$.

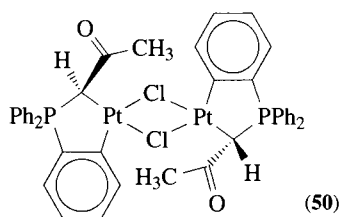
(44) (45) (6)

(46)
(47)
(7)

Nucleophilic attack by cyanate ion upon the coordinated ethylene in (48) leads to an *N*-ethylenisocyanate ligand which adds electrophilically to the platinum (assisted by another cyanate) to form a metallazaacyclopentane (49) (Equation (8)), the structure of which was definitively established by x-ray crystallography (82JA7661). Surprisingly, other nucleophiles which are known to be less reactive to ethylene and more towards Pt(II) did not lead to metallacycles (83CC40).



Platinum and palladium phosphacyclopentanes have been prepared by *ortho*-metallation reactions involving carbophosphoranes and electron-deficient platinum (or palladium) species. Thus, Me_3PtPF_6 reacted with three equivalents of $\text{C}(\text{PPh}_3)_2$ to afford a Pt–P diylide as a relatively stable red solid, characterized by NMR spectroscopy (^1H , ^{13}C and ^{31}P) <79IC686>. The reaction between acetylmethylenetriphenylphosphorane (APPY) and PtCl_2 has been studied more extensively. Originally, the product obtained by heating a 1:2 mole ratio of PtCl_2 and APPY in acetonitrile for 44 hours was formulated as $\text{Pt}(\text{APPY})_2\text{Cl}_2$. However, later studies <83OM1364, 86ICA65> showed this to be erroneous and that *ortho*-metallation had occurred to form (50). Extension to Pd–P and Pd–As analogs was reported <86ICA65, 89JOM(364)407>.



Platinum–oxygen heterocycles (e.g., (13)) have been prepared by treatment of $[\text{PtCl}_2(\text{DMSO})_2]$ with excess $\text{SnMe}_3(\text{C}_6\text{H}_4\text{OMe}-2)$ followed by addition of dppe or other ligands <81JCS(D)933>; via carbonylation of (α -hydroxyacetylene)bis(triphenylphosphine)platinum complexes <76JCS(D)185>, and from the decomposition of the initial products formed by the reaction of diazo compounds with $(\text{COD})\text{Pt}(\text{CHRCI})\text{Cl}$ <93OM2445>.

3.20.9.6 Group 14: Silicon-containing Heterocycles

3.20.9.6.1 1,3-Disilacyclopentanes and 1,3-disilacyclopentenes

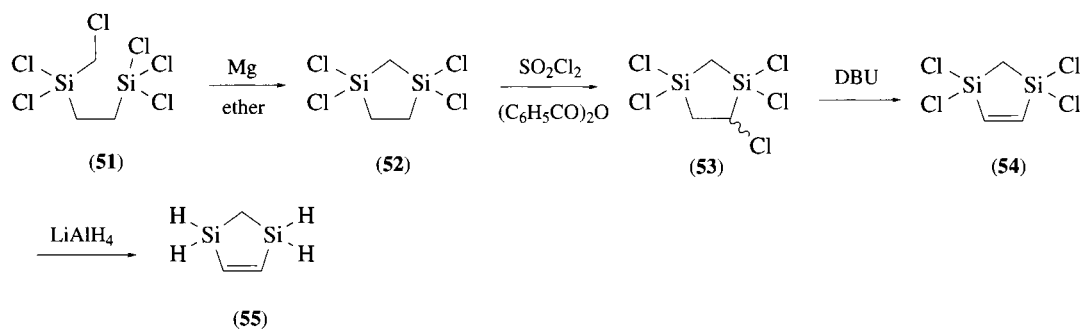
Of the ring systems which come under the purview of this chapter the most widely studied are those containing silicon, especially the disilacyclopentanes and disilacyclopentenes. While such species are often unstable, numerous routes to their formation have been described.

(i) Preparation via intramolecular cyclization of organometallic species

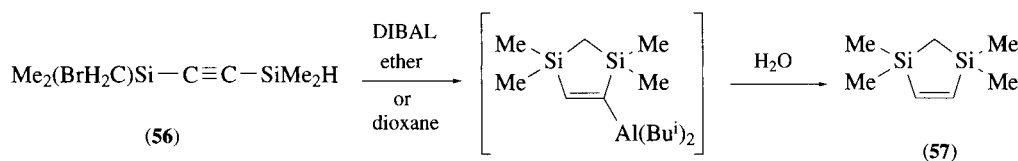
Perhaps the most general route to disilacyclopentanes involves the intramolecular attack of an *in-situ*-generated organometallic species derived from molecules of the general form $\text{XCH}_2\text{Si}(\text{Me})_n(\text{Cl})_{2-n}\text{CH}_2\text{CH}_2\text{Si}(\text{Cl})_{3-n}(\text{Me})_n$ <70ZAAC(372)21, 69DOK(188)120> and this has also been applied to the synthesis of Si–Ge analogs <69ZOB2281>. The resulting disilacyclopentanes are versatile intermediates in the preparation of more highly substituted derivatives since the chlorines can be displaced by Grignard or hydride reagents <69IZV1336>, and the corresponding disilacyclopentenes can be obtained by a route involving initial chlorination adjacent to one of the silicon atoms followed by base induced elimination of HCl <79ZAAC(458)37>. This process was employed in 1991, in the first synthesis of the parent compound, 1,3-disilacyclopent-4-ene. In this case, (51) underwent cyclization in the presence of magnesium to afford the tetrachlorodisilacyclopentane (52). The ring was then chlorinated using sulfuryl chloride to afford (53) which underwent elimination to the corresponding alkene (54) using 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). Reduction with LiAlH_4 then resulted in the preparation of the disilacyclopentene (55) (Scheme 7) <91JPC6494>.

In another interesting variant of this process, disilacyclopentenes (e.g., (57)) were prepared by the reaction of diisobutylaluminum hydride with alkynes such as (56) (Scheme 8) <70ZAAC(377)48>. In this case, *cis*-addition of $\text{Al}-\text{H}$ to the alkyne triple bond results in an increased reactivity of the $-\text{CH}_2\text{Br}$ group to the extent that spontaneous ring closure takes place in solvents of weak Lewis basicity (ether or dioxane) to afford the corresponding disilacyclopentene after hydrolytic loss of aluminum.

Distannyl butadienes such as (58) undergo stepwise Li/Sn exchange with MeLi to afford the synthon (59) for the 2,3-dianion of 1,3-butadiene (Scheme 9). Since the Li/Sn exchange is rapid, double derivatization to form (60) could be effected by the addition of 2–3 equivalents of MeLi to a solution of (58) and the electrophile <93JA6625>. However, the cyclic five-membered diene (60) was

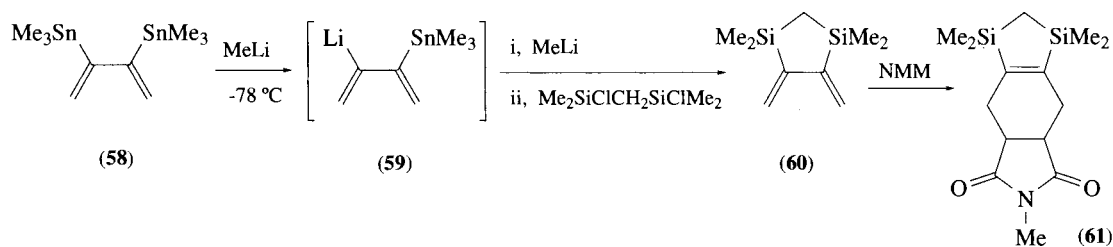


Scheme 7



Scheme 8

a very reactive Diels–Alder diene and susceptible to polymerization (even at -20°C) and was best characterized as its *N*-methylmaleimide adduct (61). This approach also has been used to prepare 1-selena-3-silacyclopentanes and 1,3-diselenacyclopentanes $\langle 84\text{JOC}3438 \rangle$. Similarly, 2,2'-dilithio-1-phenylpyrrole reacted with diphenyldichlorosilane or dimethyldichlorogermane to form the corresponding azasilole or azagermole, respectively $\langle 79\text{JOM}(166)139 \rangle$.

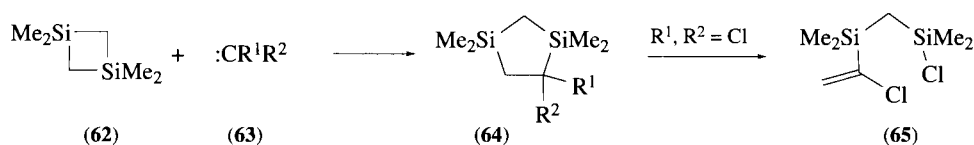


Scheme 9

(ii) Preparation via reactive intermediates

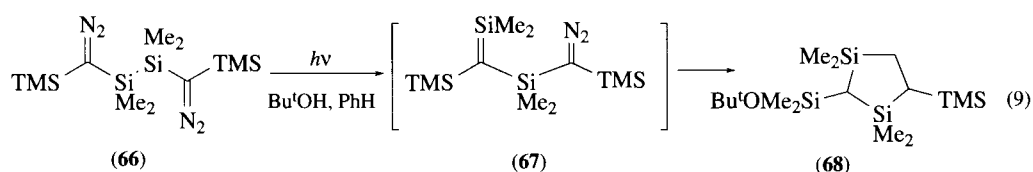
(a) *Carbenes*. Carbene insertion into a 1,3-disilacyclobutane to form a disilacyclopentane was first reported in 1971 $\langle 71\text{JA}3709 \rangle$. The results of the report showed that phenyl(bromodichloromethyl)mercury reacted with neat 1,1,3,3-tetramethyl-1,3-disilacyclobutane (62) to form the corresponding, unstable disilacyclopentane (64; $\text{R}^1, \text{R}^2 = \text{Cl}$) as a 9 : 1 mixture with its decomposition product (65) (Scheme 10). A 97% recovery of the starting material was obtained in refluxing benzene $\langle 67\text{JA}1538 \rangle$. Conclusive evidence for the formation of (64; $\text{R}^1, \text{R}^2 = \text{Cl}$) was obtained by subjecting the mixture of (64) and (65) to reduction with Li / tertiary butanol in tetrahydrofuran to give the known $\langle 70\text{ZAAC}(372)21 \rangle$ compound 1,1,3,3-tetramethyl-1,3-disilacyclopentane (64; $\text{R}^1, \text{R}^2 = \text{H}$) in 48% yield. When a mixture of (62) and ketene was photolysed (to form $^1\text{CH}_2$) the corresponding Si—C insertion product (64; $\text{R}^1, \text{R}^2 = \text{H}$) was only a very minor product ($\approx 4\%$ of the total), the remainder being unreacted starting material and 1-ethyl-1,3,3-trimethyl-1,3-disilacyclobutane, the C—H insertion product $\langle 89\text{CC}284 \rangle$. From these results, the authors concluded that the insertion of $^1\text{CH}_2$ into a strained Si—C bond was about 6 times slower than into a C—H bond.

Even poorer selectivity was observed with carboalkoxycarbenes. Thus, treatment of (62) with the carbene (63; $\text{R}^1 = \text{H}$, $\text{R}^2 = \text{CO}_2\text{Me}$) (derived by photolysis of methyl diazoacetate) gave the corresponding disilacyclopentane (64; $\text{R}^1 = \text{H}$, $\text{R}^2 = \text{CO}_2\text{Me}$) in 14% yield and the disilacyclobutanes derived from insertion into primary and secondary CH bonds in 53% and 33% yield, respectively

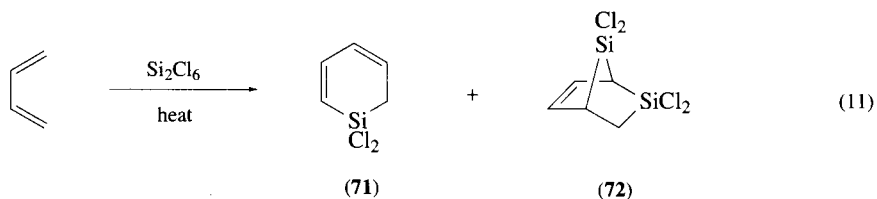
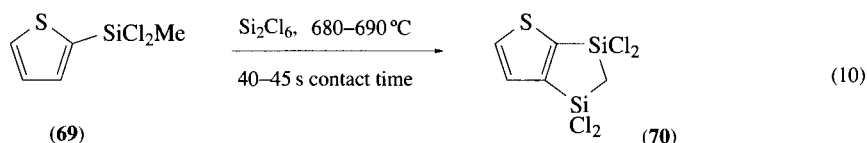


Scheme 10

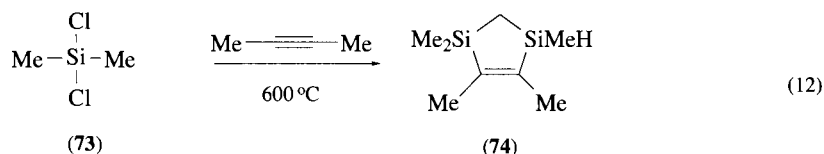
<74JOM(67)C7>. With (63; $\text{R}^1, \text{R}^2 = \text{CO}_2\text{Me}$) only a 5% yield of (64, $\text{R}^1, \text{R}^2 = \text{CO}_2\text{Me}$) was obtained along with the primary and secondary C—H insertion products in 45% and 50% yield, respectively. Photolysis of (66) in the presence of tertiary butyl alcohol gave (68) (12% yield) and 4 other products, presumably via initial silicon migration to form the silene (67) then subsequent carbene insertion into the C—H bond of one of the TMS methyl groups (Equation (9)) <95JOM(499)99>.



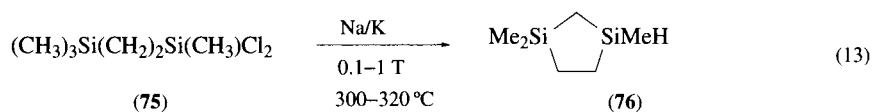
(b) *Silylenes*. Pyrolysis of hexachlorodisilane (to give silylene $:\text{SiCl}_2$) in the presence of the methyldichlorosilyl species (69) gave the disilacyclopentane (70) in 20% yield (Equation (10)) <76ZOB1278>. Other analogs of (70) were prepared in 16–76% yield. Interestingly, similar reaction with cyclopentadiene yielded a mixture of (71) and (72) (Equation (11)) <80ZOB697>.



The unusual silylene $\text{TMS}(\text{Me})\text{Si}:$ may be involved in the preparation of the 1,3-disilacyclopentene (74) (23% yield) by thermolysis of (73) in the presence of 2-butyne (Equation (12)) <78JA6236>.

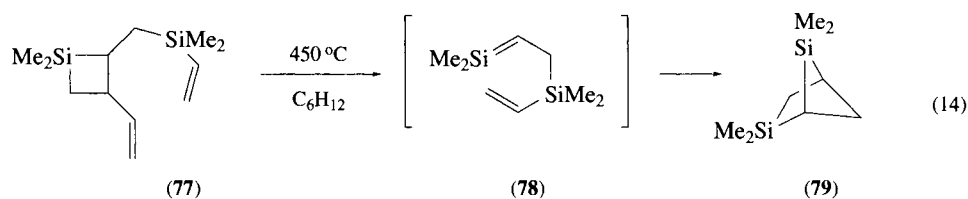


Silylene intermediates are also implicated in the reactions of certain organochlorosilanes with alkali metal vapors. Thus, treatment of (75) with K/Na alloy vapors afforded the δ (C—H) insertion products (76) in a yield less than 10% of the corresponding alkenylsilane, the β (C—H) insertion product (Equation (13)) <85JOM(292)189>.

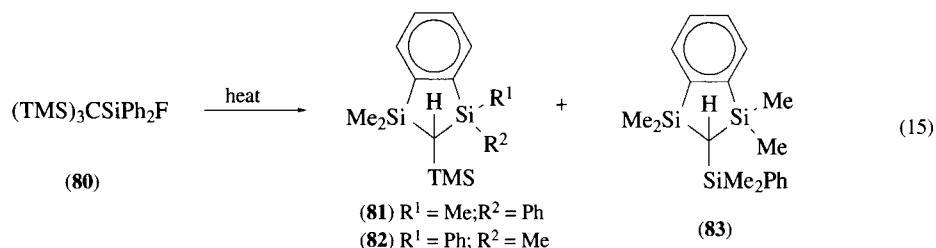


A vinyl silylene intermediate is implicated in the formation of disilacyclopentenes by thermolysis of silacyclopropenes <92OM597, 95OM1204>.

(c) *Silenes (C=Si) and free radicals.* The disila species (79) was obtained in 31% yield (along with six other products) from the pyrolysis (450°C) of the silacyclobutane derivative (77) (Equation (14)) <87OM1406>. Experimental evidence points to the intermediacy of the silene (78), and, indeed, the same intermediates ((78) and (79)) were postulated in the pyrolysis (620°C) of 1,2-divinyl-1,1,2,2-tetramethyldisilane <79JOM(168)23>.



Electrophilic aromatic substitution by silenes (though radical intermediates cannot be ruled out) has been reported by Eaborn and coworkers <80JOM(186)309>. Thus, thermolysis of the silyl fluoride (80) led to a mixture of three disilacyclopentanes (81)–(83) (Equation (15)). The structures of (81) and (82) were confirmed by x-ray crystallography and mass spectrometry, while that for (83) was strongly suggested by NMR evidence. The mechanism was presumed to involve elimination of TMSF to yield a silene, $(\text{TMS})_2\text{C}=\text{SiPh}_2$, which could equilibrate to three other silaalkenes by methyl or phenyl migrations. Subsequent cyclization would lead to the products found.



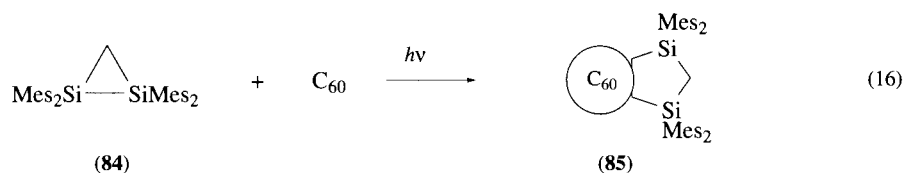
Similar kinds of products have resulted from thermolysis or photolysis of $(\text{TMS})_3\text{CSiPh}(\text{R})\text{I}$ (R = Me, Ph), though here radical intermediates are more likely <80JOM(204)169, 81CC175>.

Disilacyclopentanes and -pentenes are also obtained as minor products in the complex mixtures from pyrolysis of Me_3SiH or Me_4Si <70ZAAC(375)171, 80ZAAC(460)115>. A similar, intramolecular, low-yield (5%) preparation of a disilacyclopentane resulted from pyrolysis (400°C, <0.01 τ) of hexamethyltrimethylsilylbenzene <91CL1417> and 1,1-dimethyl-1,3-thiagermetane was formed as a minor constituent of a six-component mixture by thermolysis of 1,1-dimethyl-1,3-thiagermetane <88JOM(345)39>. A germafulvene intermediate probably is involved in the formation of 1,3-digermacyclopentene derivatives from the reaction of diethylcyclopentadienylchlorogermane with triphenylmethylenephosphorane <80IZV2668>. While interesting mechanistically, such transformations are of little synthetic value.

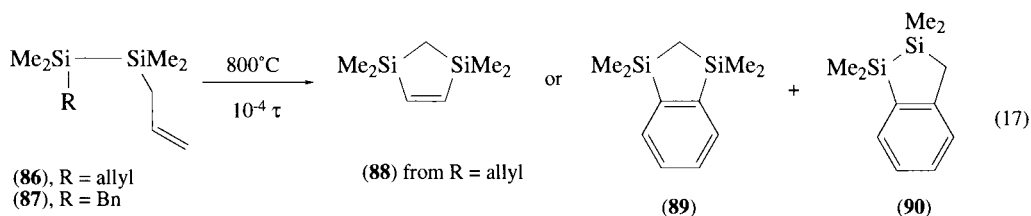
(iii) Preparation by insertion into Si—Si bonds

(a) *Photolytically.* Little work has been done in this area. Irradiation (high-pressure mercury lamp) of the disilirane (84) and buckminsterfullerene, C_{60} , in toluene gave the disilolane (85) in 82% yield (Equation (16)) <93JA10366>. No reaction occurred at 90°C. The spectral data was in accord with the assigned structure (see Section 3.20.3.2). The process has been extended to an endohedral metallofullerene $\text{Ga}@\text{C}_{82}$ <95CC1345> but the use of bis(alkylidene)disilacyclobutanes led to

rearranged 1:1 adducts, presumably via the intermediacy of the corresponding C_{60} annulated disilacyclohexanes $\langle 94OM4186 \rangle$.



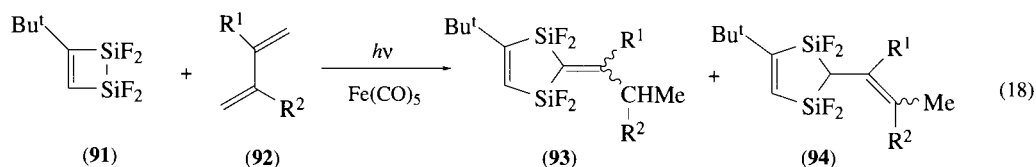
(b) *Thermally.* Vacuum flow pyrolysis (800°C , $10^{-4}\tau$) of (86) gave the disilacyclopentene (88) in 51% yield (Equation (17)) $\langle 80JA7979 \rangle$. Under similar conditions the benzyl allyl species (87) gave a mixture of disilaindanes (89) $\langle 76ZOB1278 \rangle$ and (90) in 21% and 29% yield, respectively. Similar results were obtained from pyrolysis of 1,2-dibenzyltetramethyldisilane. Experimental evidence points to a mechanism involving initial homolysis of a benzyl- or allyl-silicon bond (see Section 3.20.9.6.1.ii(c) for other radical processes).



Previously, it had been shown that pyrolysis of (86) at 620°C in a vertical nitrogen-flow system gave a complex mixture of products, including (88) (3.5%), (64; $R^1, R^2 = \text{H}$) (0.8%), 1,1,3,3-tetramethyl-1,3-disila-2-methylenecyclopentane (2.1%) and 3,3,4,5,5-pentamethyl-3,5-disilacyclopentene (2%) $\langle 79JOM(168)23 \rangle$. Formation of disilacyclopentanes by platinum-catalyzed rearrangement of vinyl disilanes also has been reported $\langle 86JAP61207389 \rangle$.

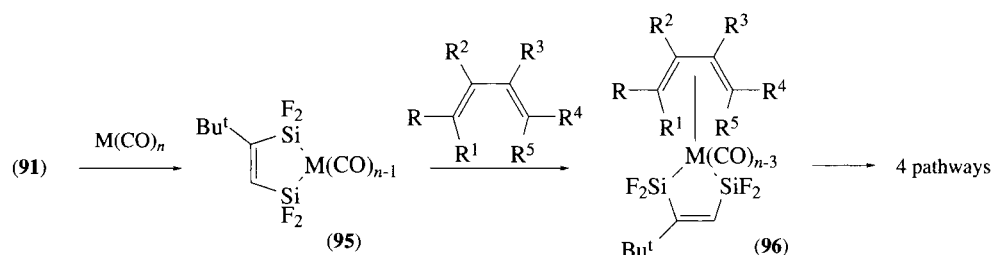
(iv) *Preparation via organometallics*

Metal carbonyl and metal phosphine complexes catalyze cycloaddition of 1,2-disilacyclobutenes (e.g., (91)) with unsaturated organic molecules $\langle 78JOM(162)C43, 75JA6746 \rangle$, presumably via metal insertion into the Si—Si bond. In an effort to assess the mechanistic parameters of such reactions, a systematic examination of the $\text{Fe}(\text{CO})_5$ mediated photochemical cycloadditions of (91) with various conjugated dienes (92) was undertaken. Surprisingly, instead of 1,4- or 1,2-addition products, air-sensitive, inseparable mixtures of alkylidenedisilacyclopentenes (93), and the isomeric alkenes (94) were obtained in 35–70% yield (Equation (18)) $\langle 87OM1861 \rangle$. Even though the products could not be separated, structural identification was possible from their spectral characteristics (see Section 3.20.3.2).



A pure sample of (94, $R^1 = R^2 = \text{H}$; *cis*) could be obtained (30°C , 60% yield) by treatment of (91) with (92; $R^1 = R^2 = \text{H}$) using molybdenum hexacarbonyl as mediator. Interestingly, with iron pentacarbonyl and 2,3-dimethyl-1,3-butadiene (92; $R^1 = R^2 = \text{Me}$), (91) formed only the alkylidene products (93; $R^1 = R^2 = \text{Me}$). The corresponding alkene (94, $R^1 = R^2 = \text{Me}$) did result exclusively from photochemical treatment of (91) with $\text{W}(\text{CO})_6$ at 0°C . Exposure of this alkene to $\text{Fe}(\text{CO})_5/h\nu$ isomerized it quantitatively to (93; $R^1 = R^2 = \text{Me}$), explaining the initial result. These, and other, findings allowed the authors to conclude that the mechanism involved an unusual 1,1-addition where the two silicon atoms added to the same carbon, C1, of the diene, and the hydrogen atoms were shifted from C1 to C4 and C3. In addition, it was concluded that, in these reactions, a π -

complex of the disilametallacycle (**96**) was the key intermediate, the electronic and steric features of which determined the subsequent reaction pathways (Scheme 11).

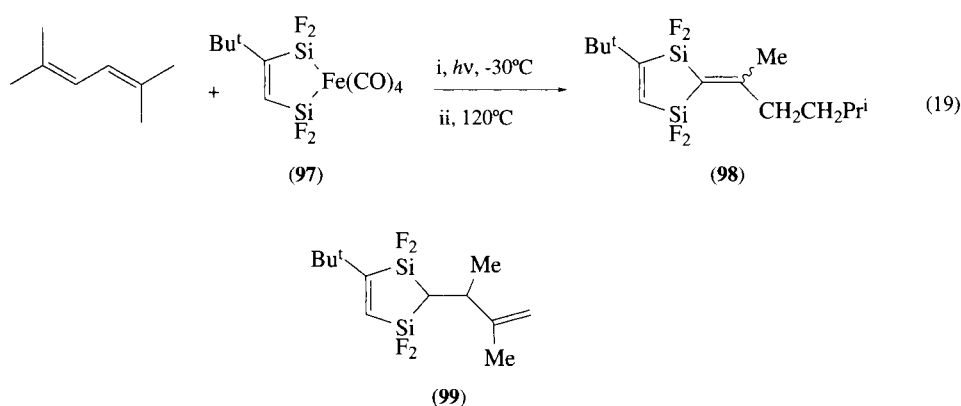


Scheme 11

In general, from intermediate (**96**), after insertion of the first silicon atom, attack of the second silicon atom may take four pathways: 1,4-addition to form a disilacyclooctadiene (favored by use of 2,3-disubstituted-1,3-dienes and $Ni(CO)_4$ <88OM1265>, $CpCo(CO)_2$ <88OM1271> or $PdCl_2L_2$ <75CL887, 78JOM(162)C43>); 1,2-addition to form a 1,4-disilacyclohexene (favored by $Fe(CO)_5$ and 1,3-dienes with at least one substituent at each end <87OM1861, 87OM1869, 87OM1882, 86JA1323>); hydrogen migration leading to 1,1-addition to form an alkylidene disilacyclopentene and disilacyclopentenyl-alkene (favored by $Fe(CO)_5$, $W(CO)_6$ and a 1,3-diene with at least one end lacking a substituent <87OM1861, 87OM1869, 87OM1878>); and fluorine migration to form a fluorosilacyclopentene-(trifluorosilyl)alkene (favored by $Cr(CO)_6$, $Mo(CO)_6$ and a 2,3-disubstituted diene) <87OM1878>.

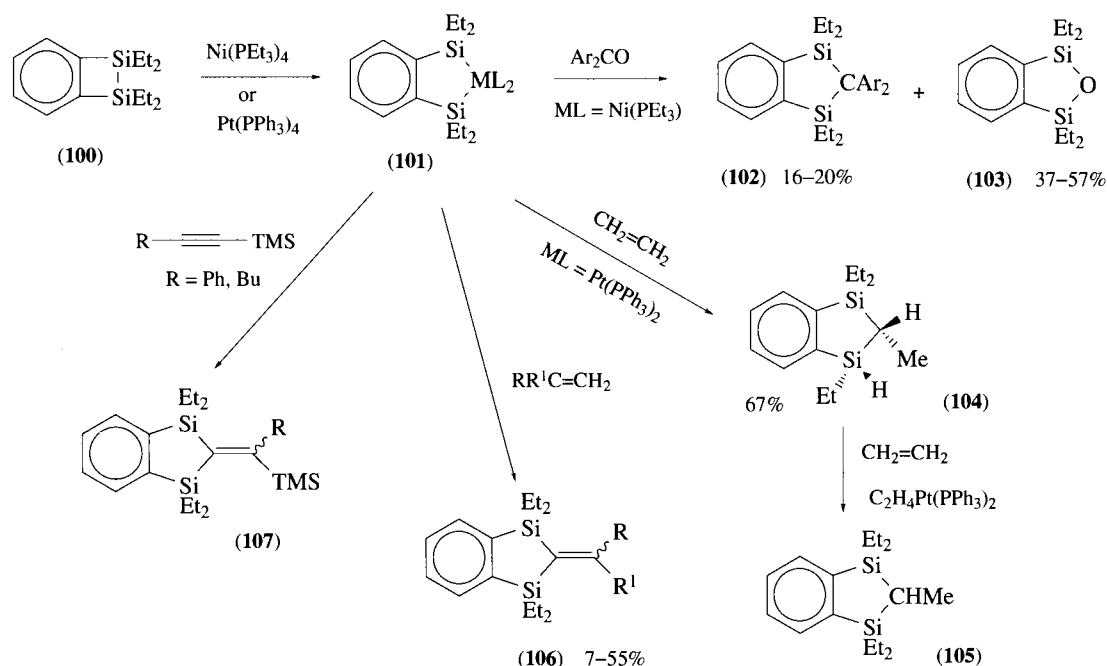
The pathway chosen depends on the geometry of the disilametallacycle intermediate (**96**), the electronic properties (e.g., hardness) of the central metal and the steric effects of the substituents on the 1,3-diene. The disilacyclopentene products (e.g., (**93**)) generally are favored by the use of dienes with at least one end unsubstituted (to allow 1,1-addition), steric crowding in the coordination sphere around the metal in the metallacycle intermediate (preventing 1,4-addition) and use of a soft metal (such as Fe) to assist in the migration of the softer base, H^- (rather than the harder F^-).

Apparent exceptions to these guidelines have been observed: for example, photolytic reaction of 1,1,4,4-tetramethyl-1,3-butadiene with (**97**) gave (**98**) as major product, presumably due to steric hindrance to silicon migration allowing prior isomerization (Equation (19)) <87OM1869>. In addition, photolytic reaction of (**91**) with (**92**; $R^1, R^2 = Me$) and $W(CO)_6$ at $90^\circ C$ gave (**94**; $R^1, R^2 = Me$), whereas with $CpCo(CO)_2$ at $60^\circ C$ the major product was (**99**). Interestingly, with 2,4-dimethyl-1,3-pentadiene, a mixture of products analogous to (**94**) and (**99**) was obtained under these conditions. Isomerization of (**99**) or (**94**; $R^1, R^2 = Me$) to (**93**; $R^1, R^2 = Me$) was achieved using $Fe(CO)_5$ under photolytic conditions <88OM1271>.



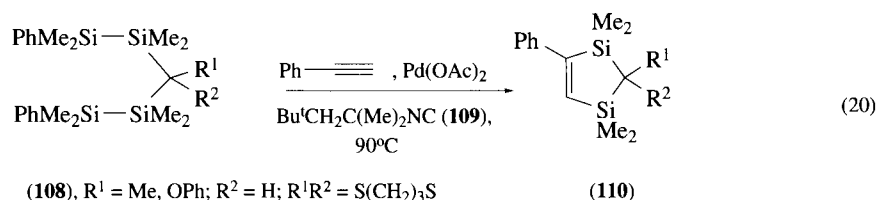
Similar findings have been reported by Ishikawa and coworkers. Using the disilacyclobutene (**100**) as the key reactant, they have found that disilacyclopentane and -ene products, e.g., (**102**)–(**107**), can be obtained using non-enolizable ketones <93OM87>, alkenes, dienes <93OM4987, 95OM114>, or alkynes <95JOM(499)35> with nickel or platinum catalysis—presumably via metal insertion intermediates such as (**101**) (Scheme 12).

Alkyne insertion into Si—Si bonds was also demonstrated for acyclic systems. Thus, treatment of (**108**) with phenylacetylene in the presence of $Pd(OAc)_2$ and isocyanide (**109**) at $90^\circ C$ gave the

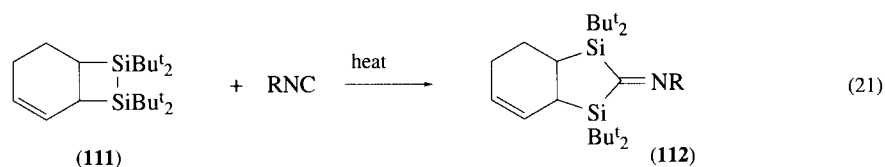


Scheme 12

disilacyclopentenes (**110**) in 67–91% yield (Equation (20)). Without substitution at the tether in (**108**) (i.e., $\text{R}^1, \text{R}^2 = \text{H}$), two major acyclic products were formed and only a 4% yield of the corresponding disilacyclopentene (**110**; $\text{R}^1, \text{R}^2 = \text{H}$) resulted $\langle 94\text{OM}4148 \rangle$. The study was extended to electron-deficient alkenes. Similar intramolecular alkyne insertion had been reported previously; exocyclic alkenes (similar to (**107**)) resulted $\langle 91\text{JOC}1948 \rangle$. While the role of the alkyl isocyanide is unclear, it is speculated that the catalytic species may be a palladium(0) isocyanide complex. More recently, in 1995, an intramolecular variant on this approach was used to prepare a bis(disilacyclopentene) $\langle 95\text{OM}1092 \rangle$.



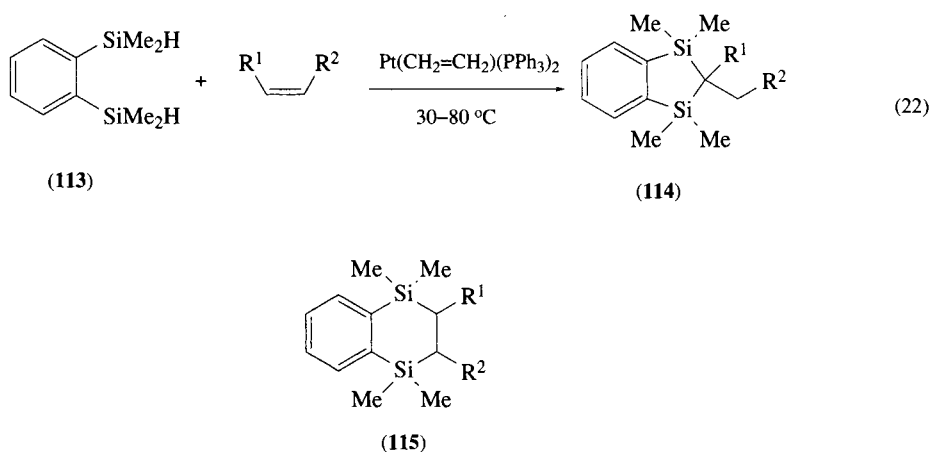
Isocyanide insertion into an Si—Si bond has been demonstrated by Weidenbruch and coworkers. Thus, the disilacyclobutene (**111**) reacted with arylisocyanides to form the iminodisilacyclopentanes (**112**) (Equation (21)). The structure of the *N*-phenyl derivative was confirmed by x-ray crystallography $\langle 93\text{JOM}(461)35 \rangle$. A similar insertion into an Ir—N or Ir—O bond also has been reported $\langle 88\text{JA}3704 \rangle$ (see Section 3.20.9.4).



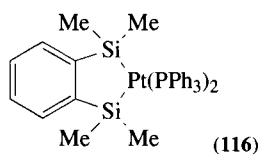
(v) Preparation via double silylation of unsaturated compounds

Alkenes undergo dehydrogenative 1,1- and/or 1,2-double silylation with *o*-bis(dimethylsilyl) benzene (**113**) in the presence of a catalytic amount of (ethylene)bis(triphenylphosphine) platinum

to afford benzo-1,3-disilacyclopentene derivatives and/or benzo-1,4-disilacyclohexenes (**114**) and (**115**), respectively (Equation (22)) <91OM16>. When the reaction of aliphatic alkenes is conducted at 30°C, simple hydrosilylation of one of the Si—H moieties occurs; however, the selectivity for 1,1-double silylation significantly increases when the reaction temperature is elevated to 80°C <92JOM(428)1>. The reaction proceeds best with styrene derivatives (presumably due to the electron-withdrawing effect of the aryl ring) but also works for ethene, simple alkenes, dienes, and α,β -unsaturated carbonyl compounds ($R^2 = \text{CO}_2\text{Me}$). When alkynes are employed, benzodisilacyclohexadienes are obtained as the major products along with only minor amounts of the benzocyclopentenenes <92BSF667>.



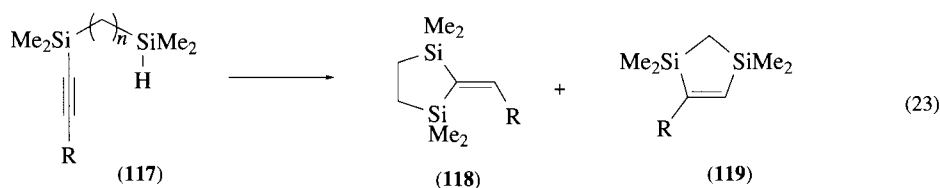
Since the reaction of styrene with *o*-bis(deuteriodimethylsilyl)benzene produced the expected disilacyclopentene with no deuterium incorporation, the mechanism of this reaction is believed to involve the intermediacy of the cyclic bis(silyl)platinum complex (**116**) first reported by Eaborn *et al.* <73JOM(63)107> from the reaction of (**113**) and the platinum catalyst. However, complex (**116**) itself did not react with styrene but when 1.1 equivalents of (**113**) was added, an 83% yield of (**114**; $R_1 = \text{H}$, $R_2 = \text{Ph}$) was obtained.



(vi) Preparation via intramolecular hydrosilylation

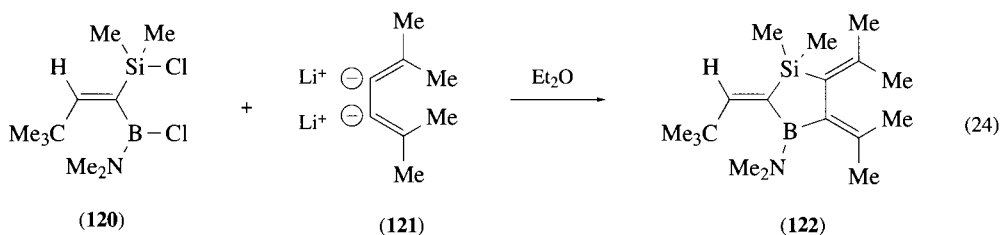
Disilacyclopentenenes possessing either an exocyclic or endocyclic double bond have been prepared by the intramolecular hydrosilylation of acetylenic disilanes, the mode of cyclization being dependent upon reaction conditions. For instance, when catalyzed by chloroplatinic acid in refluxing cyclohexane, intramolecular hydrosilylation of acetylenic disilanes such as (**117**; $R = \text{H}$ or Ph , $n = 2$) occurs to afford the cyclic products (**118**) having an exocyclic rather than endocyclic double bond in 42–58% yield (Equation (23)) <89JOM(378)1>. The strong preference for α -addition to the triple bond observed under these conditions is in contrast to the more typical β -regioselectivity observed in platinum-catalyzed hydrosilylations of acyclic alkynes or alkenes and may account for the fact that when $n = 1$ ($R = \text{H}$), only recovered starting material is obtained. Alternatively, photochemical hydrosilylation (185 nm) of (**117**; $R = \text{H}$, $n = 1$) produced a mixture of (**119**; $R = \text{H}$) and 2-methylene-1,1,3,3-tetramethyl-1,3-disilacyclobutene in absolute yields of 8% each (at 34% conversion), whereas

photolysis of (**117**, R = H, $n = 2$) gave maximum yields of 3% of (**118**, R = H) at 15% conversion <87CC759>.

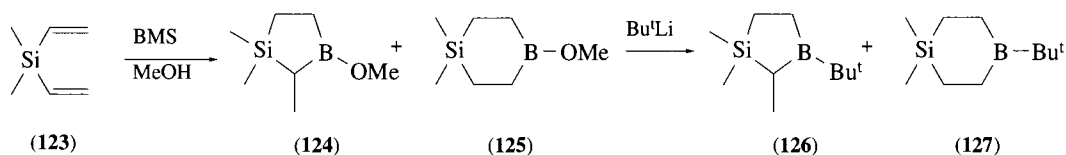


3.20.9.6.2 1-Sila-3-boracyclopentanes

Treatment of the dichloro species (**120**) with 3,4-dilithio-2,5-dimethyl-2,4-hexadiene (**121**) in diethyl ether afforded the 1-sila-3-boracyclopentane (**122**) in 41% yield (Equation (24)) <91ZN(B)1127>. This heterocycle could be distilled *in vacuo* and recrystallized from pentane at -20°C . The ¹H NMR spectrum of (**122**) exhibited two signals ($\delta = 0.43$ and 0.50) for the methyl groups (axial and equatorial) on silicon, indicating a non-planar ring (which was confirmed by an x-ray structure).

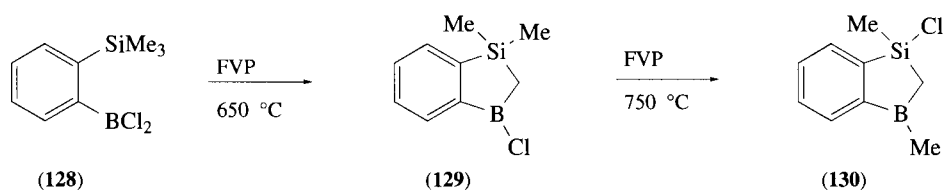


Hydroboration of divinylsilane (**123**) with borane-methyl sulfide complex (BMS), followed by methanolysis affords a 7 : 1 ratio of the silaborolane (**124**) and silaborinane (**125**) in 47% yield (Scheme 13) <84JOC2565>. Upon treatment with tert-butyllithium, the corresponding tert-butyl boracycles (**126**) and (**127**), respectively, were obtained in 60% yield.



Scheme 13

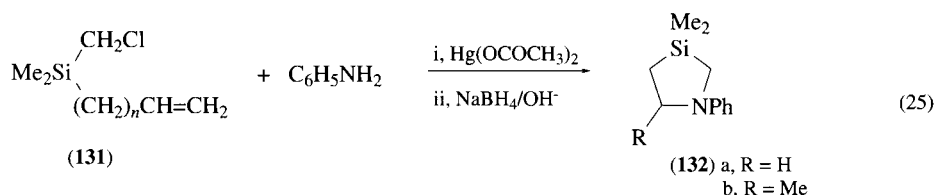
Flash vacuum pyrolysis (650°C) of (**128**) yielded the 1-sila-3-boraindane (**129**) <87JOM(331)139> which upon heating to 750°C underwent an intramolecular, mutual migration of a chloro and a methyl group to afford (**130**) (Scheme 14). A 1-sila-3-boraindane also resulted from pyrolysis (at 560°C) of PhB(=OMe)C(TMS)₃. The intermediacy of PhB=C(TMS)₂ was suggested <90CB747>.



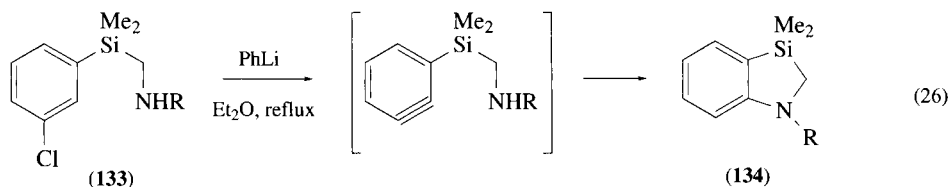
Scheme 14

3.20.9.6.3 1-Aza-3-silacyclopentanes

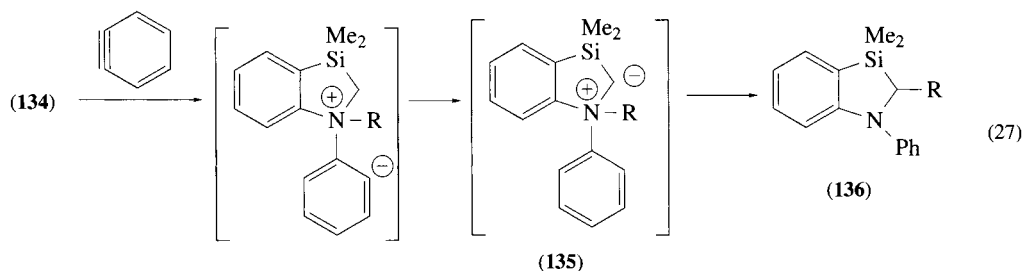
Azasilacyclopentanes are most conveniently prepared by the amidomercuration-demercuration of dimethyl(chloroalkyl)alkenylsilanes of the form (131) <87JOM(326)159, 85ZOB706>. Thus, treatment of dimethyl(chloromethyl)vinylsilane (131a, $n = 0$) or dimethyl(chloromethyl)allylsilane (131b, $n = 1$) with aniline in THF in the presence of mercury acetate, followed by reduction with sodium borohydride, afforded the azasilacyclopentanes (132a), (132b).



1-Substituted-3,3-dimethylbenzo[*d*]-1,3-azasilacyclopentanes (134; R = Me, Et, CH₂Ph) can be prepared in 40–62% yield by intramolecular cyclization of the corresponding (3-chlorophenyl)(*N*-substituted aminomethyl)dimethylsilanes (133) using phenyllithium in boiling ether (Equation (26)) <76JOM(118)1>.



Reaction of (134) with benzyne, generated from *o*-fluorobromobenzene and *n*-butyllithium, gave 1-phenyl-2-substituted-3,3-dimethylbenzo[*d*]-1,3-azasilacyclopentanes (136; R = Me, CH₂Ph) in 20–75% yield, via a Stevens rearrangement. If, however, the alkyl group on nitrogen possesses a β-hydrogen (e.g., Et), Hoffman elimination of the betaine intermediate (135) occurs to afford (136; R = H) (Equation (27)).

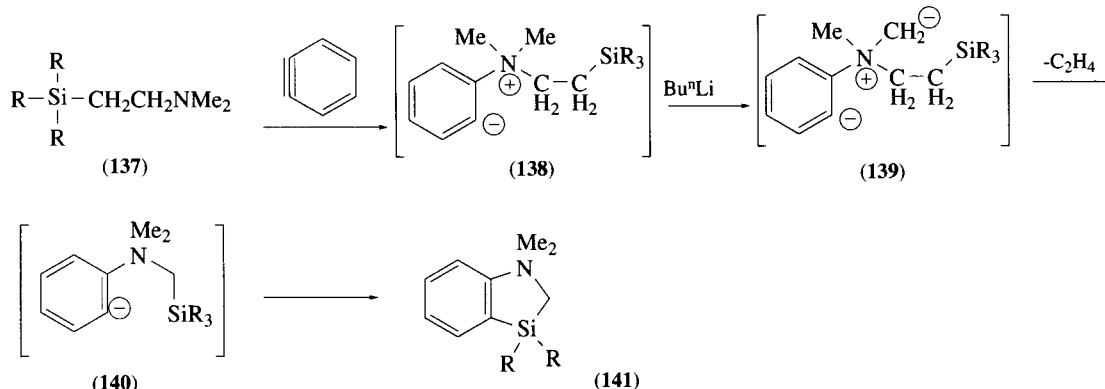


It has been found that benzo[*d*]-1,3-azasilolines (141) can be prepared by the intermolecular reaction of *N,N*-dimethyl-2-triorganosilyl ethylamines (137) with benzyne in the presence of excess *n*-butyllithium <76JOC1962>. It is postulated that deprotonation of the first betaine intermediate (138) with butyllithium affords the second intermediate (139) which undergoes silyl rearrangement with loss of ethylene. Cyclization of the resultant aromatic anion (140) onto silicon with concomitant loss of an R group then gives the heterocycle (141) (Scheme 15).

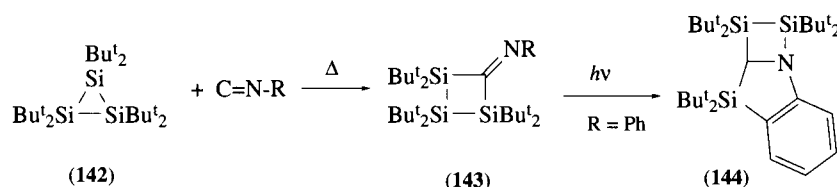
Treatment of hexa-*t*-butylcyclotrisilane (142) with several isocyanides bearing bulky substituents on the nitrogen atoms (e.g., R = Ph, 1-naphthyl) gives the ring-enlarged trisilacyclobutanamines (143), which upon photolysis undergo rearrangement to azasilacyclopentanes (144) (Scheme 16) <92JOM(441)185>. This rearrangement proceeds by formal extrusion and insertion of di-*tert*-butyl-silylene, followed by ring closure.

3.20.9.6.4 1-Oxa-3-silacyclopentanes

1-Oxa-3-silacyclopentanes can be prepared from divinyl ether (145) by a three-step process involving initial chloroplatinic-acid-catalyzed hydrosilylation with dimethyl- or diethylethoxysilane

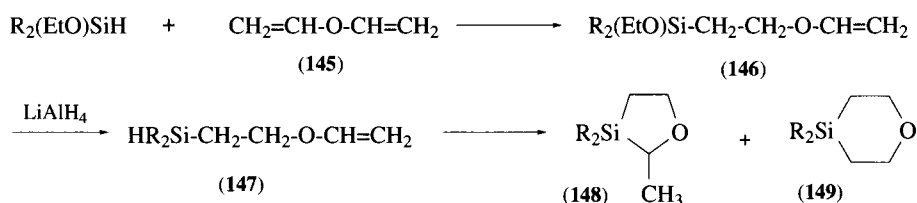


Scheme 15



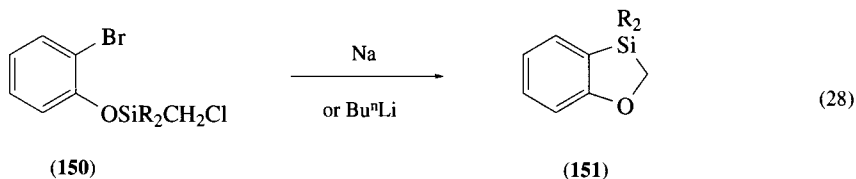
Scheme 16

to afford the mono-adduct (146) (Scheme 17). The regioselectively produced ethoxysilane is then reduced to the corresponding hydrosilane (147) using lithium aluminum hydride, and then resubjected to the platinum-catalyzed hydrosilation conditions to afford the five-membered ring heterocycle (148; R = Me, 45%) and, in the case of R = Et, some of the six-membered heterocycle (149) (50%, 2 : 1 mixture of (148) and (149)) <92JOM(427)289>



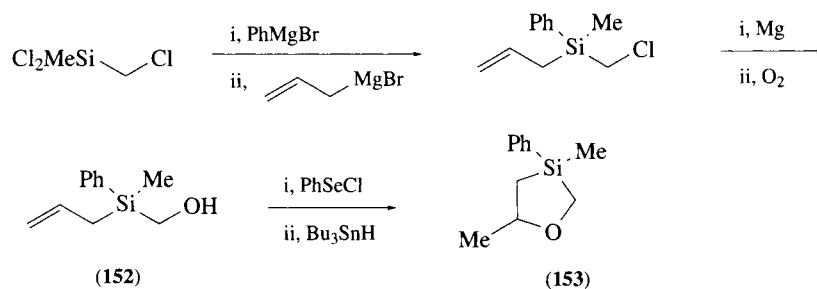
Scheme 17

2-Bromoaryloxy(chloromethyl)diorganosilanes (150) react with sodium or *n*-butyllithium via a metalation, [1,3]-carbanionic rearrangement, cyclization sequence to afford 1,3-benzoxasilolenes (151) in a one-pot-reaction (Equation (28)) <83JOM(243)1, 92PS25, 91EGP296280>.



A selenoetherification approach similar to the mercury-catalyzed cyclizations utilized for the preparation of aza silicon and germanium heterocycles has been reported. Thus, dichloromethyl-(chloromethyl)silane was treated with phenylmagnesium bromide followed by allylmagnesium bro-

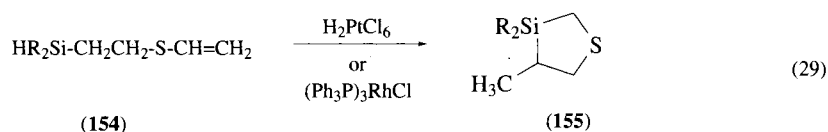
made to afford allyl(chloromethyl)methylphenylsilane in 69% yield. Subsequent reaction with magnesium and oxygen afforded the alcohol (**152**) (56% yield), which formed (**153**) by sequential exposure to phenylselenium chloride then tributyltin hydride (Scheme 18) <90JA1962>.



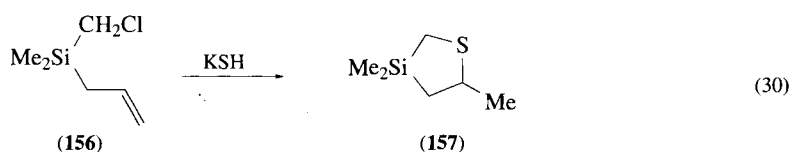
Scheme 18

3.20.9.6.5 1-Thia-3-silacyclopentanes

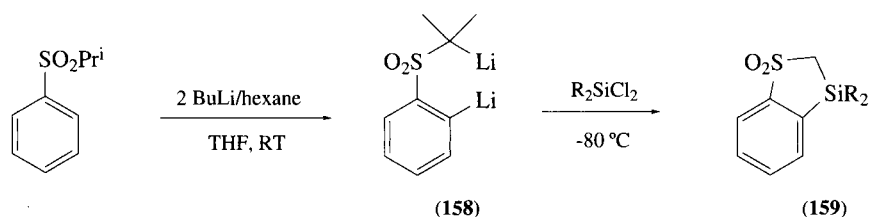
The most common routes to such species have been via intramolecular hydrosilylation of vinyl thioethers, studied extensively by Varonkov and coworkers <76IZV710, 81IZV174>. Thus, analogous to the preparation of their oxygen congeners (e.g., **148**), 1-thia-3-silacyclopentanes (**155**) have been synthesized by the intramolecular hydrosilylation of vinyl thioethers such as (**154**) (Equation (29)) <81JOM(204)13>. The dissociative ionization of such heterocycles has been studied by electron impact (EI) and photoionization (PI) mass spectrometric methods <85JOM(288)27>. Additionally, the UV spectra of these and related heterocycles were examined and their charge-transfer complexes with tetracyanoethylene were prepared <86ZOB2095>.



Alternatively, these heterocycles (e.g., **157**) can be prepared by the reaction of dimethyl-(chloromethyl)allylsilane (**156**) with alcoholic KSH (Equation (30)) <83JOM(243)271, 83ZOB2404>. A similar cyclization can be effected by the photoinduced addition of H_2S to the vinyl congener of (**156**) <82ZOB712>.



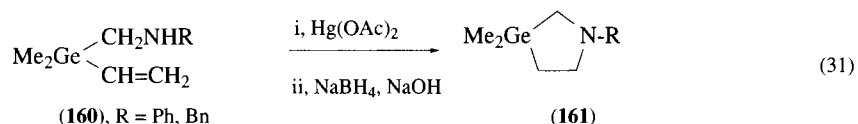
A variety of five-membered ring heterocycles containing the sulfonyl group can be prepared via dilithiation of (isopropylsulfonyl)benzene followed by reaction with gem-dihalo compounds. In this manner, the dilithio species (**158**) was prepared *in situ* and reacted with dichlorosilanes to afford the corresponding 1,3-benzothiasilole-1,1-dioxide derivatives (**159**) in 61–66% yield (Scheme 19) <93S41, 88H(27)1679>. An NMR study of the 2-lithio species obtained from the deoxy analogue of (**159**) <86TL4625> has been reported <93JA7041>.



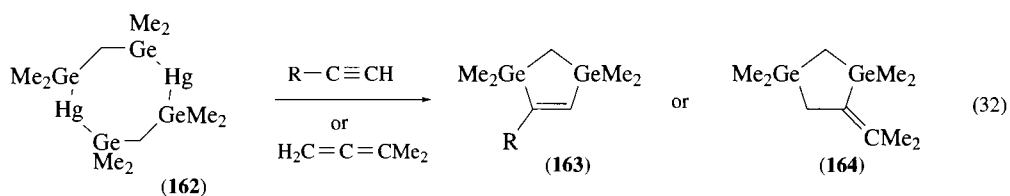
Scheme 19

3.20.9.7 Germanium-containing Heterocycles

Very little work has been done regarding germanium-containing heterocycles. The preparation of appropriate germacycles using methods similar to those for their silicon analogs has been included in the appropriate sections. In addition, azagermolidines (e.g., **161**) have been prepared (54–56% yield) by treatment of dimethyl(substituted aminomethyl)vinyl germanes (**160**) with mercuric acetate followed by sodium borohydride (Equation (31)) <88JOM(339)259>.



Of less apparent generality is the preparation of the digermolene and vinyl digermolane products (**163**) and (**164**) in 15–25% yield by treatment of (**162**) with acetylenes or dimethylallene, respectively (Equation (32)) <87OM659>.



References

EXPLANATION OF THE REFERENCE SYSTEM

Throughout this work, references are designated by a number–lettering coding of which the first two numbers denote tens and units of the year of publication, the next one to three letters denote the journal, and the final numbers denote the page. This code appears in the text each time a reference is quoted; the advantages of this system are outlined in the Introduction. The system has been used previously in the first edition of *Comprehensive Heterocyclic Chemistry*, eds A. R. Katritzky and C. W. Rees, Pergamon, Oxford, 1984 and is based on that used in the following two monographs: (a) A. R. Katritzky and J. M. Lagowski, “Chemistry of the Heterocyclic N-Oxides,” Academic Press, New York, 1971; (b) J. Elguero, C. Marzin, A. R. Katritzky and P. Linda, “The Tautomerism of Heterocycles,” in “Advances in Heterocyclic Chemistry,” Supplement 1, Academic Press, New York, 1976.

The following additional notes apply:

1. A list of journal codes in alphabetical order, together with the journals to which they refer, is given immediately following these notes. Journal names are abbreviated throughout using the CASSI (Chemical Abstracts Service Source Index) system.
2. Each volume contains all the references cited *in that volume*; no separate lists are given for individual chapters.
3. The list of references is arranged in order of (a) year, (b) journal in alphabetical order of journal code, (c) part letter or number if relevant, (d) volume number if relevant, (e) page number.
4. In the reference list the code is followed by (a) the complete literature citation in the conventional manner and (b) the number(s) of the page(s) on which the reference appears, whether in the text or in tables, schemes, etc.
5. For nontwentieth-century references the year is given in full in the code.
6. For journals which are published in separate parts, the part letter or number is given (when necessary) in parentheses immediately after the journal code letters.
7. Journal volume numbers are *not* included in the code numbers unless more than one volume was published in the year in question, in which case the volume number is included in parentheses immediately after the journal code letters.
8. Patents are assigned appropriate three-letter codes.
9. Frequently cited books are assigned codes.
10. Less common journals and books are given the code “MI” for miscellaneous with the whole code for books prefixed by the letter “B-”.
11. Where journals have changed names, the same code is used throughout, e.g. CB refers to both *Chem. Ber.* and to *Ber. Dtsch. Chem. Ges.*

Journal Codes

AAC	Antimicrob. Agents Chemother.
ABC	Agric. Biol. Chem.
AC	Appl. Catal.
AC(P)	Ann. Chim. (Paris)
AC(R)	Ann. Chim. (Rome)
ACH	Acta Chim. Acad. Sci. Hung.

ACR	Acc. Chem. Res.
ACS	Acta Chem. Scand.
ACS(A)	Acta Chem. Scand., Ser. A
ACS(B)	Acta Chem. Scand., Ser. B
AF	Arzneim.-Forsch.
AFC	Adv. Fluorine Chem.
AG	Angew. Chem.
AG(E)	Angew. Chem., Int. Ed. Engl.
AHC	Adv. Heterocycl. Chem.
AHCS	Adv. Heterocycl. Chem. Supplement
AI	Anal. Instrum.
AJC	Aust. J. Chem.
AK	Ark. Kemi
AKZ	Arm. Khim. Zh.
AM	Adv. Mater. (Weinheim, Ger.)
AMLS	Adv. Mol. Spectrosc.
AMS	Adv. Mass. Spectrom.
ANC	Anal. Chem.
ANL	Accad. Naz. Lincei
ANY	Ann. N. Y. Acad. Sci.
AOC	Adv. Organomet. Chem.
AP	Arch. Pharm. (Weinheim, Ger.)
APO	Adv. Phys. Org. Chem.
AQ	An. Quim.
AR	Annu. Rep. Prog. Chem.
AR(A)	Annu. Rep. Prog. Chem., Sect. A
AR(B)	Annu. Rep. Prog. Chem., Sect. B
ARP	Annu. Rev. Phys. Chem.
ASI	Acta Chim. Sin. Engl. Ed.
ASIN	Acta Chim. Sin.
AX	Acta Crystallogr.
AX(A)	Acta Crystallogr., Part A
AX(B)	Acta Crystallogr., Part B
B	Biochemistry
BAP	Bull. Acad. Pol. Sci., Ser. Sci. Chim.
BAU	Bull. Acad. Sci. USSR, Div. Chim. Sci.
BBA	Biochim. Biophys. Acta
BBR	Biochim. Biophys. Res. Commun.
BCJ	Bull. Chem. Soc. Jpn.
BEP	Belg. Pat.
BJ	Biochem. J.
BJP	Br. J. Pharmacol.
BMC	Bioorg. Med. Chem. Lett.
BP	Biochem. Biopharmacol.
BPJ	Br. Polym. J.
BRP	Br. Pat.
BSB	Bull. Soc. Chim. Belg.
BSF	Bull. Soc. Chim. Fr.
BSF(2)	Bull. Soc. Chim. Fr., Part 2
C	Chimia
CA	Chem. Abstr.
CAN	Cancer
CAR	Carbohydr. Res.
CAT	Chim. Acta Turc.
CB	Chem. Ber.

CBR	Chem. Br.
CC	J. Chem. Soc., Chem. Commun.
CCA	Croat. Chem. Acta
CCC	Collect. Czech. Chem. Commun.
CCR	Coord. Chem. Rev.
CE	Chem. Express
CEN	Chem. Eng. News
CHE	Chem. Heterocycl. Compd. (Engl. Transl.)
CHEC-I	Comp. Heterocycl. Chem., 1st edn.
CI(L)	Chem. Ind. (London)
CI(M)	Chem. Ind. (Milan)
CJC	Can. J. Chem.
CJS	Can. J. Spectrosc.
CL	Chem. Lett.
CLY	Chem. Listy
CM	Chem. Mater.
CMC	Comp. Med. Chem.
COC	Comp. Org. Chem.
COMC-I	Comp. Organomet. Chem., 1st edn.
COS	Comp. Org. Synth.
CP	Can. Pat.
CPB	Chem. Pharm. Bull.
CPH	Chem. Phys.
CPL	Chem. Phys. Lett.
CR	C. R. Hebd. Seances Acad. Sci.
CR(A)	C. R. Hebd. Seances Acad. Sci., Ser. A
CR(B)	C. R. Hebd. Seances Acad. Sci., Ser. B
CR(C)	C. R. Hebd. Seances Acad. Sci., Ser. C
CRAC	Crit. Rev. Anal. Chem.
CRV	Chem. Rev.
CS	Chem. Scr.
CSC	Cryst. Struct. Commun.
CSR	Chem. Soc. Rev.
CT	Chem. Tech.
CZ	Chem.-Ztg.
CZP	Czech. Pat.
DIS	Diss. Abstr.
DIS(B)	Diss. Abstr. Int. B.
DOK	Dokl. Akad. Nauk SSSR
DP	Dyes Pigm.
E	Experientia
EC	Educ. Chem.
EF	Energy Fuels
EGP	Ger. (East) Pat.
EJM	Eur. J. Med. Chem.
EUP	Eur. Pat.
FCF	Forstchr. Chem. Forsch.
FCR	Fluorine Chem. Rev.
FES	Farmaco Ed. Sci.
FOR	Fortschr. Chem. Org. Naturst.
FRP	Fr. Pat.
G	Gazz. Chim. Ital.
GAK	Gummi Asbest Kunstst.
GEP	Ger. Pat.
GEP(O)	Ger. Pat. Offen.

GSM	Gen. Synth. Methods
H	Heterocycles
HAC	Heteroatom Chem.
HC	Chem. Heterocycl. Compd.
HCA	Helv. Chim. Acta
HOU	Methoden Org. Chem. (Houben-Weyl)
HP	Hydrocarbon Process
IC	Inorg. Chem.
ICA	Inorg. Chim. Acta
IEC	Ind. Eng. Chem. Res.
IJ	Isr. J. Chem.
IJC	Indian J. Chem.
IJC(A)	Indian J. Chem., Sect. A
IJC(B)	Indian J. Chem., Sect. B
IJM	Int. J. Mass Spectrom. Ion Phys.
IJQ	Int. J. Quantum Chem.
IJS	Int. J. Sulfur Chem.
IJS(A)	Int. J. Sulfur Chem., Part A
IJS(B)	Int. J. Sulfur Chem., Part B
IS	Inorg. Synth.
IZV	Izv. Akad. Nauk SSSR, Ser. Khim.
JA	J. Am. Chem. Soc.
JAN	J. Antibiot.
JAP	Jpn. Pat.
JAP(K)	Jpn. Kokai
JBC	J. Biol. Chem.
JC	J. Chromatogr.
JCC	J. Coord. Chem.
JCE	J. Chem. Ed.
JCED	J. Chem. Eng. Data
JCI	J. Chem. Inf. Comput. Sci.
JCP	J. Chem. Phys.
JCPB	J. Chim. Phys. Physico-Chim. Biol.
JCR(M)	J. Chem. Res. (M)
JCR(S)	J. Chem. Res. (S)
JCS	J. Chem. Soc.
JCS(A)	J. Chem. Soc. (A)
JCS(B)	J. Chem. Soc. (B)
JCS(C)	J. Chem. Soc. (C)
JCS(D)	J. Chem. Soc., Dalton Trans.
JCS(F1)	J. Chem. Soc., Faraday Trans. 1
JCS(F2)	J. Chem. Soc., Faraday Trans. 2
JCS(P1)	J. Chem. Soc., Perkin Trans. 1
JCS(P2)	J. Chem. Soc., Perkin Trans. 2
JCS(S2)	J. Chem. Soc. (Suppl. 2)
JEC	J. Electroanal. Chem. Interfacial Electrochem.
JEM	J. Energ. Mater.
JES	J. Electron. Spectrosc.
JFA	J. Sci. Food. Agri.
JFC	J. Fluorine Chem.
JGU	J. Gen. Chem. USSR (Engl. Transl.)
JHC	J. Heterocycl. Chem.
JIC	J. Indian Chem. Soc.
JINC	J. Inorg. Nucl. Chem.
JLC	J. Liq. Chromatogr.

JMAS	J. Mat. Sci.
JMC	J. Med. Chem.
JMOC	J. Mol. Catal.
JMR	J. Magn. Reson.
JMS	J. Mol. Sci.
JOC	J. Org. Chem.
JOM	J. Organomet. Chem.
JOU	J. Org. Chem. USSR (Engl. Transl.)
JPC	J. Phys. Chem.
JPJ	J. Pharm. Soc. Jpn.
JPO	J. Phys. Org. Chem.
JPP	J. Pharm. Pharmacol.
JPR	J. Prakt. Chem.
JPS	J. Pharm. Sci.
JPS(A)	J. Polym. Sci., Polym. Chem., Part A
JPU	J. Phys. Chem. USSR (Engl. Transl.)
JSC	J. Serbochem. Soc.
JSP	J. Mol. Spectrosc.
JST	J. Mol. Struct.
K	Kristallografiya
KFZ	Khim. Farm. Zh.
KGS	Khim. Geterotsikl. Soedin.
KO	Kirk-Othmer Encyc.
KPS	Khim. Prir. Soedin.
L	Langmuir
LA	Liebigs Ann. Chem.
LC	Liq. Cryst.
LS	Life Sci.
M	Monatsh. Chem.
MAC	Macromol. Chem.
MC	Mendeleev Chem. J. (Engl. Transl.)
MCLC	Mol. Cryst. Liq. Cryst.
MI	Miscellaneous [book/journal]
MIP	Miscellaneous Pat.
MM	Macromolecules
MP	Mol. Phys.
MRC	Magn. Reson. Chem.
N	Naturwissenschaften
NAT	Nature
NEP	Neth. Pat.
NJC	Nouv. J. Chim.
NKK	Nippon Kagaku Kaishi (J. Chem. Soc. Jpn.)
NKZ	Nippon Kagaku Zasshi
NZJ	N. Z. J. Sci. Technol.
OCS	Organomet. Synth.
OM	Organometallics
OMR	Org. Magn. Reson.
OMS	Org. Mass Spectrom.
OPP	Org. Prep. Proced. Int.
OR	Org. React.
OS	Org. Synth.
OSC	Org. Synth., Coll. Vol.
P	Phytochemistry
PA	Polym. Age
PAC	Pure Appl. Chem.

PAS	Pol. Acad. Sci.
PB	Polym. Bull.
PC	Personal Communication
PCS	Proc. Chem. Soc.
PHA	Pharmazi
PHC	Prog. Heterocycl. Chem.
PIA	Proc. Indian Acad. Sci.
PIA(A)	Proc. Indian Acad. Sci., Sect. A
PJC	Pol. J. Chem.
PJS	Pak. J. Sci. Ind. Res.
PMH	Phys. Methods Heterocycl. Chem.
PNA	Proc. Natl. Acad. Sci. USA
POL	Polyhedron
PP	Polym. Prepr.
PRS	Proceed. Roy. Soc.
PS	Phosphorus Sulfur
QR	Q. Rev., Chem. Soc.
QRS	Quart. Rep. Sulfur. Chem.
QSAR	Quant. Struct. Act. Relat. Pharmacol. Chem. Biol.
RC	Rubber Chem. Technol.
RCM	Rapid Commun. Mass Spectrom.
RCP	Rec. Chem. Prog.
RCR	Russ. Chem. Rev. (Engl. Transl.)
RHA	Rev. Heteroatom Chem.
RJ	Rubber J.
RP	Rev. Polarogr.
RRC	Rev. Roum. Chim.
RS	Ric. Sci.
RTC	Recl. Trav. Chim. Pays-Bas
RZC	Rocz. Chem.
S	Synthesis
SA	Spectrochim. Acta
SA(A)	Spectrochim. Acta, Part A
SAP	S. Afr. Pat.
SC	Synth. Commun.
SCI	Science
SL	Synlett
SM	Synth. Met.
SR	Sulfur Reports
SRI	Synth. React. Inorg. Metal-Org. Chem.
SS	Sch. Sci. Rev.
SST	Org. Compd. Sulphur, Selenium, Tellurium [R. Soc. Chem. series]
SUL	Sulfur Letters
SZP	Swiss Pat.
T	Tetrahedron
T(S)	Tetrahedron, Suppl.
TA	Tetrahedron Asymmetry
TAL	Talanta
TCA	Theor. Chim. Acta
TCC	Top. Curr. Chem.
TCM	Tetrahedron, Comp. Method.
TFS	Trans. Faraday Soc.
TH	Thesis
TL	Tetrahedron Lett.
TS	Top. Stereochem.

UK	Usp. Khim.
UKZ	Ukr. Khim. Zh. (Russ. Ed.)
UP	Unpublished Results
URP	USSR Pat.
USP	US Pat.
WCH	Wiadom. Chem.
YGK	Yuki Gosei Kagaku Kyokaishi
YZ	Yakugaku Zasshi (J. Pharm. Soc. Jpn.)
ZAAC	Z. Anorg. Allg. Chem.
ZAK	Zh. Anal. Khim.
ZC	Z. Chem.
ZN	Z. Naturforsch.
ZN(A)	Z. Naturforsch., Teil A
ZN(B)	Z. Naturforsch., Teil B
ZOB	Zh. Obshch. Khim.
ZOR	Zh. Org. Khim.
ZPC	Hoppe-Seyler's Z. Physiol. Chem.
ZPK	Zh. Prikl. Khim.

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