

6.01

1,2-Oxa/thia-3-azoles

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6.01.1	Introduction	2
6.01.2	Theoretical Methods	2
6.01.3	Experimental Structural Methods	4
6.01.3.1	X-Ray Diffraction	4
6.01.3.2	¹ H NMR Spectroscopy	6
6.01.3.3	¹³ C NMR Spectroscopy	7
6.01.3.4	UV Spectroscopy	8
6.01.3.5	ESR Spectroscopy	9
6.01.3.6	Cyclic Voltammetry	9
6.01.3.7	IR Spectroscopy	10
6.01.3.8	Mass Spectrometry	10
6.01.4	Thermodynamic Aspects	11
6.01.5	Reactivity of Fully Conjugated Rings	11
6.01.5.1	Unimolecular Thermal Reactions	11
6.01.5.2	Electrophilic Attack at Ring Atoms	12
6.01.5.3	Nucleophilic Attack at Ring Sulfur	12
6.01.5.4	Nucleophilic Attack at Ring Carbon	14
6.01.5.5	Reactions Involving Radicals, Electron-Deficient Species, Reducing Agents, and at Surfaces	19
6.01.6	Reactivity of Nonconjugated Rings	20
6.01.6.1	Reactions of Hydrogenated Derivatives of 1,2,3-Oxathiazole S-Oxides	20
6.01.7	Reactivity of Substituents Attached to Ring Carbon Atoms	22
6.01.8	Reactivity of Substituents Attached to Ring Heteroatoms	24
6.01.9	Ring Syntheses from Acyclic Compounds Classified by Number of Ring Atoms Contributed by Each Component	25
6.01.9.1	Formation of One Bond Adjacent to a Heteroatom	25
6.01.9.2	Formation of Two Bonds: Four-Atom Fragment and Sulfur	26
6.01.9.3	Formation of Two Bonds: [3+2] Atom Fragment by Cycloaddition	27
6.01.9.4	Formation of Two Bonds: [3+2] Atom Fragment by Other Processes	28
6.01.10	Ring Syntheses by Transformation of Another Ring	30
6.01.11	Synthesis of Particular Classes of Compounds and Critical Comparison of the Various Routes Available	31
6.01.12	Important Compounds and Application	31
6.01.13	Further Developments	33
	References	33

6.01.1 Introduction

In this chapter, the chemistry of 1,2,3-dithiazoles and 1,2,3-oxathiazoles is covered for the period from 1996 to 2005 inclusive. 1,2,5-Oxathiazoles have not been investigated during this period.

The synthesis, theoretical and extensive spectral study of new families of neutral heterocyclic 1,2,3-dithiazolyl radicals have been described by the Oakley group, and these compounds have been proposed as conductive molecular materials. A new application of Burgess reagent (methoxycarbonylsulfamoyltetraethylammonium hydroxide, inner salt) in the synthesis of enantiopure 1,2,3-oxathiazole di-*S*-oxides has been realized by Nicolaou and co-authors in the years reviewed. An abundance of new chemistry has been revealed for 4-chloro-1,2,3-dithiazolo-5-imines, 5-one, 5-thione, and 5-ylidenes easily obtained from Appel salt (4,5-dichloro-1,2,3-dithiazolium chloride). The reactions of cyclic sulfamidates giving enantiopure aminoacids, β -aminoalcohols, and sugars with functional groups have been intensively investigated.

1,2,3-Dithiazoles investigated are given in **Figure 1(a)**: these are 1,2,3-dithiazolium cations **1**, 1,2,3-dithiazolyl radicals **2**, 1,2,3-dithiazole-3-ones **3** and related compounds **4**, their 2-oxides **5**. 1,2,3-Oxathiazoles have been obtained and investigated in the form of their *S*-oxides (**Figure 1(b)**) and named as cyclic sulfamidates **7** and **8** and sulfimidates **6**, **9**, and **10**.

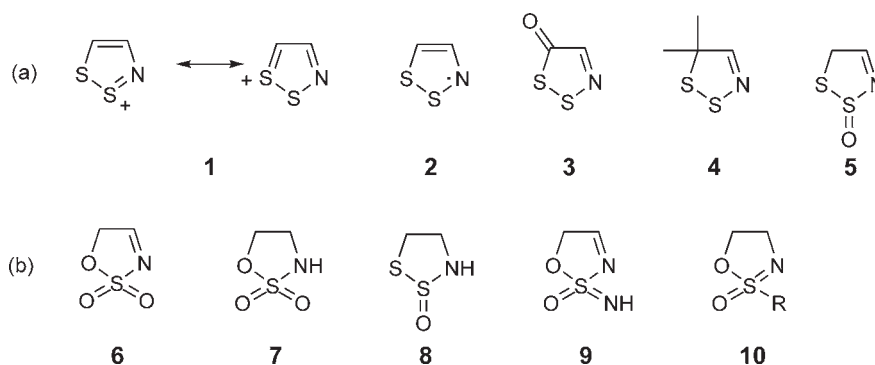
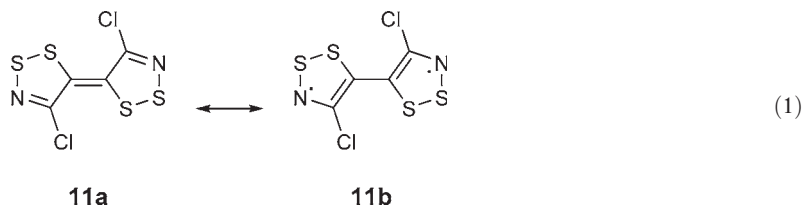


Figure 1 Known 1,2-Oxa/thia-3-azoles.

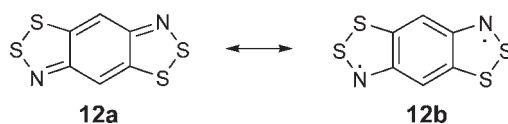
6.01.2 Theoretical Methods

Charge distribution and π -bond orders in condensed 1,2,3-dithiazoles was the main subject for calculation in the 1980s <1996CHEC-II(4)409>. Heteropentalenes containing 1,2,3-dithiazole and 1,2,3-oxathiazole moiety were also of significant interest.

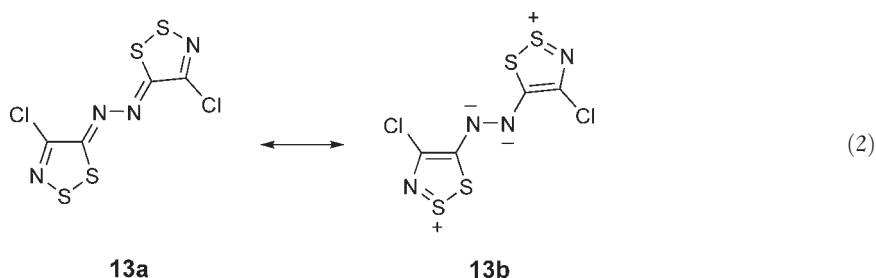
A series of density functional theory (DFT) calculations at the B3LYP/6-31G** level on the novel tetrathiadiazafulvalene **11** has shown that these molecules exhibit closed shell **11a** rather than biradical **11b** ground states, as a result of strong interannular interaction across the bridgehead C-C bond (Equation 1) <1999JA6657>.



Electron correlation calculations using the DFT method on the benzo-bis(1,2,3-dithiazole) **12** have been performed. The asymmetry of the pairwise combination of two singly occupied molecular orbitals (SOMOs) leads, upon mixing with benzene, to a much greater splitting of the two frontier orbitals a_u and b_g , and a quinoid singlet ground state **12a**. The diradical singlet **12b** is predicted to lie 0.72 eV above the singlet ground state of **12a** <1997JA12136>.

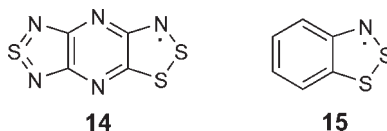


Calculation of the frontier molecular orbital (FMO) interaction showed that the effect of the high electronegativity of the N–N bridge on the electronic distribution in bis(1,2,3-dithiazole) **13** is of particular importance; it stabilizes the singlet state relative to the diradical triplet by lowering of highest occupied molecular orbital (HOMO) and polarizes the two occupied π -levels onto the azine bridge. From the charge distribution, it is apparent that a diazine-bridged bis(1,2,3-dithiazole) is best described using covalent formula **13a** rather than by means of polar structure **13b** (Equation 2) <2001IC2709>.

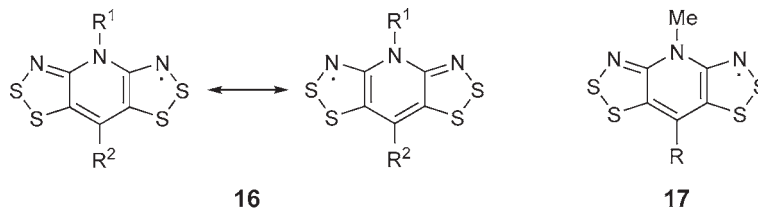


Dispersion of the valence and conduction bands in the bis(1,2,3-dithiazolyl) radical **14** has been determined by extended Hückel band structure calculations which suggest that the band gap (ca. 0.4 eV) has a value which is considerably smaller than that found in other radical dimer structures and arises from the weakness of the intradimer interaction <1999JA969>.

The distribution of the total spin density in radicals **14** and **15** was calculated with UB3LYP/6-31G* methods <2001PCA7615>. A significant spin delocalization was found in the benzoannulated 1,2,3-dithiazolyl derivative **15**. In addition to polar resonance forms, there are also nonpolar allylic-type resonance forms allowing for spin delocalization onto the adjacent benzene ring. The disproportionation energies for radicals **14** and **15**, calculated by the same method, were compared with the available conductivity data for radicals showing a qualitative correlation. Low disproportionation energies and hence high conductivity were obtained for large π -systems, such as dithiazole **14** containing an –N–S–S– array of heteroatoms <2001PCA7626>.



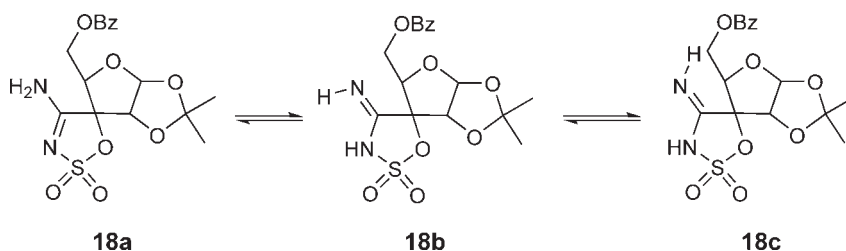
A series of extended Hückel theory (EHT) band calculations on crystal structures **16** and **17** have been performed <2003JA14394, 2004CM1564>. They show that the dispersion curves plotted along the stacking direction arise from the SOMOs of the radicals in the cell unit, that is, the putative half-filled conduction band of the molecular metal. Clearly, none of the materials are metallic, but the dispersion curves nonetheless provide insight into the extent of the intermolecular interaction along and perpendicular to the slipped π -stacks.



- a: $R^1 = \text{Me}$; $R^2 = \text{Cl}$
 b: $R^1 = \text{Et}$; $R^2 = \text{Cl}$
 c: $R^1 = \text{Pr}$; $R^2 = \text{Cl}$
 d: $R^1 = \text{Me}$; $R^2 = \text{H}$
 e: $R^1 = \text{Et}$; $R^2 = \text{H}$
 f: $R^1 = \text{Pr}$; $R^2 = \text{H}$

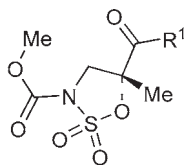
- a: $R = \text{Me}$
 b: $R = \text{Ph}$

To explain the reactivity observed in the methylation of spiro sugar **18**, an *ab initio* theoretical study using the UB3LYP/6-31G* basis set was carried out <1999T12187>. The total electronic energy values show that amine **18a** is energetically the most stable tautomer (Scheme 1). The geometry calculations showed that the nitrogen of the amino group is in the same plane as the spiro oxathiazolidine ring. The electronic density values on the nitrogen of amine **18a** and imines **18b** and **18c** are high; consequently, these compounds should be good nucleophiles. According to the electronic parameters for the amine **18a**, the highest value of electronic density is located on the *endo*-nitrogen whereas for the imines **18b** and **18c** the highest electronic density is located on the *exo*-nitrogen. Thus, in a charge-controlled reaction, the methylation of amine **18a** would take place of the *endo*-nitrogen and on the *exo*-nitrogen in the imine **18b** and **18c**. These calculations are in agreement with the experimental results of the methylation of compound **18**. The *ab initio* calculations were carried out on simplified structure **18** without taking into consideration the rest of the sugar structure of these molecules.



Scheme 1

A theoretical study was carried out to shed light on the different reactivities of sulfamides **19a** and **19b** with fluoride anion in S_N2 and E2 reactions <2004CC980>. All ground state and transition state (TS) geometries were located using hybrid density functional theory (B3LYP). For sulfamide **19a**, the TS obtained for the E2 reaction was slightly lower in energy ($0.60 \text{ kcal mol}^{-1}$) than that resulting from the nucleophilic attack of the fluoride anion. In contrast, with sulfamide **19b**, the difference in energy between TS in E2 and TS in S_N2 is considerably higher with the S_N2 route being favored by ca. 2 kcal mol^{-1} . This situation is in qualitative agreement with the chemoselectivity experimentally observed.



19a: $R^1 = \text{N(OMe)Me}$
19b: $R^1 = \text{OMe}$

6.01.3 Experimental Structural Methods

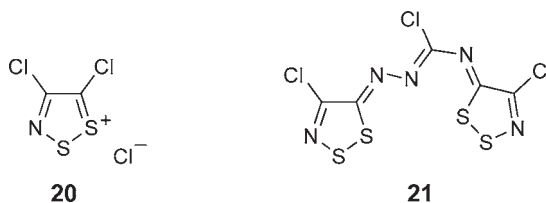
2,5-Diaza-1,6-dioxa-6a-thiapentalene has been extensively studied by various diffraction methods: X-ray, neutron and electron spectroscopy <1996CHEC-II(4)409>. There has been substantial progress in the spectral investigation of disubstituted 1,2,3-oxathiazolidine 2-oxides. Infrared (IR) and mass spectra were less employed for dithiazoles and oxathiazoles than other methods.

6.01.3.1 X-Ray Diffraction

The X-ray analysis of 4,5-dichloro-1,2,3-dithiazolium chloride **20**, often referred to as the Appel salt, reveals a pattern of bonding within the dithiazole ring that indicates delocalization that extends around the ring from one sulfur atom

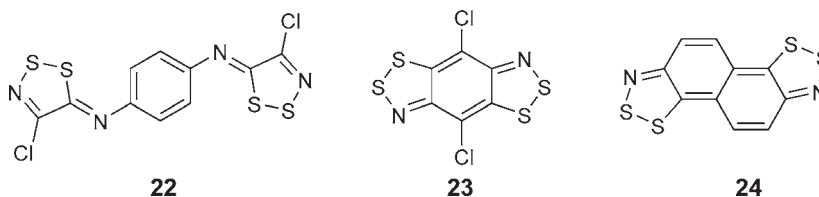
to the other, and indeed there is also evidence for a shortening of the S–S bond length (2.034(2) Å) compared with that normally associated with the S–S single bond <2002J(P1)1535>. The distance seen here is only marginally longer than that reported for the corresponding separation (2.023 Å) in a fully delocalized dithiole ring. In the Appel salt **20**, there is a short triangular and almost in-plane approach of the chloride anion to the sulfur centers of the dithiazole ring. In addition, in salt **20**, there is also a near-linear side-on approach of the chloride anion to the S–S bond: the chloride ion is also positioned over the center of the dithiazole ring of an adjacent molecule at a distance compatible with an electrostatic interaction.

A single crystal structure analysis shows bis(1,2,3-dithiazole) **21** to have a planar structure, all of the atoms being required to lie within a crystallographic mirror plane <2002J(P1)1535>. The two dithiazole rings have essentially identical geometries, but a pattern of bonding that differs markedly from that seen in salt **20**. Here with the exception of the C=N linkages which have pronounced double bond character, all the bonds are noticeably lengthened compared to their values in salt **20**, and are more consistent with conventional single bonds.



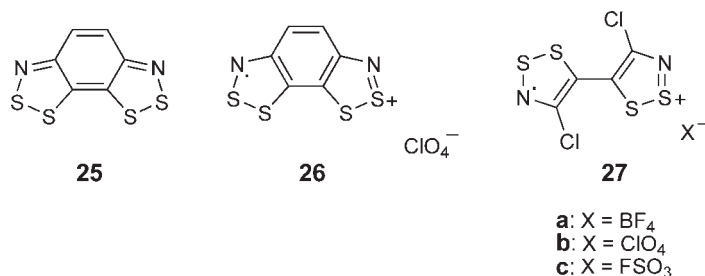
The crystal and molecular structures of bis(1,2,3-dithiazoles) **13** and **22** have been determined by single-crystal X-ray diffraction <2001IC2709>. Molecules of dithiazole **13** lie on a crystallographic center of inversion and are planar to within 0.03 Å. The intramolecular bond lengths of compound **13** are similar to those seen in bis(dithiazole) **11** (see below) and, along with the long N–N bond, are consistent with the azine resonance structure. Molecules of benzene-bis(dithiazole) **22** are also crystallographically centrosymmetric but are far from planar. To avoid potential steric congestion between S-1 and the C-3 proton, the 1,2,3-dithiazole ring (which is planar to within 0.07 Å) is rotated about the N(1)–C(4) bond to form a dihedral angle of 137.30(7)° with the plane of the benzene ring. As a result of this torsional motion, conjugation with the benzene bridge is restricted. The packing of molecules in bis(dithiazole) **22** consists of a more conventional slipped stack structure along χ , with the registry of adjacent stacks being somewhat ruffled by the twist in the phenylene bridge.

The molecules of condensed bis(1,2,3-dithiazoles) **23** and **24** lie on crystallographic inversion centers and are essentially planar to within 0.02 Å <1997JA12136>. These molecules adopt slipped π -stack structure; adjacent molecules approach one another in a side-on manner.

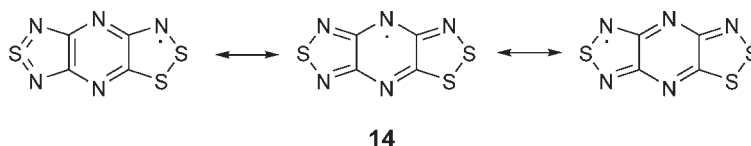


Simple ionic packing arrangement of radical cation **26** (that is, alternating cations and anions) affords few interannular cation/cation contacts; the shortest intermolecular S $\cdots$ S approach (3.740 Å) is well outside the van der Waals distance (3.6 Å) for two sulfurs <1999CM164>. A comparison of the intramolecular distance in neutral bis(dithiazole) **25** and its radical cation **26** reveals the expected differences; that is, the S–S, S–N, and S–C bonds are shortened, and the N–C bonds are lengthened by one-electron oxidation.

trans-Dichlorotetrathiadiazafulvalene **11** and its radical-cation salts **27** were investigated by X-ray crystallography. For compounds **11**, the intramolecular S–S, S–N, and S–C distances are all slightly longer than those observed in 1,2,3-dithiazolium salts <1998CC1039>, and this is in the agreement with values predicted by *ab initio* calculations <1999JA6657>. The crystal structures of radical cations **27** are interspersed with the corresponding anions. Molecules in adjacent layers are linked, up and down, by intermolecular S2 $\cdots$ S3' and S2 $\cdots$ S4' contacts, which again are near the van der Waals limit.



The radicals **14**, which are planar to within 0.07 Å, are loosely associated into centrosymmetric or head-to-tail dimers with the closest intradimer S··S contact being 3.233 Å. Interannular orbital interactions at this range are weak but sufficient to quench paramagnetism, that is, to generate a weak ‘chemical bond’ between two radicals. Within the individual halves of the dimer, the bond lengths show changes that reflect the long-range nature of the electron delocalization in the radical. The shortening of the N(1)–C(2) bond heralds considerable double bond character. This change, coupled with the shortening of N(2)–C(3) and N(5)–C(4), and the lengthening of N(2)–C(2), suggests the collective involvement of the series of valence bond resonance structures **14** shown in [Scheme 2](#) <1999JA969>.

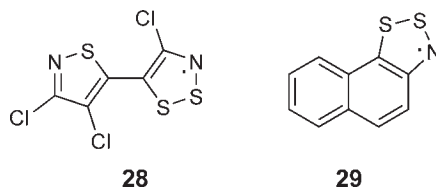


Scheme 2

The crystals of dithiazolyl radical **28** consist of planar (to within 0.03 Å) undimerized radicals aligned in a slipped π -stack arrangement running parallel to the χ -axis <2002CC1872>. There are no S··S intermolecular interactions between the radicals that are inside the normal van der Waals contact of 3.6 Å. The closest S··S interactions outside this range are the head-to-head contact (3.843 Å), the head-to-tail contact (3.626 Å), and the π -stacking contact (3.707 Å).

Crystals of compound **16** consist of slipped π -stacks of undimerized radicals running parallel to Z (**b**: R¹ = Et, Pr; R² = Cl) and χ (**a**: R¹ = Me; R² = Cl) <2002JA9498>. As such, they represent the first example of undimerized 1,2,3-dithiazolyl radicals. In all examples, there are numerous close intermolecular S··S contacts between neighboring dithiazole rings. Most of these contacts are inside the van der Waals contact for sulfur (3.6 Å), and some of those in structure **16a** are among the shortest nonbonded S··S contacts that have been observed in undimerized heterocyclic sulfur–nitrogen radicals.

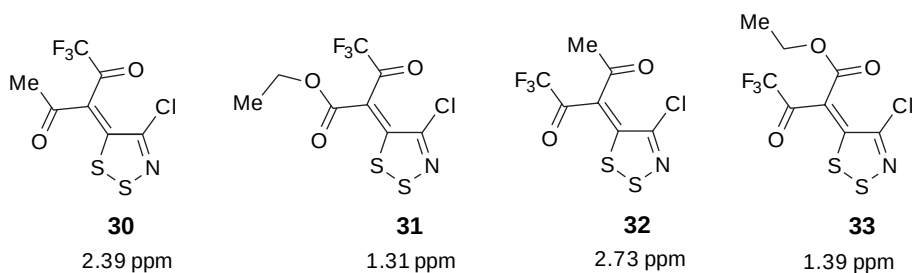
The crystals of radical **29**, which are diamagnetic by electron spin resonance (ESR), consist of cofacial dimers with four dimers per unit cell linked by two long, albeit unequal (3.053 and 3.309 Å), interannular S–S bond <2005IC1837>. This mode of association has not hitherto been observed for 1,2,3-dithiazolyls. Dimers of radical **29** do not form π -stacked arrays; instead, they adopt the closed packed herringbone arrangement which allows for a clustering of the radical heads so as to maximize S··S and S··N contacts.



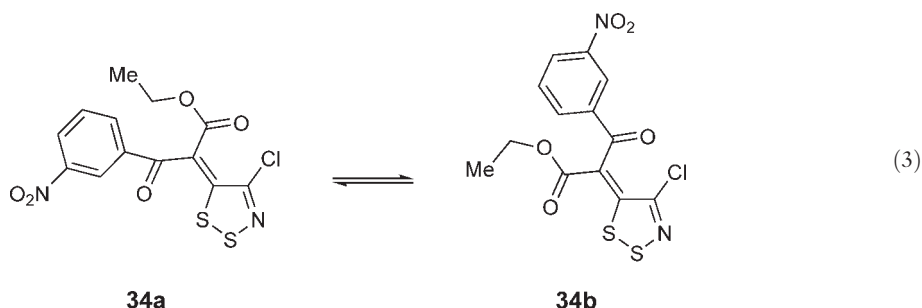
6.01.3.2 ¹H NMR Spectroscopy

¹H nuclear magnetic resonance (NMR) spectroscopy was used for the study of stereoisomerism in 5-alkylidene-4-chloro-5H-1,2,3-dithiazoles <1999T9651>. The signals of the methyl groups in compounds **30** and **31**, which are *syn*

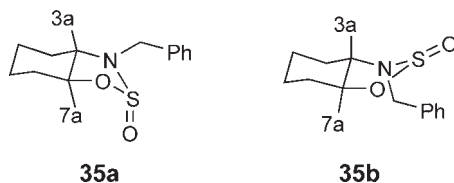
to S1 of the 1,2,3-dithiazole moiety, appear upfield compared with those having the opposite stereochemistry (compounds **32** and **33**, respectively).



With the help of ^1H NMR, it was shown that the mixture of stereoisomers **34a** and **34b** exists in an equilibrium between two isomers, which is slowly achieved in 24 h (ratio 53:47 at room temperature) (Equation 3). NMR data of the carbethoxy group suggest that **34a** having the group *anti* to S-1 is the major compound <1999T9651>.



The conformations of *trans*-fused cyclohexathiazolidines **35a** and **35b** were determined by ^1H NMR spectroscopy <1996ACS1036>. From the anisotropy effect of the $\text{S}=\text{O}$ bond it is obvious that, of the two *trans* conformations, **35a** ($\delta_{\text{H-3a}}$ 2.60 and $\delta_{\text{H-7a}}$ 4.57 ppm) is the one with pseudoequatorial sulfinyl oxygen. Similar consideration has been made for corresponding *cis*-isomers.

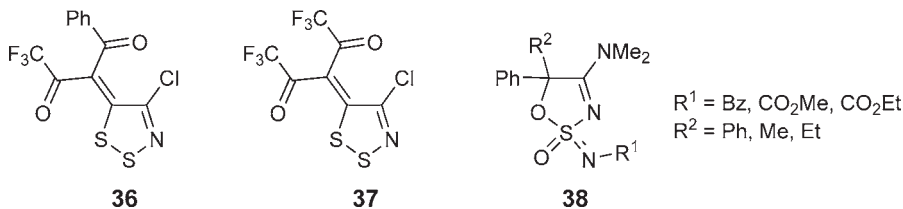


The absolute configuration at C-3 for the *spiro* derivative **18a** was unequivocally determined by nuclear Overhauser effect (NOE) experiments. Thus, irradiation of the NH_2 group caused enhancements of the signals for H-2 and H-5 of the tetrahydrofuran (THF) ring. These correlations indicated that the NH_2 group is on the upper side of the furanose ring and are only compatible with a *ribo* configuration of the furanose moiety <1999T12187>.

6.01.3.3 ^{13}C NMR Spectroscopy

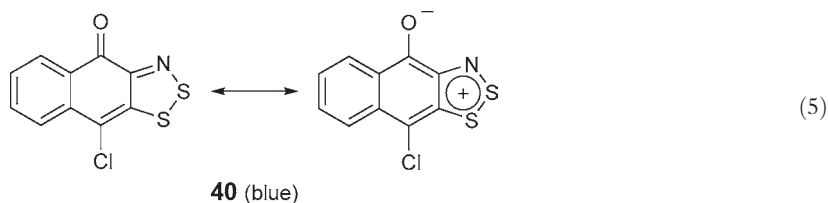
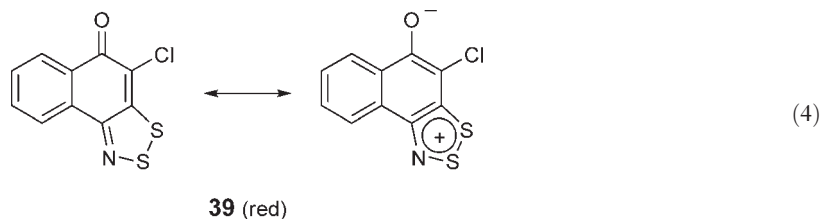
The ^{13}C spectrum of dithiazole **36** whose stereochemistry was clearly determined by X-ray crystallography exhibited signals corresponding to the CF_3CO and PhCO carbonyl carbons at 173.3 and 191.1 ppm <1999T9651>. Based on the spectrum of ylidene **36**, the signal at 172.4 ppm exhibited by ylidene **37** can be assigned to the carbonyl carbon *syn* to S-1 of the dithiazole ring and the other peak that appeared downfield (182.2 ppm) can be assigned to the carbonyl carbon *anti* to S-1 of dithiazole **37**. Similarly the ^{13}C NMR signal at 171.9 and 186.2 ppm exhibited by a mixture of compounds **30** and **32** were assigned to the CF_3CO carbonyl group *syn* **32** and *anti* **30** to S-1, respectively. The same propensity of the ^{13}C NMR chemical shifts was observed for the carbonyl carbons of the acetyl groups in ylidenes **30** and **32**. That is, compound **30** having an acetyl group *syn* to S-1 exhibited the signal of the carbonyl carbon at 188.0 ppm, whereas dithiazole **32** having the corresponding absorption at 197.8 ppm.

The oxathiazoles **38** can be identified, even if they are not stable enough to survive preparative chromatography, by the characteristic low-field resonances ($\delta \sim 97\text{--}98$ ppm) for the C-5 ring atom indicating a neighboring oxygen <1996J(P1)1629>.



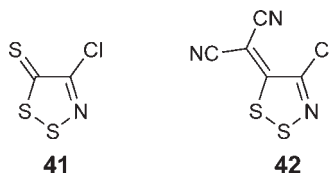
6.01.3.4 UV Spectroscopy

Structurally similar naphthodithiazolones **39** and **40** are both formally 14π heteroaromatic systems with analogous possibilities for electronic delocalization <1998T223>. The striking difference in color and electronic spectra of dithiazole **39** (λ_{max} 461 nm, $\log \epsilon$ 4.03) and dithiazole **40** (λ_{max} 602 nm, $\log \epsilon$ 3.63) is presumably associated with the angular tricyclic structure of dithiazole **39** compared with the higher-energy linear structure of dithiazole **40** (Equations 4 and 5), as found in similar carbocyclic systems like phenanthrene and anthracene and their aza derivatives.

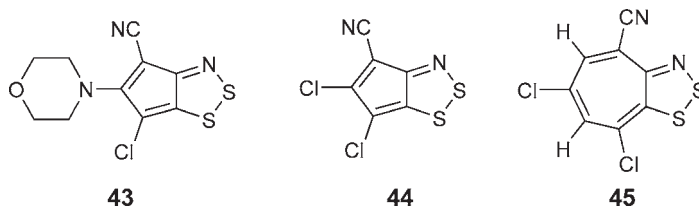


The intense $\pi\text{--}\pi$ -transition in bis(dithiazole) **24** (622 nm) <1998CC1939> is due to the longer wavelength of the corresponding absorption maxima in bis(dithiazoles) **23** (522 nm) and **11** (565 nm) <1998CC1039>.

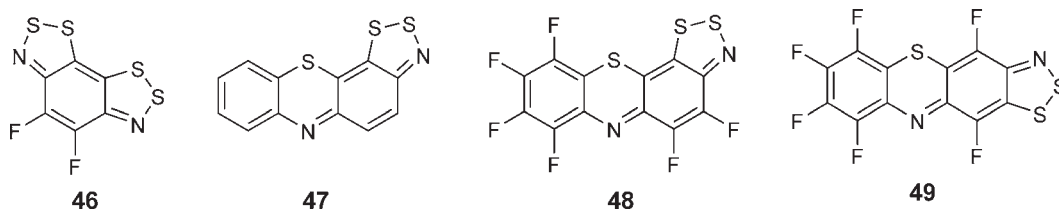
4-Chloro-1,2,3-dithiazoles **41** and **42** show strong ultraviolet (UV) absorption at λ_{max} 423–431 nm ($\log \epsilon$ 3.8–4.0) and a weaker absorption at λ_{max} 330 nm ($\log \epsilon$ 3.2–3.3) <1998J(P1)2505>.



The UV spectra of condensed dithiazole **43** (λ_{max} 412 nm, $\epsilon = 23\,928$) contrasted the UV spectrum of the chloro derivative **44** (λ_{max} 546 nm, $\epsilon = 2618$) <2005EJO5055>. Apparently, the morpholino group in dithiazole **43** disrupts the charge-transfer band between the two rings by conjugation between the amine and cyano groups. The UV spectrum of cycloheptadithiazole **45** showed a broad spectral absorption in the near-IR region (λ_{max} 700 nm, $\epsilon = 864$).

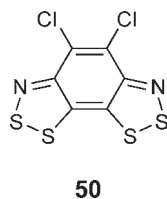


The 5-5-6 fused dithiazole **46** and angular 5-6-6-6 **47** and **48** systems reveal strong ($\log \epsilon = 3.9\text{--}4.2$) absorption at ca. 570–635 nm, whereas the linear 5-6-6-6 system **49** absorbs at shorter wavelength, 533 nm ($\log \epsilon = 4.7$), with only a weak dependence of the corresponding $\pi \rightarrow \pi^*$ transitions in extended polyheteroatom π -system upon substitution of fluorine for hydrogen. Additionally, the 5-6-6-6 systems **47–49** demonstrate strong fluorescence in the range of ca. 660–680 nm [\[2005EJI4099\]](#).



6.01.3.5 ESR Spectroscopy

A solution of radical cation of **23** in liquid sulfur dioxide exhibits an extremely strong and persistent ESR signal as a 1:2:3:2:1 quintet, confirming that spin density is fully delocalized over both nitrogen atoms [\[1997JA12136\]](#). The effects of spin-orbit coupling (at sulfur) on the g -value are more pronounced in the dithiazolyl cation radical of **23** than in simple monofunctionalized dithiazolyls, and, consistently, the observed g -value of 2.0114 is larger than in, for example, benzo-1,2,3-dithiazolyl **15** ($g = 2.008$). Similarly, the more extensive delocalization of spin density in the cation radical of **23** relative to simple 1,2,3-dithiazolyls leads to a smaller hyperfine coupling constant at nitrogen ($a_N = 0.201$ mT). Additional coupling to two pairs of hydrogens with $a_N = 0.079$ and 0.048 mT in cation radical of **50** is also observed [\[1998CCC1939\]](#). The ESR spectrum of compound **14** is considerably more complex but spectral simulations reveal the effects of hyperfine coupling to all five nitrogen nuclei. Spin density is moved away from the 5-position and is redistributed not only to the nitrogen attached to the 4-position of the 1,2,3-dithiazole ring but also to the other nitrogens of the thiadiazolopyrazine ligand. As a result of this reorganization of spin density, the radical **14** resists association via C–C bond formation [\[1999JA969\]](#).



In addition to the expected triplet ($a_N = 0.498$ mT) arising from hyperfine coupling to the dithiazole nitrogen of radical **28**, the spectrum also displays appreciable ($a_N = 0.135$ mT) coupling to the isothiazolyl nitrogen, as well as smaller coupling to two of the three chlorines present in the molecule. This is indicative of substantial spin delocalization away from the dithiazolyl ring [\[2002CCC1872\]](#).

The a_N constants and g -values of known 1,2,3-dithiazolyl radicals are listed in [Table 1](#).

6.01.3.6 Cyclic Voltammetry

Electrochemical properties were examined to gain more quantitative insight into the redox properties of this system. Cyclic voltammetry on bis(dithiazole) **23** in acetonitrile (with Pt electrodes and 0.1 M $n\text{-Bu}_4\text{NPF}_6$ as supporting electrolyte) reveals a reversible oxidation wave with $E_{1/2}(\text{ox}) = 0.93$ V and a second, irreversible oxidation process

Table 1 ESR g -values, hyperfine coupling constants (a_N) of 1,2,3-dithiazolyl radicals and cation radicals, and half-wave potentials of 1,2,3-dithiazolyls

Structure	g -Value	a_N (mT)	$E_{1/2}^{(0/+)} (V)$	$E_{1/2}^{(+/2+)} (V)$	$E_{pc}^{(0/-)} (V)$	Reference
11	2.0117	0.096	0.80	1.25	−0.95	2001IC2709
13	2.0102	0.236	1.36	1.60	−0.91 ^a	2001IC2709
14	2.009	0.514	1.14		0.15	1999JA969
16a	2.0083	0.310	0.005	1.415	−0.835	2004CM1564
16d	2.0082	0.317	−0.130	1.294	−0.952 ^a	2004CM1564
16e	2.0082	0.318				2003JA14394
16f	2.0082	0.310				2002JA9498
17a	2.0084	0.317	−0.136	1.278	−0.94	2004CM1564
17b	2.0086	0.320	−0.104	1.305	−0.956	2004CM1564
23	2.0114	0.201	0.93	1.5 ^a	−0.95	1997JA12136
24	2.0106	0.235	0.41	0.66	−1.06	1998CC1939
25	2.0117	0.161	0.61	1.10	−0.98	1999CM164
28	2.00875	0.498	0.565		−0.389 ^a	2002CC1872
29	2.0081	0.748	0.207		−0.91 ^a	2005IC1837
50	2.0117	0.143	0.81	1.37	−0.96	1999CM164

^aIrreversible.

with an anodic peak potential $E_{pa} = 1.5$ V <1997JA12136>. Attempts to suppress the irreversibility of the $[23]^{+}/[23]^{2+}$ couple by varying the voltage sweep rate and substrate concentrations were unsuccessful. Reduction of compound **23** occurs via a single, broad, and strongly irreversible wave with a cathodic peak potential $E_{pc} = -0.95$ V.

A listing for known 1,2,3-dithiazoles of the half-wave potentials $E_{1/2}(ox)$ of the first and second oxidation as well as the cathodic peak potential (E_{pc}) for the reduction process is given in Table 1.

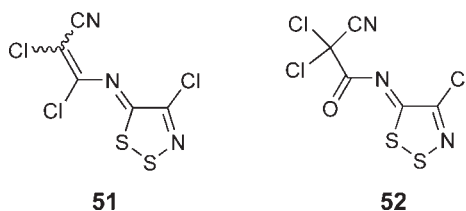
6.01.3.7 IR Spectroscopy

The IR data recorded in KBr shows that the carbonyl stretching absorptions of the trifluoroacetyl group in 1,2,3-dithiazoles **32**, **33**, and **36**, which have the trifluoroacetyl carbonyl group *syn* to S-1, showed absorption at 1573–1586 cm^{-1} , whereas compounds **31** and **37** having carbonyl group *anti* to S-1 showed absorptions at 1718–1731 cm^{-1} <1999T9651>. That is, the carbonyl group *anti* to S-1 needs more energy than that of *syn* analogs to be a vibrationally excited site.

The IR spectrum of 4-chloro-1,2,3-dithiazole-5-thione **41** shows strong bands at 1041, 1029, and 1013 cm^{-1} in the region for sulfine symmetric and asymmetric stretching <1998J(P1)2505>.

6.01.3.8 Mass Spectrometry

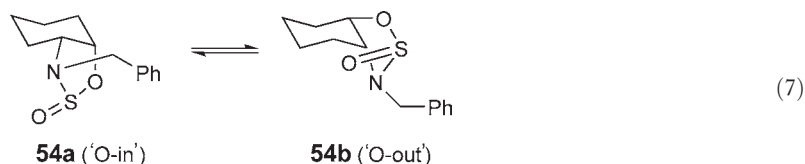
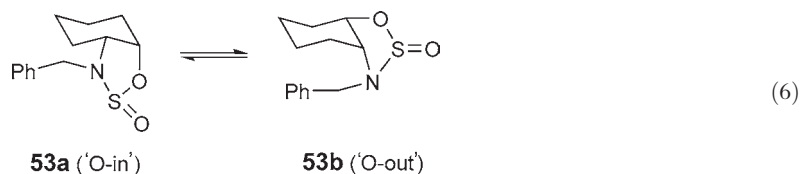
The presence of the 1,2,3-dithiazole ring in a mixture of isomers **51** was supported by the fragment ions m/z 137 (C_2ClNS_2) for the chlorinated ring, 125 (CClNS_2), 102 (C_2NS_2) the ring itself, 93 (CClNS) the $\text{Cl-C}\equiv\text{N-S}$ unit, 70 (C_2NS) and 64 (S_2) <1998J(P1)2505>. These assignments were supported by high-resolution mass spectrometry (HRMS), which also identified the fragment ions m/z 120 ($\text{C}_3\text{Cl}_2\text{N}$) and 85 (C_3ClN) from substituents of the dithiazole ring. The fragmentation of molecule **52** occurred so readily that a strong parent ion, m/z 287, could only be obtained by fast atom bombardment (FAB) spectrometry <1998J(P1)2505>.



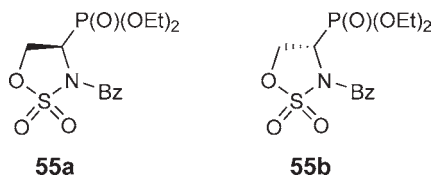
6.01.4 Thermodynamic Aspects

An equilibrium of substituted 1,2,3-oxathiazolidine *S*-oxide stereoisomers was described in CHEC-II(1996) <1996CHEC-II(4)409>.

It has been reported that according to NMR spectra both *cis*-isomers of cyclohexaoxathiazolidines **53** and **54** are in conformational equilibrium at room temperature, and isomer **53** is a ca. 1:1 mixture of the 'O-in' and 'O-out' conformers, and that there is a roughly 4:1 preference for the 'O-in' **54a** conformation in the isomer **54** (Equations 6 and 7) <1996ACS1036>.



The enantiomeric purity of the sulfamides **55a** and **55b** was established using Whelk O-2 chiral high-performance liquid chromatography (HPLC) <2005TA1583>, and in each case chiral HPLC confirmed an enantiomeric excess of at least 97%. These two sulfamate oils proved to be very stable when stored for up to a year at -20°C .



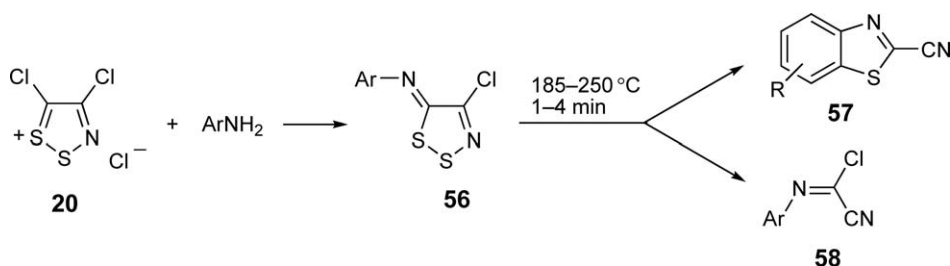
6.01.5 Reactivity of Fully Conjugated Rings

Reactivity of conjugated 1,2,3-dithiazole-type structures has been covered in CHEC-II(1996) <1996CHEC-II(4)409>. Thermal rearrangement of 1,2,3-dithiazoles, as a rule, is accompanied by the loss of one sulfur atom or molecular diatomic sulfur (S_2) <1996CHEC-II(4)409>. Electrophilic reactions at ring nitrogen and carbon are rare and usually lead to ring opening or rearrangement. Oxidation of 1,2,3-dithiazoles occurs at the S(2) atom. Nucleophilic attack at ring carbon is present mostly in Appel salt and the imino derivatives <1996CHEC-II(4)409>. Herz salts were extensively investigated with various reducing procedures including electrochemical processes.

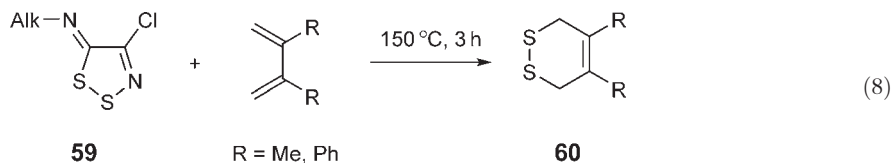
In this section, the majority of new reactions are devoted to a continuation of the Appel salt chemistry, and its keto, thio, and ylidene derivatives, but imino-1,2,3-dithiazoles have attracted special attention by the Rees group.

6.01.5.1 Unimolecular Thermal Reactions

N-Arylimino-1,2,3-dithiazoles **56**, which can be easily prepared from primary aromatic amines and Appel salt **20**, give 2-cyanobenzothiazoles **57** on heating, thus providing a simple two-step route to these heterocycles from the appropriate amines <1997J(P1)201>. This thermolysis is favored by electron-donating substituents in the aniline ring, and retarded by electron-withdrawing groups in favor of a second pathway in which both dithiazole sulfur atoms are lost to form cyanoimidoyl chlorides **58** (Scheme 3). This is the sole pathway when both aniline *ortho*-positions are substituted. The analogous *N*-alkyl imines **59** also decompose with the loss of both sulfur atoms as singlet diatomic sulfur, which is intercepted by 2,3-diphenyl- and 2,3-dimethylbutadienes to give 1,2-dithiins **60** (Equation 8).

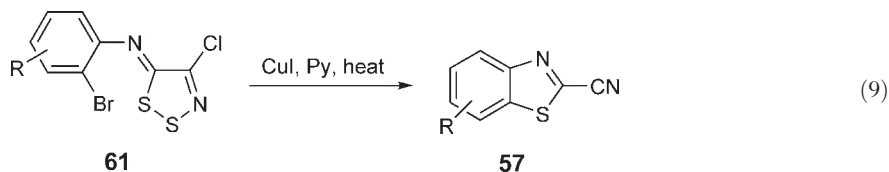


Scheme 3

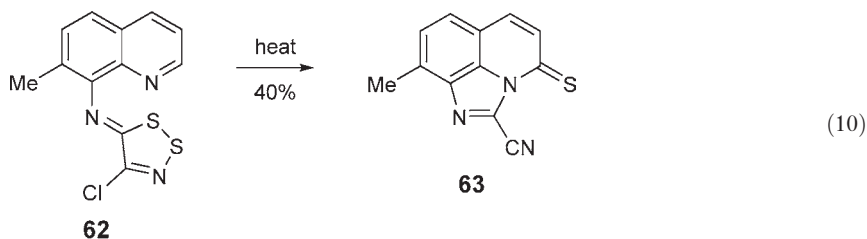


The cyclization procedure of imines **56** was developed by using microwave heating in such high boiling solvents as *N*-methylpyrrolidin-2-one at 150 °C, or even an ecofriendly solvent-free process in the presence of graphite at the same temperature <2003SC3795>. Yields are moderate (45–52%).

Heating the *o*-bromophenyl derivatives of imines **61** in the presence of cuprous(I) iodide in pyridine at reflux afforded 2-cyanobenzimidazoles **57** in good yields (Equation 9) <1998J(P1)3925>. Conducting this reaction in a focused microwave reactor resulted in reduced reaction time with no loss in yields. The electrocyclization and fragmentation process previously suggested may be facilitated by halogen complexation with copper salt.



Quinolylimino-1,2,3-dithiazoles **62** undergo by thermolysis an unusual rearrangement to give imidazoquinolinethiones **63** (Equation 10); delivery of a sulfur atom to the quinoline 2-position appears to be intramolecular and possibly involves a [1,3] sigmatropic shift of a carbon–sulfur bond <2000J(P1)555>.



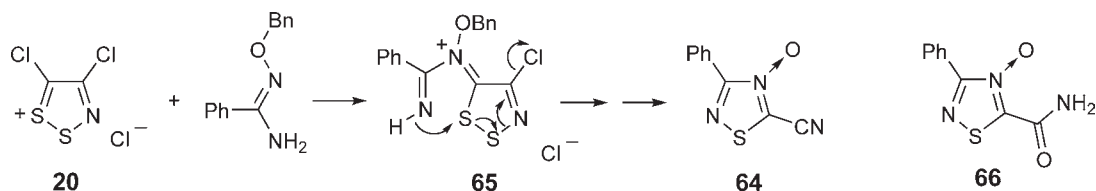
6.01.5.2 Electrophilic Attack at Ring Atoms

No significant developments have been reported in this area since the publication of CHEC-II(1996) <1996CHEC-II(4)409>.

6.01.5.3 Nucleophilic Attack at Ring Sulfur

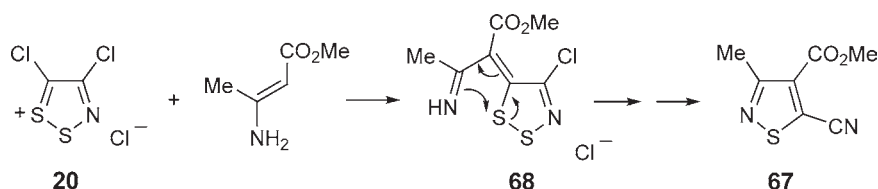
Nucleophilic attack at ring sulfurs can proceed at S-1 as well as S-2 atoms. The cleavage of the S–S bond in the 1,2,3-dithiazole ring and formation of sulfur heterocycles in the first case, or the formation of compounds with C=S group by the attack on S-2 atom, are the results of these reactions.

The previously unknown 1,2,4-thiadiazole-4 oxides **64** were prepared by condensation of benzamidoximes or their derivatives with Appel salt (**Scheme 4**) <1996CC1273>. The reaction mechanism includes attack of the imino group in **65** on the S-1 atom of the 1,2,3-dithiazole ring. The *N*-oxides are shown to be the 4-isomers by analysis of the NMR and mass spectra of ^{15}N -labeled and unlabeled products and X-ray structure determination of the derived carbox-amide **66** <1999J(P1)2243>.



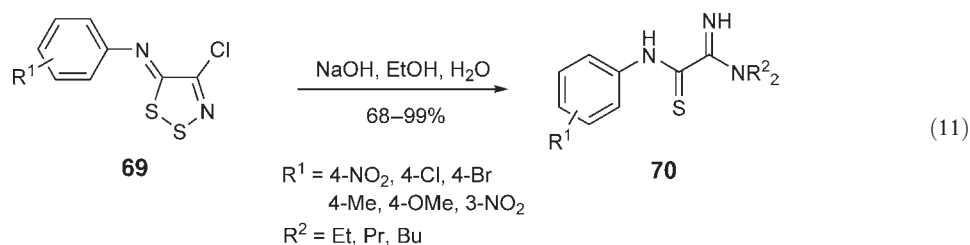
Scheme 4

Methyl 3-aminocrotonate reacts with Appel salt **20** to give isothiazole **67** in high yield (78%) (**Scheme 5**) <1998J(P1)77>. The spontaneous conversion of the presumed intermediate **68** into the isothiazole also requires nucleophilic attack on the S-1 atom.

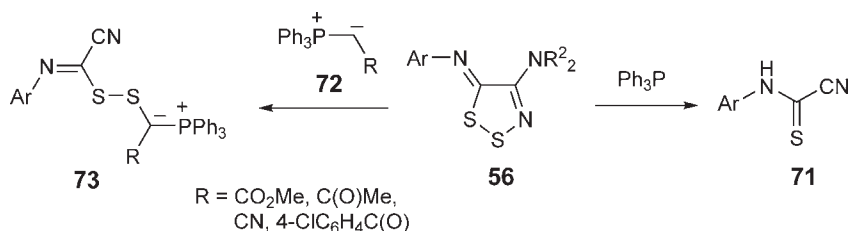


Scheme 5

Various reagents of a nucleophilic or reductive nature can attack at S-2 of 1,2,3-dithiazole ring. Treatment of arylimines **69** with NaOH in aqueous EtOH afforded thiocarbamoylamidines **70** in good to excellent yields (**Equation 11**) <1996T8413>. The formation of amidines **70** was explained by a nucleophilic attack of hydroxide ion at S-2 with the cleavage of S-S bond.



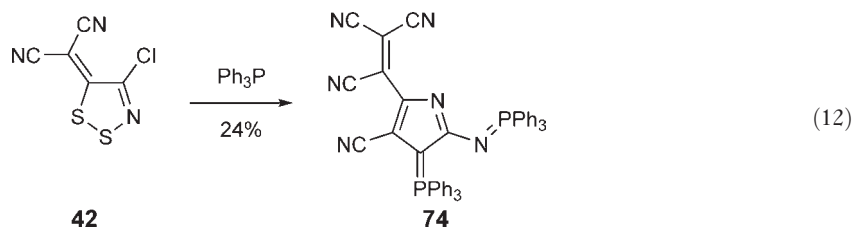
Triphenylphosphine and phosphonium ylides are known as convenient reagents to extrude sulfur with formation of triphenylphosphine sulfide. Imino 1,2,3-dithiazoles **56** reacted with Ph_3P in moist dichloromethane to give *N*-arylcyanothioformamidines **71** (**Scheme 6**) <1996BML529>. These compounds can be obtained also from imines



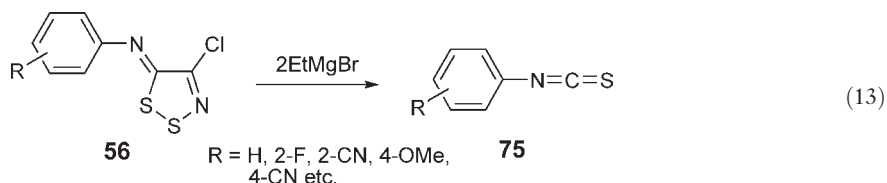
Scheme 6

56 and stable phosphoranes **72**. However, the major products in this reaction were dithiomethylenephosphoranes **73**, which unequivocally confirmed the initial attack at the S-2 atom <1996TL869>.

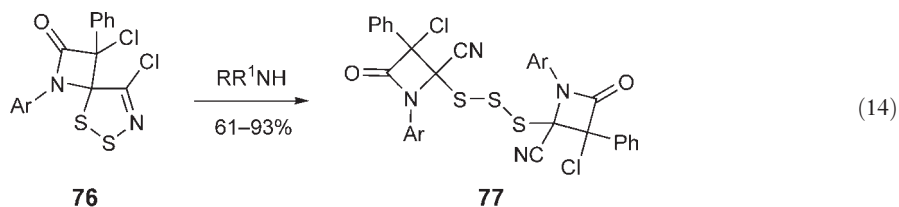
Treatment of dicyanomethylenedithiazole **42** with an excess of Ph_3P gives complex ylide **74** whose structure was confirmed by X-ray analysis (Equation 12) <1998J(P1)2765>. A mechanism for this ylide formation, involving an initial attack of Ph_3P at S-2 atom, has been proposed.



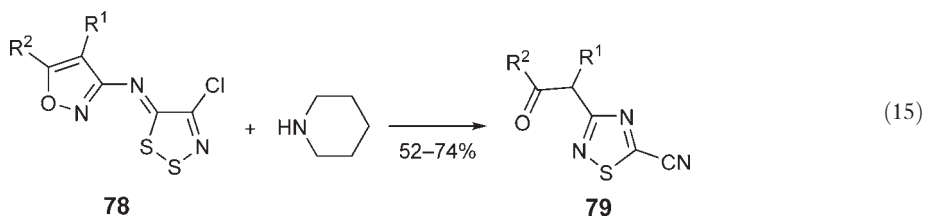
Opening of the dithiazole ring in imine **56** can occur by the action of Grignard reagent and is presumably initiated by attack at S-2. Further addition of a second molecule of Grignard reagent to the reaction mixture results in the formation of arylisothiocyanate **75** (Equation 13) <1998J(P1)889>.



Primary and secondary amines are found to cleave the 1,2,3-dithiazole ring in spiro azetidin-1,2,3-dithiazoles **76** to afford azetidinetrisulfides **77** in good to excellent yields (Equation 14) <2001CC1412>.



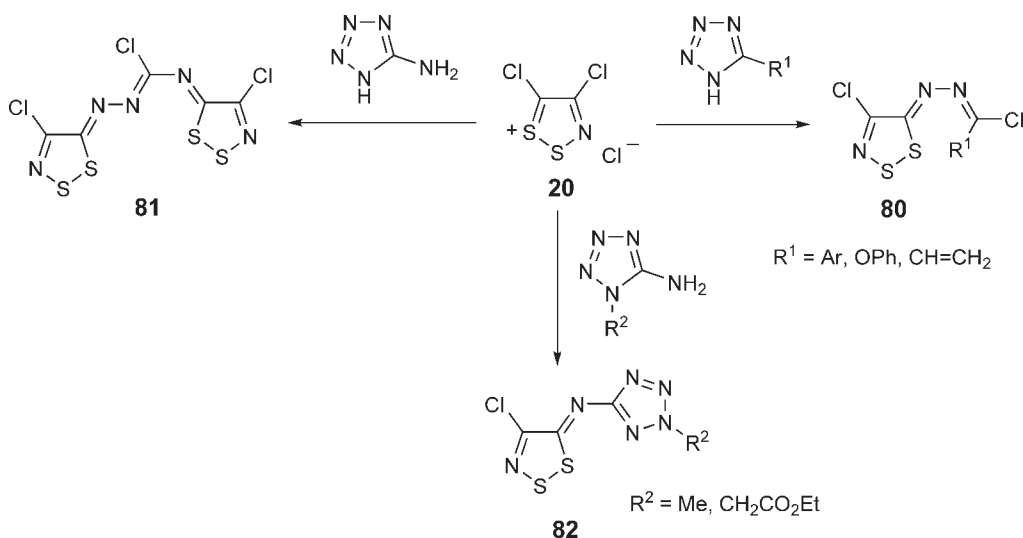
Another example of the initial attack of secondary dialkylamines onto the S-2 atom is the rearrangement of isoxasolylimino 1,2,3-dithiazoles **78** into cyanothiadiazoles **79** in the reaction with piperidine (Equation 15) <1999H(51)811>.



6.01.5.4 Nucleophilic Attack at Ring Carbon

Appel salt **20** is sensitive to attack of nitrogen, oxygen, and sulfur nucleophiles, especially at the 5-carbon, to form corresponding 5-imines **56**, ketone, thione **41**, and 5-ylidenes (i.e., **42**) which can participate in further reactions with nucleophiles at the same carbon atom with extrusion of diatomic sulfur (S_2) and chloride anion. This chemistry started in 1985 when Appel salt was discovered, and is extensively studied at the present time.

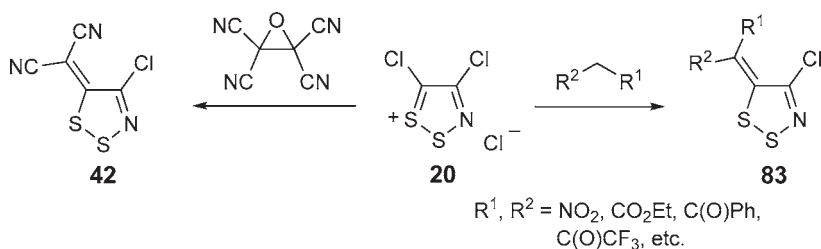
5-Substituted tetrazoles react rapidly with salt **20** at room temperature to give hydrazoneyl chlorides **80** in high yield <2002J(P1)1535>. 5-Aminotetrazole reacts further to afford extended bis(imino)dithiazole **81** (Scheme 7). The proposed mechanisms include the attack of a tetrazole nitrogen on the carbon atom of Appel salt followed by opening



Scheme 7

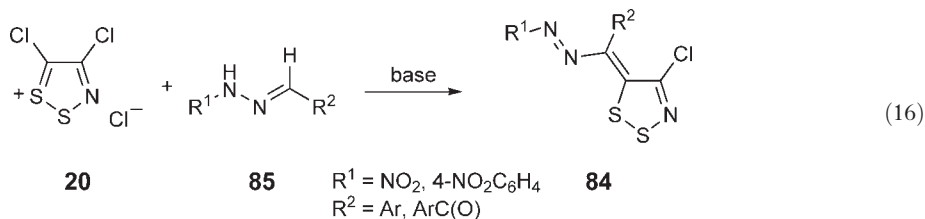
of the tetrazole ring. The 5-amino-2-alkyltetrazoles, with N-2 of the ring blocked, reacted with Appel salt, as expected for primary heteroaromatic amines, to give the imino adducts **82** in high yield.

A series of symmetrical and unsymmetrical active methylene compounds was reacted with salt **20** to give 5-alkylidene-1,2,3-dithiazoles **83** <1999T9651>. More surprisingly, tetracyanoethylene oxide gives under these conditions dicyanomethylene derivative **42** (Scheme 8) <1998J(P1)2505>.

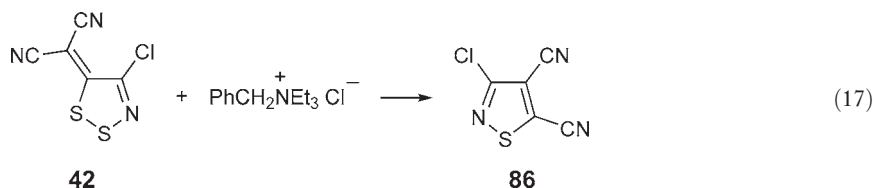


Scheme 8

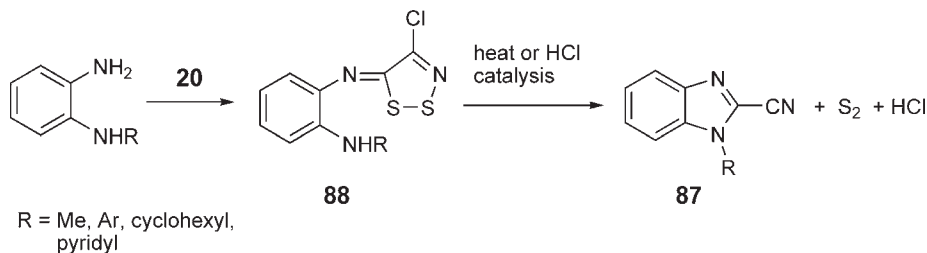
Previously unknown azomethylene derivatives of 1,2,3-dithiazoles **84** were synthesized by the reaction of Appel salt **20** with N-monosubstituted hydrazones **85** (Equation 16) <2004JHC37>. Their formation probably includes the generation of the carbon anion, under the action of a base, which then adds to salt **20**.



Chloride ion in benzyl(triethyl)ammonium chloride can activate a nitrile group in dicyanomethylenedithiazole **42** which then cyclizes onto S-1 to form the aromatic isothiazole ring and a new cyano group (Equation 17) <1997J(P1)3345>. The yield of isothiazole **86** is quantitative.

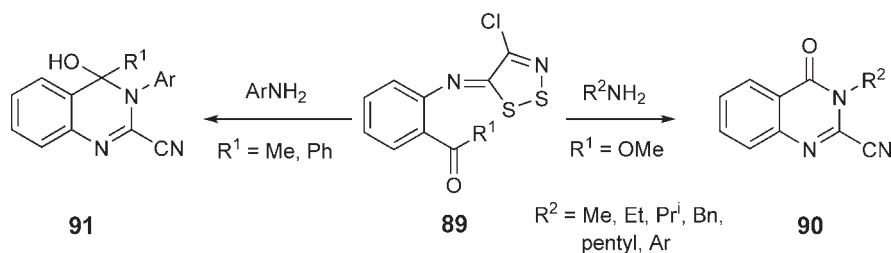


N-monosubstituted 1,2-diaminobenzenes react with Appel salt **20** in dichloromethane to give the corresponding 2-cyanobenzimidazoles **87** either directly or through thermal or acid-catalyzed rearrangement of the intermediate imino-1,2,3-dithiazoles **88**, which can be isolated (Scheme 9). The reaction mechanism includes reversible attack of the *o*-amino group on the dithiazole ring <1998T9639>.



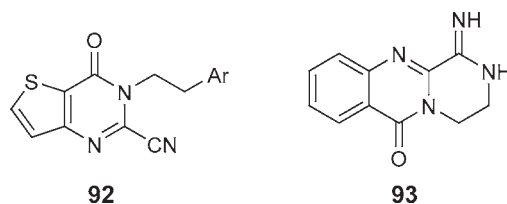
Scheme 9

The reaction of imine **89** ($\text{R}^1 = \text{OMe}$) with sterically less hindered primary alkylamines <1998JHC659> or arylamines <2002SL1423> unexpectedly gives quinazolines **90** or **91**, respectively, in moderate to good yields (Scheme 10).



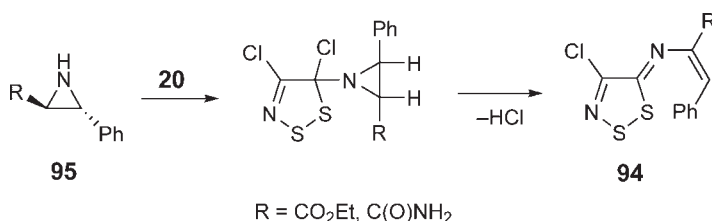
Scheme 10

Thienopyrimidinones **92** were also synthesized by this reaction <2002H(57)1471>. Ethylene diamine produces in this conversion the novel and rare tricyclic pyrazinoquinazolinone **93** <2004TL3097>.



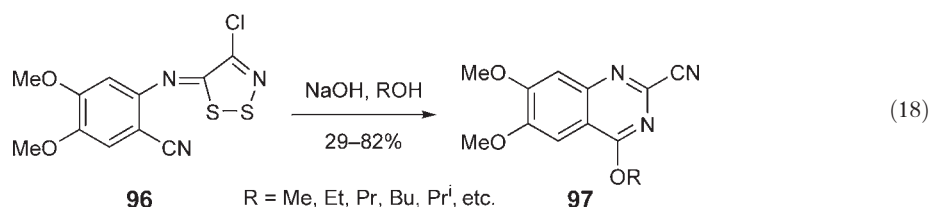
An interesting synthesis of *N*-vinyl-1,2,3-dithiazolylimines **94** from Appel salt **20** and aziridines has been described <2005H(65)1601>. This procedure involves elimination of hydrogens from different nitrogen and carbon atoms. The reaction with aziridinecarboxylic acid ester or its amide **95** having the *trans*-configuration produces one of the possible

isomers (Scheme 11). Apparently, the aziridine ring opening occurs almost in parallel with the formation of the double bond.

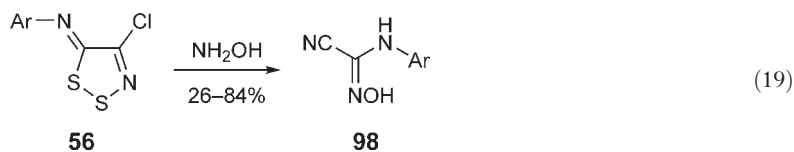


Scheme 11

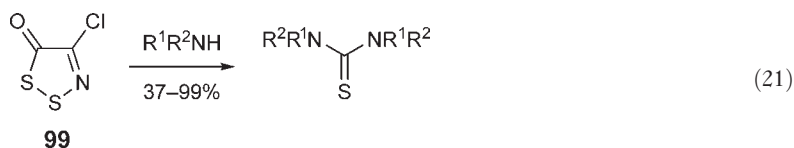
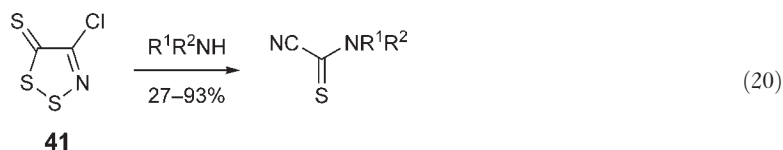
The treatment of iminodithiazole **96** with alcohol and a base gives quinazoline-2-carbonitriles **97** in good yield (Equation 18). A reasonable mechanism would appear to be addition of alkoxide ion to the cyano group and cyclization with the attack on C-5 of 1,2,3-dithiazole ring followed by elimination of S_2 and HCl <1998T6475>.



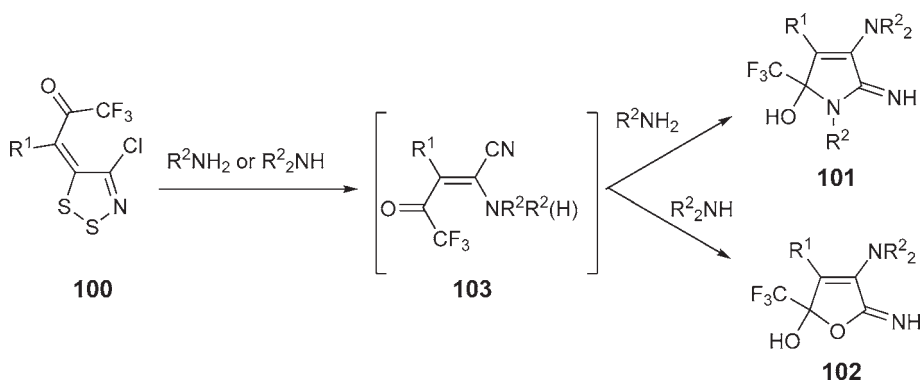
The reaction of 5-arylimino-1,2,3-dithiazoles **56** with hydroxylamine proceeds smoothly to give *N*-arylcyanohydroxamides **98** (Equation 19), which can be utilized as starting materials for the synthesis of 4-substituted-2-cyanoquinazolines and 4-aryl-3-cyano-1,2,4-oxadiazin-5(6*H*)-ones <1999H(51)2653>.



Primary and secondary alkylamines have been used for the preparation of *N*-alkyl- and *N,N*-dialkylcyanothioformamides, respectively, in the reaction with 4-chloro-1,2,3-dithiazole-5-thione **41** (Equation 20) <1996TL3709>. 4-Chloro-1,2,3-dithiazole-5-one **99** in the reaction with mono- and di-alkylamines afforded *N,N'*-disubstituted ureas in moderate to good yields (Equation 21) <2001TL8197>. The reaction was proposed to be similar to the corresponding thione **41** but displacement of a cyano group by another molecule of alkylamine accompanies this conversion.

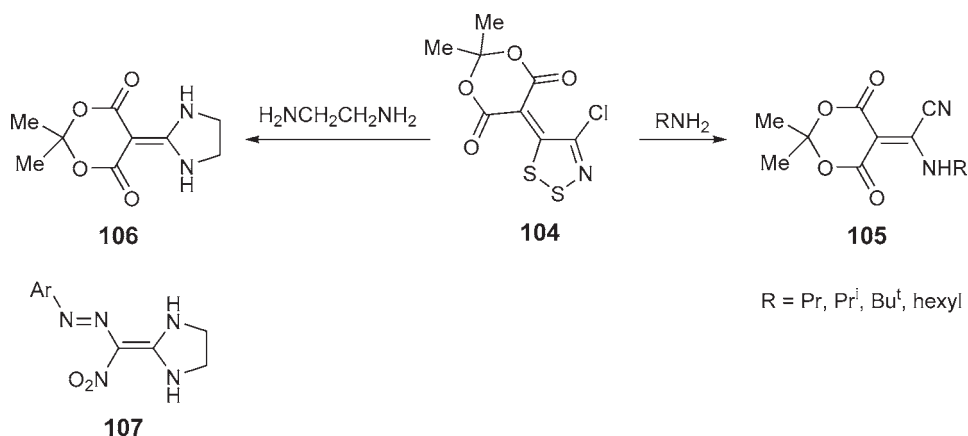


The behavior of ylidene derivatives **100** in the reaction with primary and secondary alkyl amines differs significantly from that of the corresponding imines **56**, thione **41**, and ketone **99**. Trifluoroacetyl derivatives **100** gave dihydroiminopyrroles **101** (22–55%) in the reaction with primary alkylamine and with dialkylamines under the same conditions gave dihydroiminofurans **102** (18–62%) (Scheme 12) <1998TL6895>. Cyanoenaminoketone **103** was proposed as a key intermediate in the formation of these heterocycles.



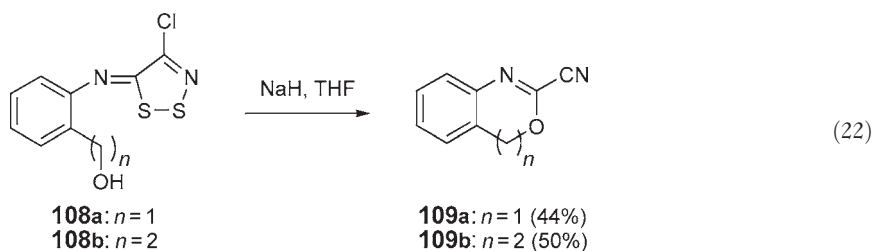
Scheme 12

In a similar transformation of ylidene **104**, obtained from Appel salt **20** and Meldrum's acid, with primary aliphatic amines, the reaction has been stopped at the stage of (alkylamino)cyanomethylidene **105** <2000J(P1)3107>. Ethylene diamine and other diamines gave under the same conditions imidazolidin-2-ylidenes **106** as a result of final substitution of the cyano group by the second amino group. Corresponding imidazolidines **107** were formed in the reaction of ethylene diamine with the azomethyne derivative of 1,2,3-dithiazole **84** (Scheme 13) <2004JHC37>.



Scheme 13

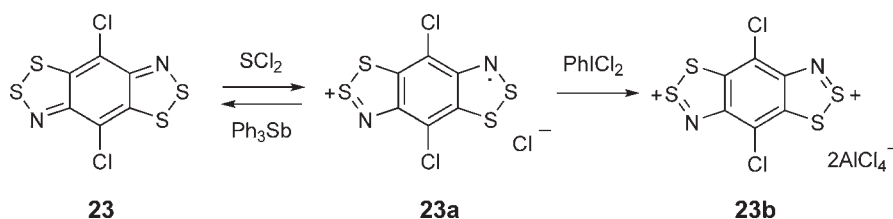
Iminodithiazoles **108** prepared from Appel salt **20** and *o*-aminobenzyl- and *o*-aminophenethyl-alcohols can be converted into 3,1-benzoxazine **109a** and 3,1-benzoxazepine **109b** by treatment with sodium hydride in THF (Equation 22) <1997SL704>. The oxygen-containing heterocycles **109** are apparently formed by cyclization of the alkoxide from dithiazole **108** onto the imine bond, followed by loss of S₂ with generation of the cyano group.



(22)

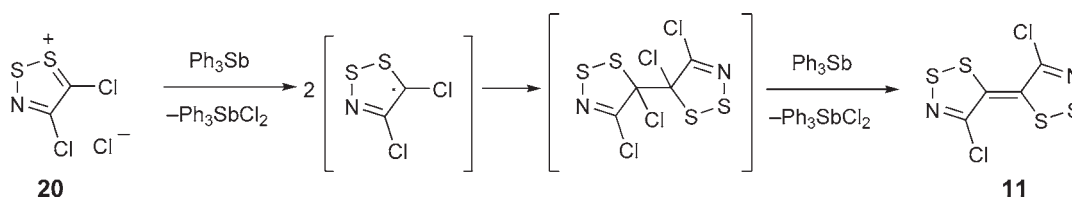
6.01.5.5 Reactions Involving Radicals, Electron-Deficient Species, Reducing Agents, and at Surfaces

Reduction of the radical cation of bis(dithiazole) **23a** with triphenylantimony affords the neutral heterocycle **23** <1997JA12136>. Oxidation of compound **23** to radical cation **23a** can be effected by heating a chlorobenzene solution with an excess of sulfur dichloride. Further oxidation of **23a** with PhICl_2 or SOCl_2 in the presence of AlCl_3 in liquid SO_2 gives the closed shell dicationic salt **23b** (Scheme 14).



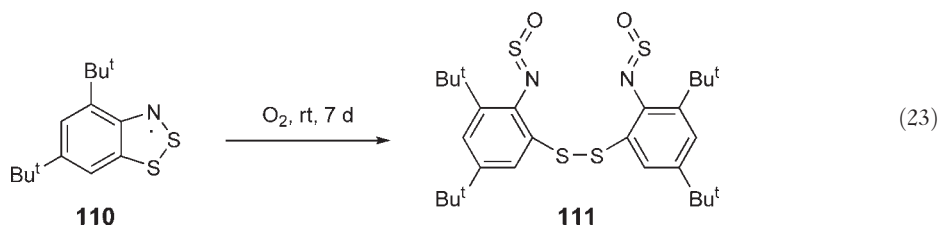
Scheme 14

Reductive coupling of Appel salt **20** with triphenylantimony (2 equiv) yields tetrathiadiazafulvalene **11**, which is the first example of this heterofulvalene system (Scheme 15) <1999JA6657>. The most successful procedure employed liquid SO_2 as a solvent at -70°C ; the bis(dithiazole) **11** could be isolated in 30% yield.

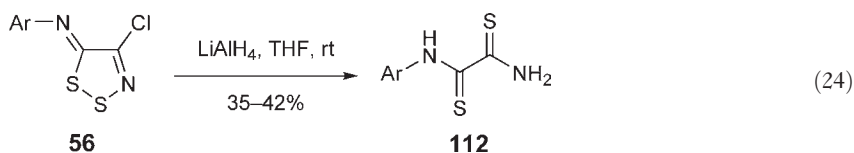


Scheme 15

1,2,3-Benzodithiazolyl radical **110** reacts in concentrated benzene solution ($\sim 0.15\text{ M}$) with dissolved oxygen to give disulfide **111** in quantitative yield (Equation 23) <2005MC14>. A mechanism for this unusual transformation was proposed based on the kinetics data and B3LYP/6-311G** calculations.



Readily accessible aryliminodithiazoles **56** can be converted by LiAlH_4 reduction into the rearranged *N*-aryldithiooxamides **112** (Equation 24) <1999S1345>. Although the yields are moderate (35–42%), this reaction provides a convenient two-step synthesis of unsymmetrical rubenic acid derivatives from arylamines.

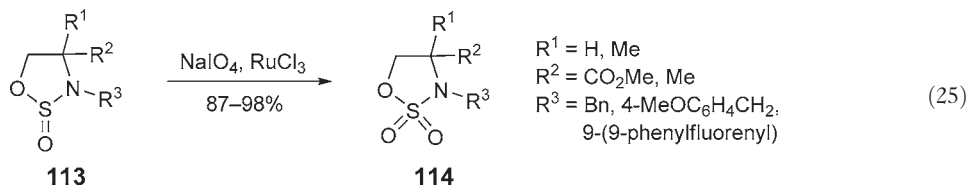


6.01.6 Reactivity of Nonconjugated Rings

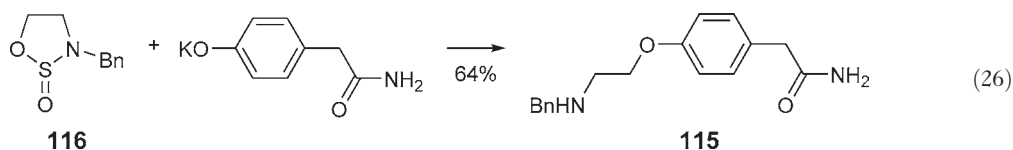
The reactivity of cyclic sulfonamides and sulfinimides was discussed in CHEC-II <1996CHEC-II(4)409>. Nucleophilic substitution in both rings leads to cycle opening, and these compounds are found to be excellent precursors for the synthesis of important biological active compounds, for example, α -amino acids.

6.01.6.1 Reactions of Hydrogenated Derivatives of 1,2,3-Oxathiazole S-Oxides

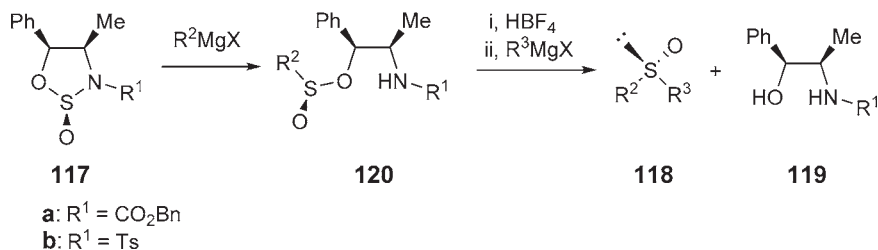
The modern protocol for oxidation of cyclic sulfinimides **113** to corresponding sulfonamides **114** includes treatment with sodium periodate and catalytic ruthenium trichloride (Equation 25) <1999J(P1)1421, 1999TL3831, 2000OL2595>. Yields are almost quantitative.



A synthesis of *o*-arylethanolamine **115**, a key precursor for β -agonists intended for the treatment of non-insulin-dependent diabetes, has been developed using the reaction of *N*-benzyloxathiazolidine-*S*-oxide **116** with potassium phenoxide (Equation 26) <1999OPD253>.

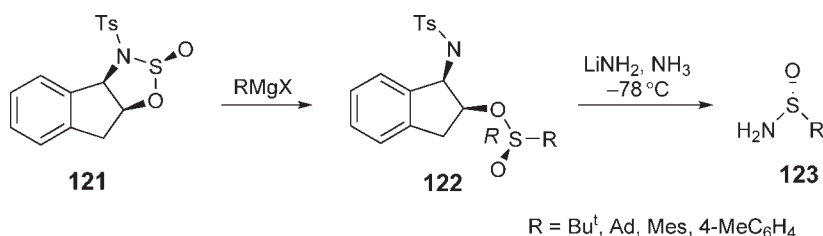


By employing the reaction of cyclic sulfimides **117** with 2 equiv of Grignard reagent and HBF_4 , a large number of structurally diverse sulfoxides, including alkyl aryl, diaryl, dialkyl, and aryl vinyl sulfoxides, were prepared in 50–78% yield and high enantioselectivity, evidencing the great scope of this methodology (Scheme 16) <2003OL75, 2003AGE2032>. An intermediate sulfinate **120** could be isolated from the reaction mixture, and it proved to be an even better sulfinating agent than the usual sulfinates, thus making easier the attack of the second Grignard reagent.



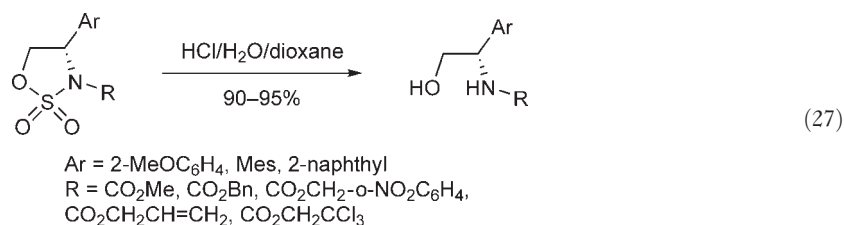
Scheme 16

A similar synthesis of enantiopure (*R*)-sulfinamides **123** from indane-derived toluenesulfonyl 1,2,3-oxathiazolidine-2-oxide **121** has been developed. This method includes chemoselective ring opening with inversion of configuration at the sulfur atom, using Grignard reagent at the first step and lithium amide in liquid ammonia in the second step (Scheme 17) <2002JA7880>. Intermediate stable and crystalline sulfinate esters **122** were isolated in >95% yield in diastereopure form.

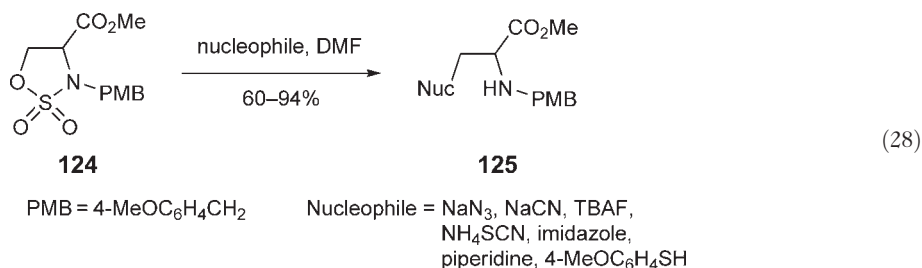


Scheme 17

Cyclic sulfamidates can be converted into β -aminoalcohols (Equation 27). The deprotection protocol (1:1 mixture of aqueous HCl/dioxane, room temperature) had sufficient scope for general synthetic utility; several sulfamidates were readily deprotected giving aminoalcohols under these conditions. High yields were observed in all examples, despite relatively large variations in the reaction time that is necessary to complete conversion <2002AGE834>.



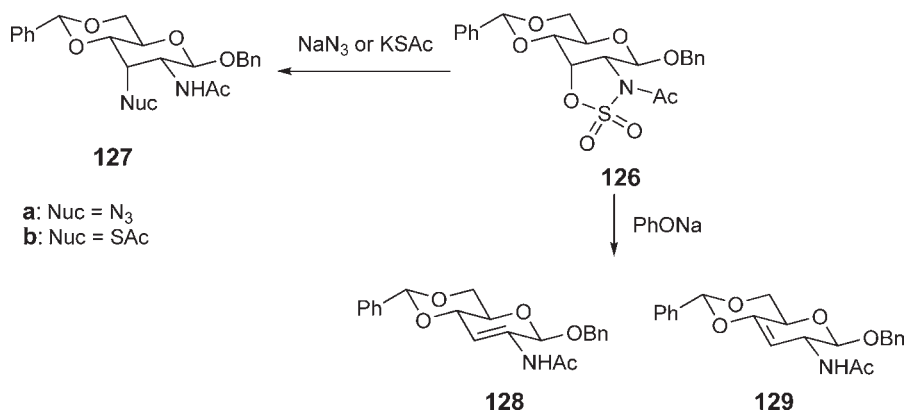
Reaction of cyclic sulfamidates with nucleophiles was extensively studied. Various nucleophiles were found successfully to substitute sulfamidate **124** at the C-3 atom in dimethylformamide (DMF) at room temperature and provide good yields of compound **125** (Equation 28). In the reaction with amines and thiophenol, the presence of caesium carbonate increased the product yields significantly <1999J(P1)1421>. In the case of fluoride anion <1999TL3831> or carbon nucleophiles <1996S259, 2002TL1915>, the final products are formed by hydrolytic cleavage of sulfate monoester with diluted sulfuric acid.



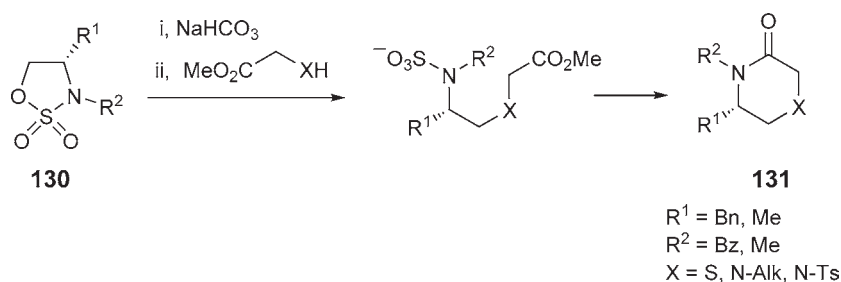
Surprisingly, when the cyclic sulfamidate derived from *N*-acetyl-D-allosamine **126** was treated with different nucleophiles, three types of products were formed by nucleophilic displacement of sulfamide at C-3 and proton abstraction at C-2 or C-4 (Scheme 18) <1997T5863>. Potassium acetate and sodium azide effectively provide regioselective ring opening to afford thio and azido derivatives **127**. When oxy-anions were used as nucleophiles, elimination was the main pathway (sugars **128** and **129**).

The regiospecific nucleophilic displacement of 1,2-cyclic sulfamidates **130** with methyl thioglycolate or α -amino esters **130** can be accompanied by lactamization (thermal, base mediated, or cyanide catalyzed) to give thiomorpholin-3-ones and piperazin-2-ones **131** (Scheme 19) <2003OL811>. If malonate esters, phosphonate-stabilized esters, or aryl-substituted enolates were used as nucleophiles in this reaction, trisubstituted pyrrolidines were obtained in high yield <2004OL4727>.

The cyclic sulfonimide **132** reacts readily with carbon nucleophiles, for example, methyl lithium, to afford the methylsulfoximine **133** which can be deprotonated by an excess of lithium hexamethyldisilazide (LHMDS) and reacted with a second equivalent of the sulfonimide yielding the bis(sulfoximine) **134** in a one-pot sequence with 62% yield (Scheme 20) <2004ASC1295>.



Scheme 18



Scheme 19

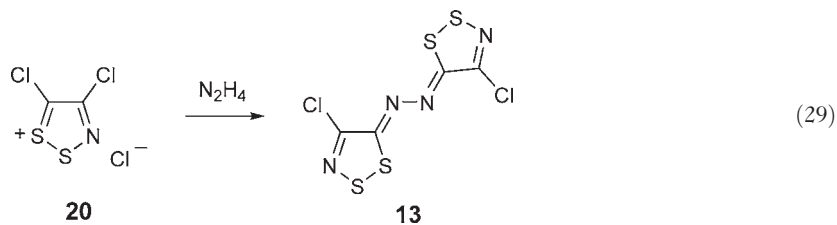


Scheme 20

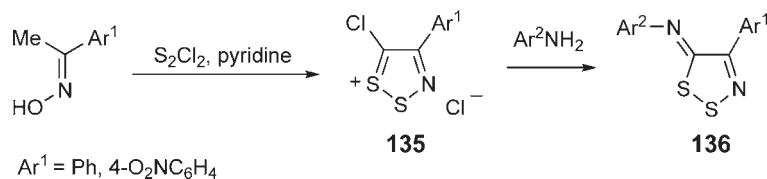
6.01.7 Reactivity of Substituents Attached to Ring Carbon Atoms

Much attention was paid in CHEC-II(1996) to nucleophilic substitution in chlorinated cyclopenta- and cyclohepta-1,2,3-dithiazoles <1996CHEC-II(4)409>.

Bifunctional 1,2,3-dithiazole **13** bridged by an azine spacer has been prepared from Appel salt **20** and hydrazine, with a goal to determine the extent of communication between the two dithiazole rings as a function of the electronic and steric demands of the bridge (Equation 29) (see Section 6.01.2) <2001IC2709>.

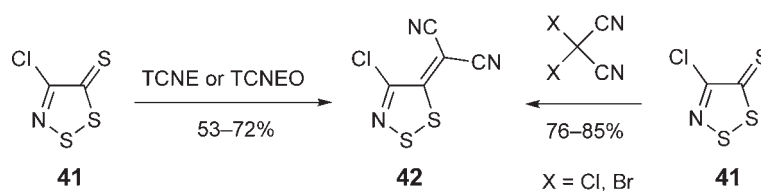


Acetophenone oxime and its 4-nitro derivative gave with S_2Cl_2 the 1,2,3-dithiazolium chlorides **135**. These are analogs of Appel salt **20** which were not isolated but converted to the 5-arylimino derivatives **136** by the reaction with arylamines (Scheme 21) <1997BSB605>.



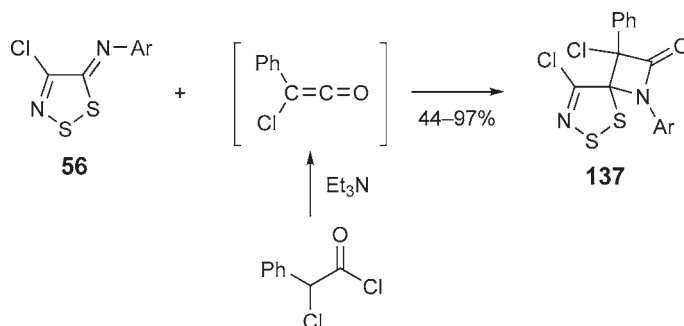
Scheme 21

Tetracyanoethylene (TCNE) or its oxide (TCNEO) reacted with thione **41** to give the dicyanomethylene product **42** (Scheme 22) <1997J(P1)3345>. This product can be obtained also from the same thione **41** and dihalogenated malononitriles <2002J(P1)1236> in higher yields.



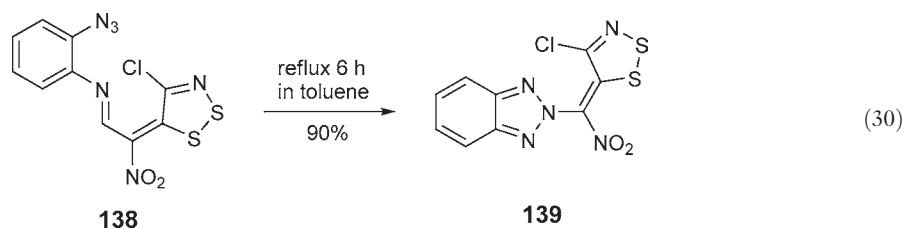
Scheme 22

Treatment of 5-arylimino-4-chloro-1,2,3-dithiazoles **56** with *in situ*-generated (chloro)phenylketene gave azetidinone-1,2,3-dithiazoles **137** in high to moderate yields through [2+2] cycloaddition to the N=C-Ar imine bond (Scheme 23) <2001CC1412>.

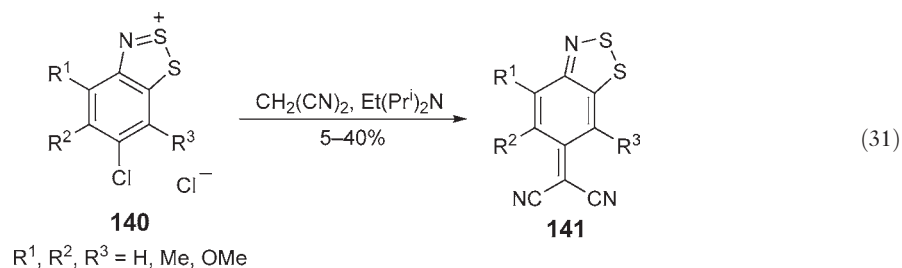


Scheme 23

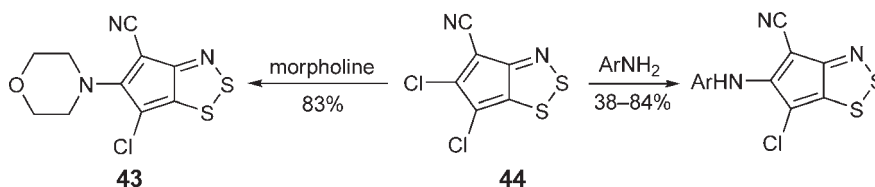
The thermolysis of the 1,2,3-dithiazole **138**, containing an azide group in the *ortho*-position relative to the diazo group, produced in high yield the previously unknown benzotriazole **139** containing the 1,2,3-dithiazole fragment (Equation 30) <2004JHC37>.



Herz salts bearing chlorine at the 6-position **140** react with malononitrile to afford highly colored ylidenes **141** in low to moderate yields (Equation 31) <2002J(P1)315>. The reaction is general but complex; few by-products were isolated.



Chlorinated cyclopenta-1,2,3-dithiazole **44** is susceptible to nucleophilic substitution with amines, and in all cases only the 5-chlorine atom of dithiazole **44** is substituted (Scheme 24). The selectivity in these reactions is apparently due to the activation of the *vic*-position to the cyano group of the dithiazole **44**, which is a unique feature of this compound <2005EJO5055>.

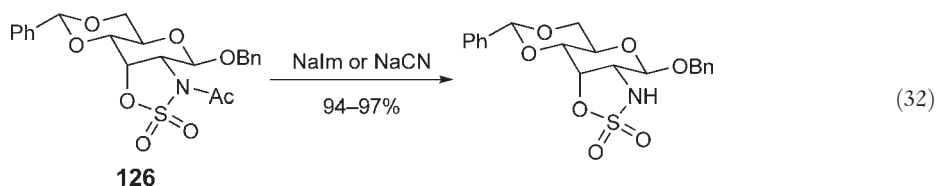


Scheme 24

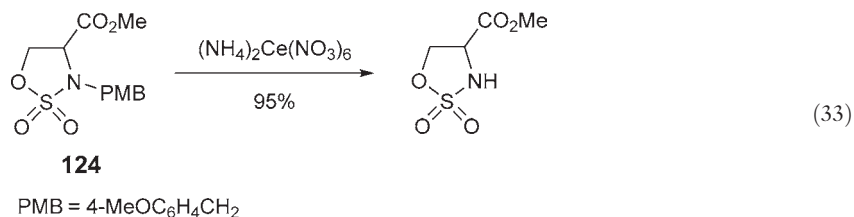
6.01.8 Reactivity of Substituents Attached to Ring Heteroatoms

This topic was not covered in CHEC-II(1996).

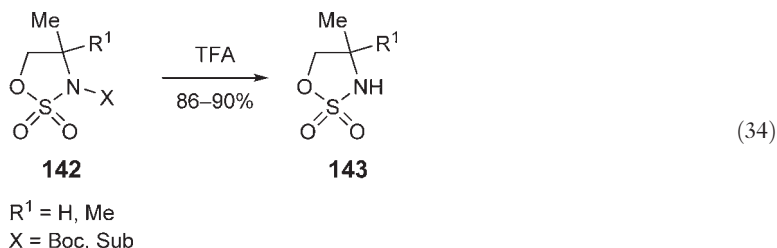
Sodium imidazolate (NaIm), sodium cyanide, and other reagents smoothly deacetylate the cyclic 2,3-sulfamidate **126** (Equation 32) <1997T5863>.



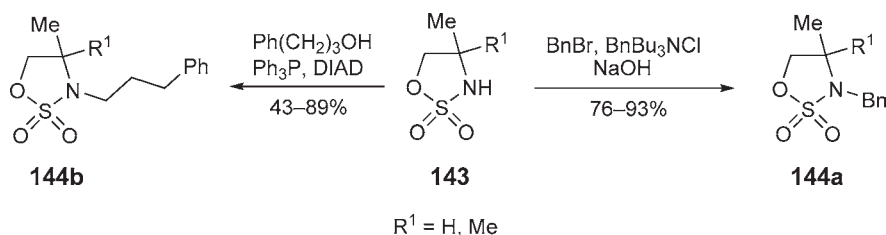
Removal of the *p*-methoxybenzoyl (PMB) group in sulfamide **124** was effected with ceric ammonium nitrate (Equation 33) <2001OL405>.



Deprotection of the *tert*-butoxycarbonyl- (BOC) and dibenzosuberyl- (Sub) substituted sulfamidates **142** was readily accomplished at room temperature with an excess of trifluoroacetic acid in CH₂Cl₂ (Equation 34) <2002JOC5164>.



Unprotected cyclic sulfamidates are relatively poor electrophiles compared to their N-substituted counterparts and quite resistant to nucleophilic attack. However, better results were obtained in a phase-transfer-catalyzed reaction: treatment of sulfamidate **143** with an excess of benzylbromide, BnBu_3NCl , and NaOH affords N-benzylated products **144a** in high yield. The Mitsunobu reaction proved even more useful for N-alkylation of 1,2,3-oxathiazole **143**: 3-phenylpropanol in the presence of diisopropylcarboxylate (DIAD) and triphenylphosphine yielded phenylpropyl-substituted sulfamidates **144b** (Scheme 25) <2002JOC5164>.



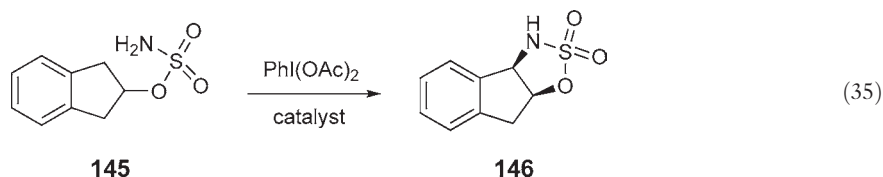
Scheme 25

6.01.9 Ring Syntheses from Acyclic Compounds Classified by Number of Ring Atoms Contributed by Each Component

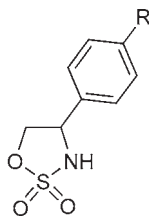
Much attention was given in CHEC-II(1996) <1996CHEC-II(4)409> to the synthesis of 1,2,3-dithiazoles. Cyclic and acyclic oximes were found to be important precursors to their preparation. The discovery of 4,5-dichloro-1,2,3-dithiazolium chloride (Appel salt **20**) from the reaction of commercial and cheap acetonitrile and disulfur dichloride gave strong impulse to the synthesis of various 1,2,3-dithiazole derivatives. Formation of the 1,2,3-oxathiazole ring involved almost exclusively the conversion of *vic*-aminohydroxyl compounds to the *S*-oxide derivatives.

6.01.9.1 Formation of One Bond Adjacent to a Heteroatom

Sulfamate indan-2-yl ester **145** is oxidized by iodobenzene diacetate to give condensed 1,2,3-oxathiazole di-*S*-oxides **146** (Equation 35). Various rhodium <2001JA6935, 2004HCA1607>, manganese(III) Schiff base <2005TL5403>, and ruthenium porphyrin <2002AGE3465> catalysts can be used for this transformation. Enantioselective intramolecular amidation is achieved with good yields.



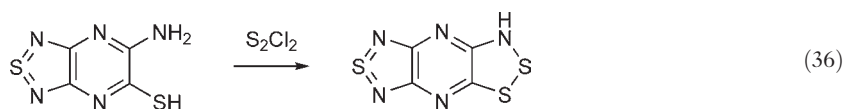
Monocyclic optically active cyclic sulfamidates **147** can also be obtained by this method <2005TL5403>.



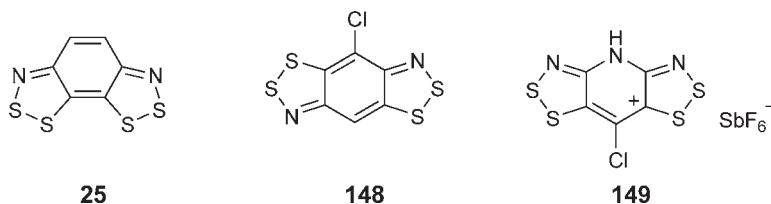
147: R = Cl, Me, OMe

6.01.9.2 Formation of Two Bonds: Four-Atom Fragment and Sulfur

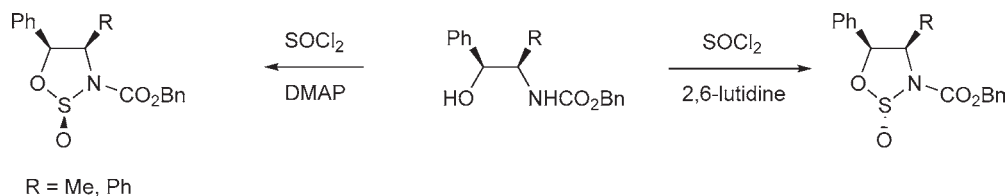
A series of condensed 1,2,3-dithiazoles were prepared by Oakley and co-workers by the reaction of *o*-aminoaromatic and heterocyclic thiols and S_2Cl_2 . This approach is preferable to the common Herz reaction which fails when applied to some aromatic amines, especially to phenylenediamines (Equation 36) <1999JA969>. In some cases, less accessible SCl_2 can be used <2001CJC1352>.



The great advantage of this method is the synthesis of bis(1,2,3-dithiazoles) from diaminodithiols <1997JA12136, 1999CM164, 2000JA7602>. Reduction of radical cations formed with Ph_3Sb leads to neutral heterocycles **148** and **25** as air-stable crystalline solids or to the cation **149**.

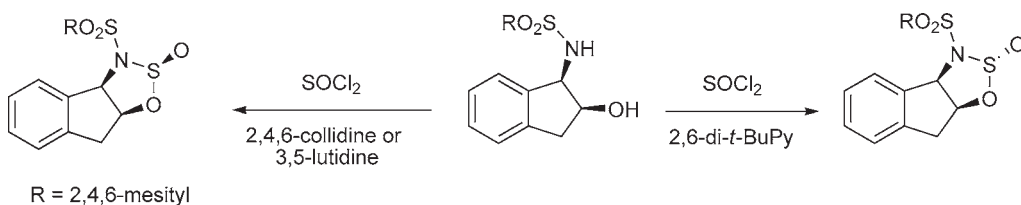


β -Aminoalcohols are extensively used for the synthesis of 1,2,3-oxathiazolidine mono- and di-*S*-oxides. The standard synthesis of cyclic sulfimidates, namely the reaction of aminoalcohol with $SOCl_2$ in the presence of an amine as a base, has been developed. Various bases have been employed: Et_3N <1996ACS1036, 1999J(P1)1421>, *N*-ethyl-diisopropylamine <1999TL3831>, pyridine <2002JOC5164>. Yields are moderate. The most effective reagent is a mixture of Et_3N and imidazole (yield 99%) <2000OL2595>. 1,2,3-Oxathiazolidine 2-oxides are usually obtained as a mixture of two stereoisomers at sulfur. Recently it was found that stereoselective cyclization of β -aminoalcohols can be achieved in the preparation of monocyclic (Scheme 26) <2003OL75, 2004JOC8533> and fused (Scheme 27) <2002JA7880, 2003AGE2032> sulfimidates.

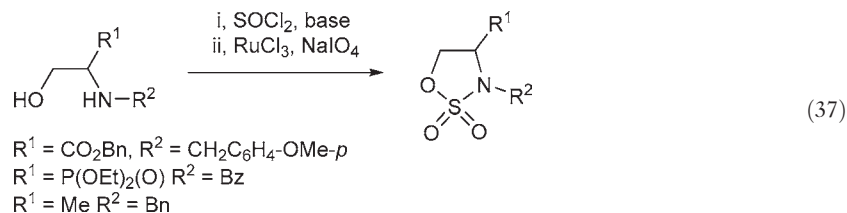


Scheme 26

Cyclic sulfimidates can be easily oxidized to the corresponding sulfamidates. The preparation of sulfamidates from *vic*-aminoalcohols can be achieved in one step without isolation of intermediate mono-*S*-oxides (Equation 37) <2001OL405, 2002TL1915, 2005TA1583>. Yields are from moderate to high.



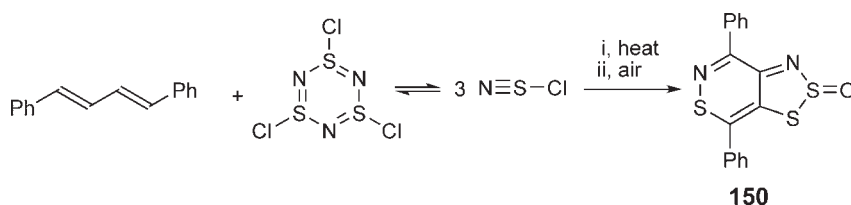
Scheme 27



The cyclic sulfamidates of the allosamine derivative **126** (see Scheme 18) are prepared by reaction with 1,1'-sulfuryl diimidazole [<1996CC127>](#), and this method seems to be promising for the synthesis of other sulfamidates.

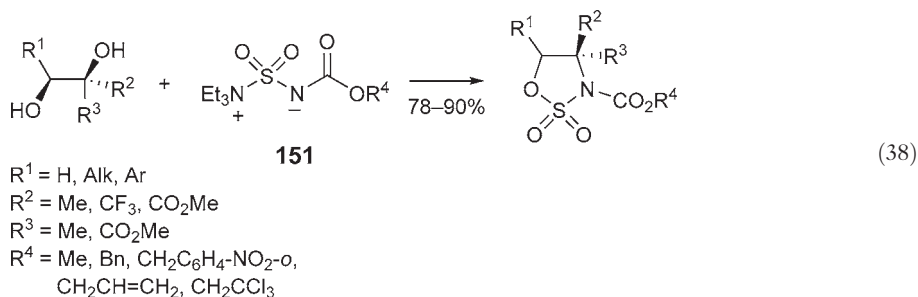
6.01.9.3 Formation of Two Bonds: [3+2] Atom Fragment by Cycloaddition

Dithiazole[4,5-*d*]thiazine *S*-oxide **150** is formed in low yield by the reaction of trithiazyl trichloride ($(\text{NSCl})_3$), which is in thermal equilibration with its monomer ($\text{N}\equiv\text{S}-\text{Cl}$), with 1,4-diphenyl-1,3-butadiene followed by oxidation with air (Scheme 28) [<1998CC1207>](#). The structure of product **150** was confirmed by X-ray crystallography. The mechanism of this transformation involves an initial 1,4-cycloaddition process.



Scheme 28

A recent development in the synthesis of cyclic sulfamidates is the reaction of *vic*-diols with methoxycarbonylsulfamoyltriethylammonium hydroxide inner salt **151** ($R^4 = \text{Me}$) (Burgess reagent) [<2002AGE834, 2004JA6234, 2004CC980, 2004CEJ5581, 2005JOC5721>](#). Nicolaou *et al.* found that various 1,2-diols react with Burgess and other similar reagents to give 1,2,3-oxathiazolidine di-*S*-oxides in high yield and as practically enantiopure compounds (ratio of enantiomers >98:2) (Equation 38).

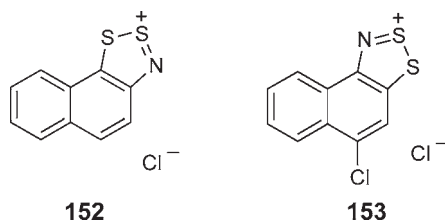


This methodology was successfully used for the synthesis of α -disposed sulfamidates of diverse carbohydrate templates (D-glucose, D-galactose, L-rhamnose) <2004JA6234, 2004CEJ5581>.

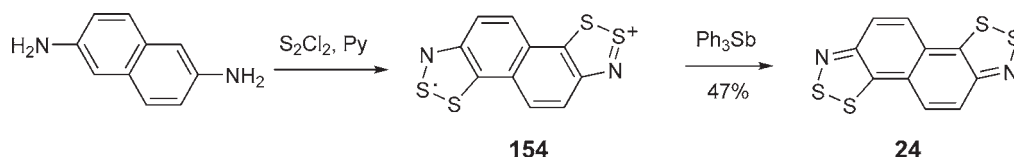
Fused and nonfused epoxides can be successfully transferred to corresponding cyclic sulfamidates by the reaction with Burgess reagent <2003SL1247>.

6.01.9.4 Formation of Two Bonds: [3+2] Atom Fragment by Other Processes

The traditional synthesis of 1,2,3-dithiazolium salts fused with aromatic or heteroaromatic rings by the reaction of aryl- or hetarylaminines and S_2Cl_2 (i.e., the Herz reaction: see <1984CHEC(6)897, 1996CHEC-II(4)409>) was continued by the Oakley group <1998CC1939, 2002CC2562, 2004CM1564, 2005IC1837>. In the case of 2-aminonaphthalene, the reaction leads exclusively to ring closure at the more reactive 1-position affording product **152** in good yield; chlorination of the naphthalene framework is not observed <2005IC1837>. By contrast, the analogous reaction of 1-aminonaphthalene with sulfur halides is inevitably accompanied by ring chlorination at the 4-position giving product **153**.

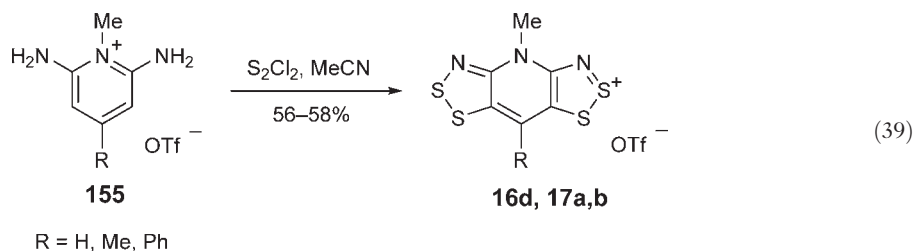


Further attention is given to the reaction of aryl- and heteryldiamines with S_2Cl_2 . In contrast with the complex reaction of 1,5-diaminonaphthalene, the condensation of 2,6-diaminonaphthalene with S_2Cl_2 in the presence of pyridine proceeds via electrophilic ring closure at both *peri*-positions to afford naphtho[2,1-*d*:6,5-*d'*]bis[1,2,3]dithiazole radical cation **154**, which is reduced by Ph_3Sb to neutral compound **24** (Scheme 29) <1998CC1939>. Chlorination of the remaining C-H positions does not occur.

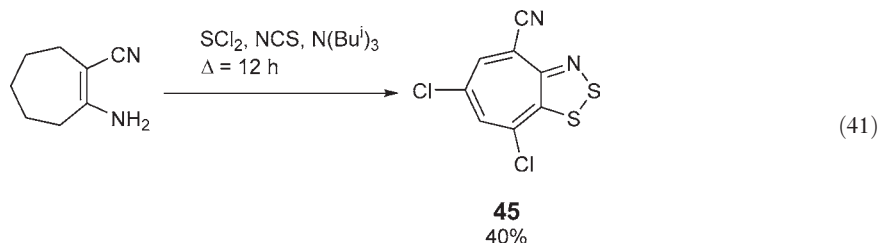
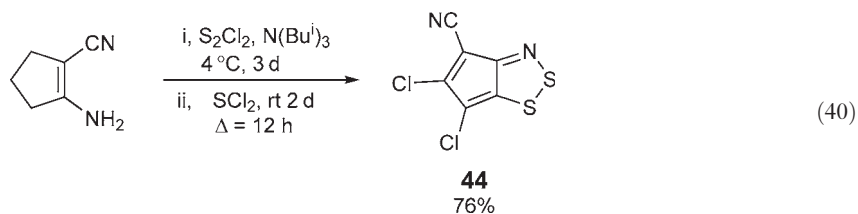


Scheme 29

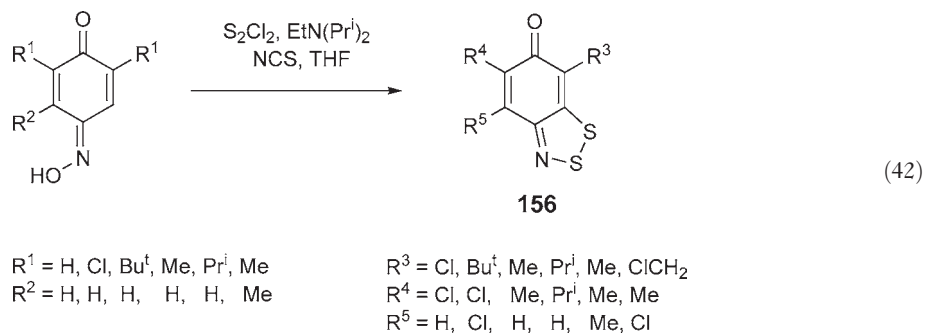
The double Herz condensation of *N*-methyl-2,6-diaminopyridinium triflate **155** and its 4-substituted derivatives with S_2Cl_2 at reflux in MeCN gives in moderate yields the appropriate bis[1,2,3]dithiazolopyridinium triflates **16d**, **17a**, and **17b** (Equation 39) <2002CC2562, 2004CM1564>. For R = H and R = Me, reaction times and reaction temperature must be minimized to prevent chlorination.



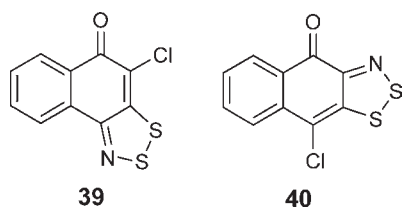
2-Aminocyclopent-1-ene- and 2-aminocyclohept-1-enecarbonitriles react with a mixture of S_2Cl_2 , SCl_2 , and Bu_3N to give chlorinated derivatives of cyclopenta- **44** and cyclohepta- **45** dithiazoles (Equations 40 and 41) <2005EJO5055>.



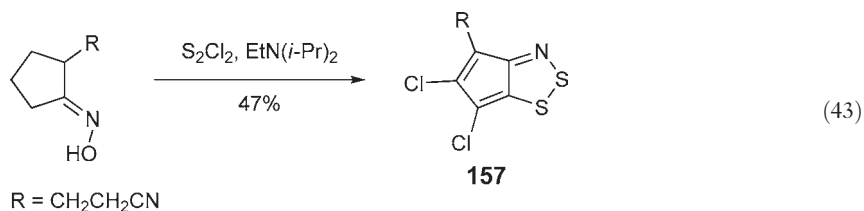
6*H*-1,2,3-Benzodithiazol-6-ones **156** are prepared from *p*-benzoquinone-4-oximes, S₂Cl₂, *N*-ethyldiisopropylamine, and *N*-chlorosuccinimide (NCS; Equation 42) <1998T223>. Some ring chlorination occurs, but 2,6-substituents are retained in the products except for a *tert*-butyl group, which is replaced by chlorine.



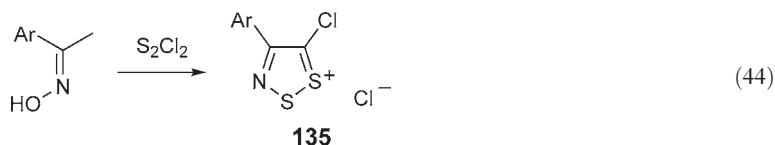
1,4-Naphthoquinone 4-oxime and 1,2-naphthoquinone 2-oxime similarly give the dithiazole derivatives **39** and **40** <1998T223>.



Cyclopenta-1,2,3-dithiazole system **157** is formed by the reaction of 2-substituted cyclopentanone oximes and S₂Cl₂ (Equation 43) <2001CC403>. Exhaustive chlorination accompanied this reaction as in the case of other cyclopentadithioles (see CHEC-II(1996) <1996CHEC-II(4)409>).



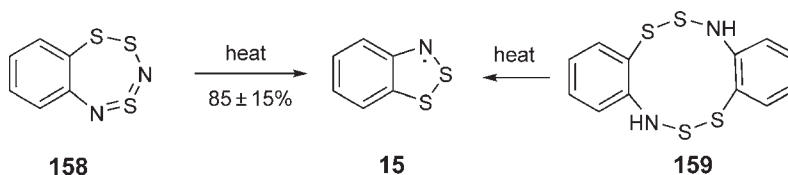
A possibility for the synthesis of the extensively studied 4,5-dichloro-1,2,3-dithiazolium chloride (Appel salt) **20** analogs was found in the reaction of acetophenone oxime and its 4-nitro derivative with S_2Cl_2 (Equation 44) <1997BSB605>.



6.01.10 Ring Syntheses by Transformation of Another Ring

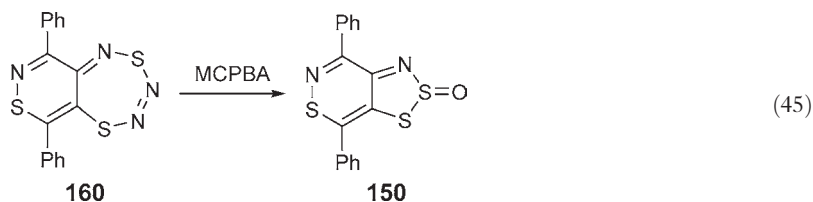
Conversion of polysulfur polynitrogen heterocycles such as pyrazolotrithiadiazepines or tetrathiatriazepines by heating, either neat or in solvents, gives 1,2,3-dithiazoles nonfused and condensed. In some cases, the formation of 1,2,3-oxathiazoles and 1,2,3-dithiazoles has been explained by ring rearrangements <1996CHEC-II(4)409>.

Various sulfur–nitrogen heterocycles can serve as a source of 1,2,3-dithiazolyl radicals. The thermolysis of benzo-trithiadiazepin **158** and dibenzotetrathiadiazecine **159** in hydrocarbons afforded the 1,2,3-benzodithiazolyl radical **15** (Scheme 30) <2003MC178>.

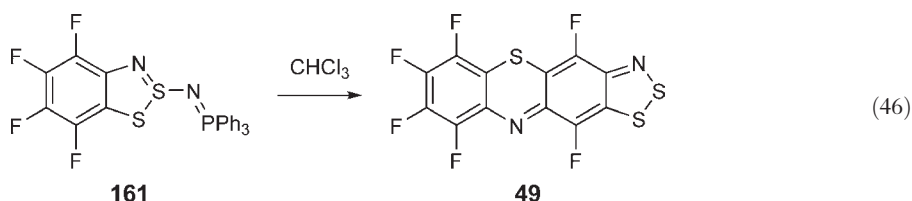


Scheme 30

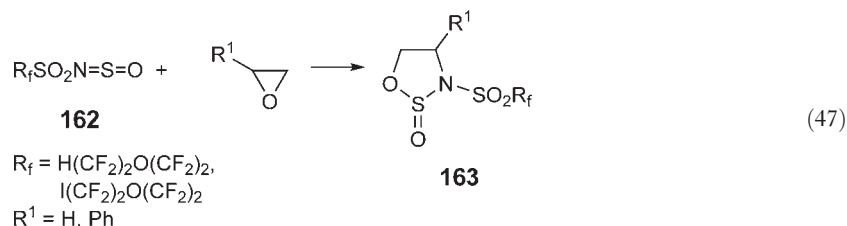
Condensed dithiatriazepine **160** was rapidly and cleanly converted into dithiazole-*S*-oxide **150** by oxidation with *m*-chloroperoxybenzoic acid (MCPBA) in dichloromethane at room temperature (Equation 45) <1998CC1207>.



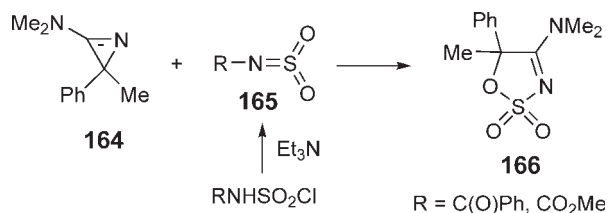
A mixture of several compounds, including eight new condensed 1,2,3-dithiazoles, as a rule in low yields, was prepared by the thermolysis of benzodithiazine and its perfluoro derivative <2005EJI4099>. The structure of all of them was proved by X-ray analysis. One of these, 1,2,3-dithiazole **49**, can be obtained by spontaneous transformation of phosphinimine **161** (Equation 46).



Reaction of *N*-sulfinyl derivative **162** with oxiranes in the presence of a catalyst such as Et_4NBr and $LiCl$ or $LiBr$ gave the cyclocondensation products – 1,2,3-oxathiazolidines **163** (Equation 47) <1996JFC49>.



Reaction of 2-dialkylaminoazirines **164** with *N*-sulfonylalkylamines **165**, prepared *in situ* from sulfamoylchlorides and triethylamine, gave 1,2,3-oxathiazoles **166** (Scheme 31) <1996J(P1)1629>.



Scheme 31

6.01.11 Synthesis of Particular Classes of Compounds and Critical Comparison of the Various Routes Available

The widely used and well-known synthesis of 1,2,3-dithiazolium salts <1996CHEC-II(4)409> by the treatment of aryl- and hetaryl amines with S_2Cl_2 (Herz reaction) has been extended by Oakley and co-workers. Special attention has been paid to the double Herz reaction of diamines (Scheme 29; Equation 39) which affords condensed radical cations, which are important precursors to neutral heterocyclic radicals and promising conductive molecular materials. Cyclic enamino-carbonitriles were used for the synthesis of 4-cyanochlorinated cyclopenta- and cyclohepta-dithiazoles (Equations 40 and 41). Preparation of fused 1,2,3-dithiazoles from cyclic oximes has been extended for benzodithiazol-6-ones and cyclopentadithiazoles (Equations 42 and 43). An important feature in this field is the synthesis of Appel salt analogs by the reaction of acetophenone oxime and its 4-nitroderivative with S_2Cl_2 (Equation 44).

O-Mercaptohetaryl amines were converted to condensed dithiazoles: this approach is successful in some cases where Herz reaction fails. Bis(1,2,3-dithiazoles) can be obtained by this method which is one of the most important developments in the chemistry of dithiazoles.

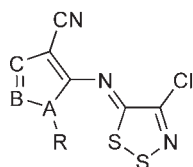
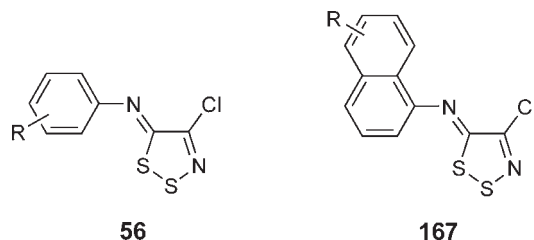
The traditional synthesis of cyclic sulfimides from β -aminoalcohols and SOCl_2 in the presence of amine as a base has been developed further to the preparation of the enantiopure monocyclic as well fused sulfimides (Schemes 26 and 27). 1,2,3-Oxathiazolidine mono-*S*-oxides are readily oxidized to corresponding sulfamides by RuCl_3 and NaIO_4 , and the synthesis of sulfamides can be performed in a one-pot procedure from *vic*-aminoalcohols without isolation of intermediate sulfimides (Equation 37). The reaction of sulfamate esters **145** with $\text{PhI}(\text{OAc})_2$ and various catalysts proved to be a reliable method for the enantioselective preparation of cyclic sulfamides **146** (Equation 35).

A very recent and important development by Nicolaou *et al.* in the synthesis of 1,2,3-oxathiazolidines is the use of the Burgess reagent in the reaction with a number of 1,2-diols to afford enantiopure compounds (Equation 38). New Burgess-type reagents were prepared and successfully involved in the reaction with *vic*-diols. α -Disposed sulfamides of diverse carbohydrate templates were obtained. Oxiranes were found to be important precursors for the 1,2,3-oxathiazoles mono- and di-*S*-oxides by treatment with *N*-sulfinylalkanesulfonylamides and Burgess reagent, respectively.

6.01.12 Important Compounds and Application

N-Arylimino-1,2,3-dithiazoles **56** showed significant antibacterial activity against Gram-positive bacteria <1996BML529, 1998EJM149>. The unsubstituted aromatic compound **56** ($\text{R} = \text{H}$) and its *o*-methoxy derivative appear to be the most active in the series tested.

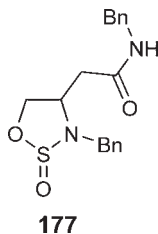
For the four fungi tested, the minimum fungicidal concentrations of 1,2,3-dithiazols **56** and **167** were no more than two times greater than the minimum inhibitory concentration (MIC) showing a good and significant fungicidal activity <1998EJM149>. It seems to be evident that the aromatic portion of the molecule does not interfere with the antimicrobial activity, which probably depends on the 1,2,3-dithiazole ring acting as a potent inhibitor of some enzymes like serine proteases. The *in vitro* antifungal activity of compounds **168–176** was determined against yeasts (*Candida albicans* ATCC 10231, *Candida utilis* ATCC 9950, *Candida lipolytica* CBS 6124, *Saccharomyces cerevisiae* ATCC 26785, *Pichia stipitis* CBS 5776) and moulds (*Aspergillus niger* L32 and *Penicillium* sp.) <2002BMC449>. All the derivatives showed significant antifungal activity against the yeasts tested. The compounds **172–176** exhibit the highest antifungal activity showing good MIC values in the range 10–50 $\mu\text{g m}^{-1}$. Particularly, the efficacy of these products against the moulds can be compared with that showed by amphotericin B used as a reference compound for inhibition against fungi.



- 168:** R = Me; A = B = N; C = CH
169: R = Ph; A = B = N; C = CH
170: R = Bn; A = B = N; C = CH
171: R = Ph(CH₂)₂; A = B = N; C = CH
172: R = Ph(CH₂)₃; A = B = N; C = CH
173: R = CMe₃; A = B = N; C = CH
174: R = Ph(CH₂)₂; A = C = N; B = CH
175: R = 2,4-Cl₂C₆H₃(CH₂)₂; A = B = N; C = CH
176: R = o-xylyl; A = B = C = N

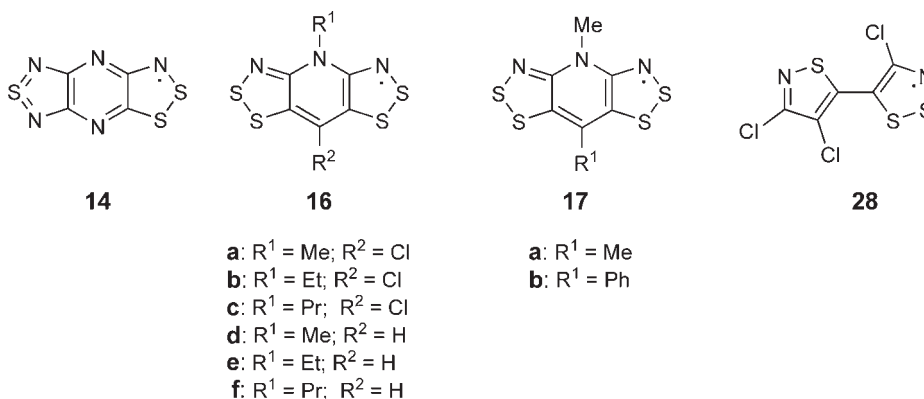
The antiproliferative activity of 1,2,3-dithiazoles **168–176** has been tested *in vitro* on human myeloid leukemia K562 and L1210 murine leukemia cell lines and compared to the antiproliferative effects of the natural product distamycin A. All the imines **168–176** are active at concentration ranging from 3 to 10 μM and they retain antiproliferative activities comparable to those exhibited by distamycin A.

1,2,3-Oxathiazolidine-2-oxide **177** was found to show significant antimicrobial activity against *Staphylococcus aureus* P-209 <1999KFZ141>.



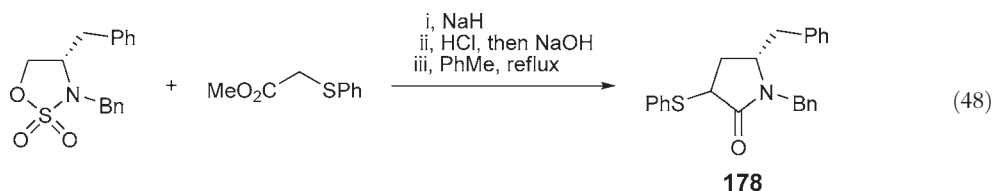
The heterocyclic π -donor benzobis(1,2,3-dithiazole) **25** was proposed as a donor for charge-transfer (CT) conductors <1999CM164>.

As appealing alternative to conventional synthetic conductors, which require CT between two components as a means of generating charge carriers, neutral heterocyclic radicals, including derivatives of 1,2,3-dithiazolyls, are considered as potential conductive molecular materials, since a stack of π -radicals functions like an array of atoms in an elemental metal. A few examples of dithiazolyl radicals have been synthesized by Oakley and co-workers, such as thiadiazolo-dithiazolopyrazinyl **14** <1999JA969>, chlorobis(dithiazolo)pyridinyl **16a–c** <2002CC1872>, perchloro-isothiazolyl-1,2,3-dithiazolyl **28** <2002CC1872>, bis[1,2,3]dithiazolopyridinyls **16d–f** <2002CC2562>, and substituted bis[1,2,3]dithiazolopyridinyls **17** <2004CM1564>.

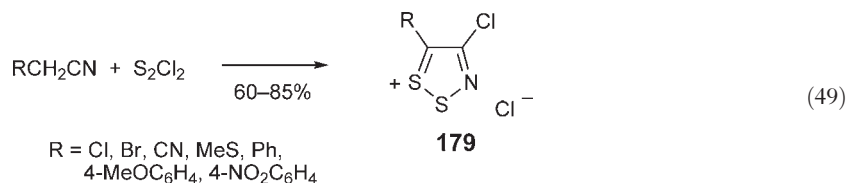


6.01.13 Further Developments

Structurally representative series of 1,2-cyclic sulfamidates react with enolates derived from methyl α -phenylthioacetate to give 5-substituted α -phenylthiolactams <2006OBC1868>. With the enantiomerically pure 1,2-cyclic sulfamidates, this reaction proceeds with no detectable loss of stereochemical integrity affording product **178** (Equation 48).



A series of monosubstituted acetonitriles were treated with disulfur dichloride at room temperature in dichloromethane to afford 5-substituted-4-chloro-1,2,3-dithiazolium chlorides **179** <2005MI346> (Equation 49). Several of the dithiazolium chlorides **179** were converted into corresponding 4-substituted-3-chloro-1,2,5-thiadiazoles by treatment with aqueous ammonia.



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Biographical Sketch



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6.02

1,3-Oxa/thia-2-azoles

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6.02.1	Introduction	38
6.02.2	Theoretical Methods	38
6.02.3	Experimental Structural Methods	40
6.02.3.1	X-Ray Diffraction	40
6.02.3.2	¹ H NMR Spectroscopy	42
6.02.3.3	¹³ C and ¹⁴ N NMR Spectroscopy	43
6.02.3.4	IR, UV, and Photoelectron Spectroscopy	43
6.02.3.5	ESR Spectroscopy	44
6.02.3.6	Cyclic Voltammetry	45
6.02.3.7	Mass Spectrometry	45
6.02.4	Thermodynamic Aspects	46
6.02.5	Reactivity of Fully Conjugated Rings	46
6.02.5.1	Thermal and Photochemical Formally Unimolecular Reactions	46
6.02.5.2	Electrophilic Attack at Ring Nitrogen and Carbon	47
6.02.5.3	Electrophilic Attack at Ring Sulfur	47
6.02.5.4	Nucleophilic Attack at Ring Carbon	47
6.02.5.5	Nucleophilic Attack at Ring Sulfur	47
6.02.5.6	Reactions Involving Radicals, Electron-Deficient Species, Reducing Agents, and at Surfaces	47
6.02.5.7	Cyclic Transition State Reactions with a Second Molecule	48
6.02.6	Reactivity of Nonconjugated Rings	48
6.02.6.1	Reactions of Hydrogenated Derivatives of Fully Conjugated Ring Compounds	48
6.02.7	Reactivity of Substituents Attached to Ring Carbon Atoms	50
6.02.8	Reactivity of Substituents Attached to Ring Heteroatoms	50
6.02.9	Ring Syntheses from Acyclic Compounds Classified by Number of Ring Atoms Contributed by Each Component	51
6.02.9.1	Formation of One Bond between Two Heteroatoms	51
6.02.9.2	Formation of One Bond Adjacent to a Heteroatom	51
6.02.9.3	Formation of Two Bonds from Four-Atom Fragment and Nitrogen	51
6.02.9.4	Formation of Two Bonds: [3+2] Atom Fragment by Cycloaddition	53
6.02.9.5	Formation of Two Bonds: [3+2] Atom Fragment by Other Processes	54
6.02.10	Ring Syntheses by Transformation of Another Ring	55
6.02.11	Synthesis of Particular Classes of Compounds and Critical Comparison of the Various Routes Available	56
6.02.12	Important Compounds and Application	56
6.02.13	Further Developments	57
	References	57

6.02.1 Introduction

Research in the reviewed period 1995–2005 has covered more the chemistry of 1,3,2-dithiazoles and less the chemistry of 1,3,2-dioxazoles. 1,3,2-Oxathiazoles and their derivatives were not investigated in this period. Much attention has been paid to the neutral 1,3,2-dithiazolyl radicals including their synthesis, theoretical and structural study, and application. Special attention was given to their magnetic properties and conductivity. 1,3,2-Benzodithiazole *S*-oxides were of interest as enantiomeric compounds and intermediates for the preparation of enantiopure amines and alcohols.

The main structural types of the azoles are given in **Figure 1**. Most of them are experimentally available and stable at room temperature. The basic parent structures are shown in row **A** and named as 1,3,2-dithiazoles, 1,3,2-dithiazolidines, 1,3,2-dioxazoles, and 1,3,2-dioxazolidines. Row **B** represents the known 1,3,2-dithiazolium and dithiazolidinium cations and 1,3,2-dithiazolyl and 1,3,2-dithiazolidinyl radicals, respectively.

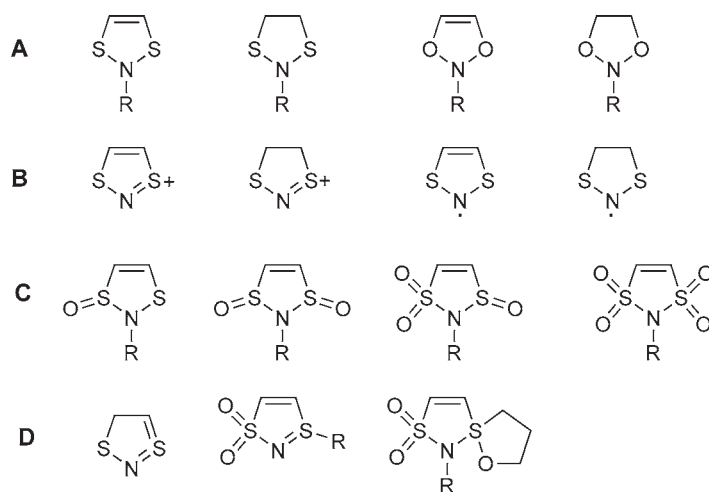


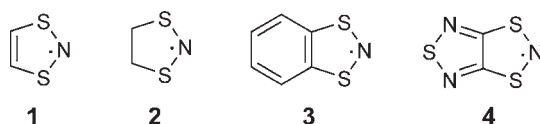
Figure 1 Known 1,3-oxa/thia-2-azoles.

Mono-, di-, tri-, and tetra-*S*-oxides have been reported for 1,3,2-dithiazoles (row **C**). The new structural types shown in row **D** are characterized by tetravalent ring sulfur. Most of these structural types are known as benzofused derivatives.

6.02.2 Theoretical Methods

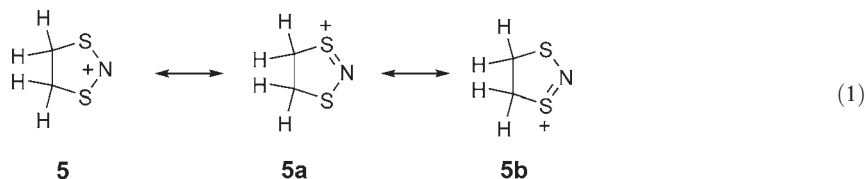
Calculations of electronic and geometrical structures of 1,3,2-dithiazolyl cations and corresponding radicals performed in the decade 1980–90 were reviewed in CHEC-II(1996) <1996CHEC-II(4)433> and showed that radicals are more stable than cations. Special attention was given to the association of radicals to dimers. The stabilization energy of the 1,3,2-dioxazolyl cations was found to be lower than that of the radicals, and therefore cations are more stable.

The electronic structures and isotopic hyperfine coupling constants of a series of neutral 1,3,2-dithiazolyl radicals **1–4** were investigated by means of density functional theory (DFT) <1996MRC913>.

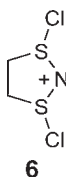


The calculated geometries for the molecules **2** and **3** are not in as good agreement with the experimental parameters as the nitrogen-free closed shell sulfur heterocycles. The error may be partly due to the fact that experimental molecular geometries are studied in the crystal rather than in the gas phase. Isotopic hyperfine coupling constants (hfcc's) were calculated through Fermi contact analysis, and most of them are close to the experimental values <1996MRC913>.

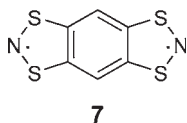
The structure of cation **5** was calculated by *ab initio* methods (RHF 16-31G*) <1996JCD1997>. Confidence in the results is supported by the good agreement between the calculated and experimentally observed geometries of the related 1,3,2-dithiazolium cations. The calculated S–N distance in dithiazole **5** (1.575 Å) is slightly longer than that found in ClSNSCl⁺ (1.528 Å) containing more electronegative substituents. The calculated charges on sulfur (0.70) and nitrogen (−0.42) and the S–N bond order (1.7) indicate that **5** may be represented by valence-bond structures **5a** and **5b** with some polarization of charge onto nitrogen and increase in positive charge on sulfur (Equation 1).



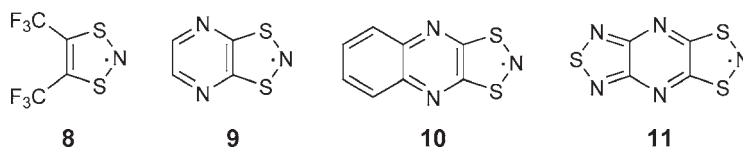
The calculated geometry of cation **5** is puckered with an S–C–C–S dihedral angle of 14.2° similar to that found (27.4°) experimentally for cation **6**. The planar structure of dithiazole **5** is calculated to be only 1.6 kJ mol^{−1} higher in energy than the puckered ground state. The two equivalent puckered forms of cation **5** are probably in rapid equilibrium with a very low (less than 2 kJ mol^{−1}) energy barrier.



Ab initio molecular orbital calculations of diradical **7** have been performed <1997JA2633>. Strong mixing occurs between the b₁ singly occupied molecular orbital (SOMO) of the dithiazole rings with π -systems of benzene, and the extent of intramolecular exchange interaction between the two unpaired spins is a primary concern. The benzo-dithiazole system in diradical **7** is not formally disjoint as in-phase and out-of-phase combination of radical SOMO's mix, to different extents, with orbitals of the bridging benzene ring. In order to probe the energetic differences between the triplet ³B_{2u} and diradical singlet ¹B_{2u} states, calculations have been performed with cep-31+g** basis set at both the Hartree–Fock and single-point configuration interaction (CI) level. These showed that despite the formal nondegeneracy of the b_{1u} and b_{3g} orbitals, the two spin states are remarkably close in energy, with the singlet lying slightly (ca. 0.5 kcal mol^{−1}) above the triplet.

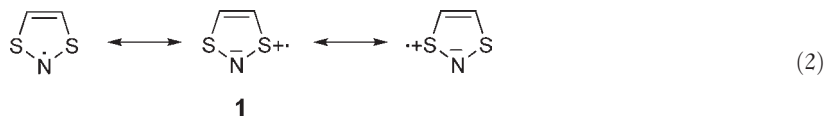


Molecular parameters of seven radical 1,3,2-dithiazolyls **1**, **3**, **4**, **8–11** were systematically investigated by *ab initio* and DFT methods <2001PCA7615>. Statistical analysis of the differences between the calculated and experimental values for radical **8** indicates that both methods overestimate most distances; nevertheless, the unrestricted Hartree–Fock (UHF) performs better than the UB3LY1 method for compatible basis sets. The mean deviation of distances decreases from 1.0 pm for 3-21G(d) to 0.2 pm for 6-31G(2df) basis sets in the UHF method. The mean difference in the calculated and experimental interatomic angles shows low basis set sensitivity.



Fermi constants were calculated for all these compounds using the UHF and UB3LYP methods. The analysis shows that the UHF method generally performs poorly, while all DFT calculations give hfcc close to the experimental values <2001PCA7615>.

The distribution of the total spin density in radicals was calculated using the UB3LYP16-31g* method. In systems **1**, **3**, **4**, and **8–11**, the spin density is localized on the –S–N–S– fragment with minor spin distribution onto the π -framework, presumably through a spin polarization mechanism. For instance, in 1,3,2-dithiazolyl **1**, virtually all positive spin density is localized on the –S–N–S– array due to the two polar resonance structures shown in Equation (2). A very similar spin distribution is observed in ring-fused derivatives **3**, **4** and **9–11** <2001PCA7615>.



DFT calculations on the 1,3,2-dithiazolyl radical **4** using the molecular geometry determined from the single crystal studies indicate that the unpaired electron resides in a π^* orbital which is delocalized over the entire molecule <2001JMC1992>. However, the spin density distribution is asymmetric with 84% based on the SNS fragment and just 22% on the NSN fragment. The slight excess of spin density on the heteroatoms, nitrogen and sulfur, is compensated by a small (3%) negative spin density at each carbon. A comparison of the theoretical and calculated spin densities at nitrogen indicates an excellent agreement and provides a firm basis for interpreting the magnetic behavior of 1,3,2-dithiazolyl radical **4**. Importantly, the delocalization of π -spin density suggests that intermolecular interactions between both dithiazolyl and thiadiazolyl rings may be important in propagating the magnetic exchange interactions.

From the calculation of atomic spin magnetic moments, it was found that the spontaneous magnetic moments for radical **4** mainly come from the nitrogen atom and both sulfur atoms of the 1,2,3-dithiazole ring, and heteroatoms of the thiadiazole ring give little contribution to the magnetism <2004MI204>.

1,3,5-Trithia-2,4,6-triazapentalenyl radical **4** exhibits a large first-order magnetic and structural phase transition between a paramagnetic high-temperature phase which can be regarded from *ab initio* calculations as a kind of Peierls transition of the quasi-one-dimensional system that has a half-filled conduction band <2004MI689>.

An accurate full-potential density functional method is used to study the mechanism of the origin of magnetism and the magnetic interactions in the 1:1 complex of 1,3,5-trithia-2,4,6-triazapentalenyl **4** and bis(hexafluoroacetylacetonato) copper(II) (Cu(hfac)₂). The results revealed that the spontaneous magnetic moments for the **4**–Cu(hfac)₂ mainly come from the Cu and N1 atoms of the dithiazole **4**, and the oxygen and other nitrogen and sulfur atoms also contribute to the magnetism. In complex **4**–Cu(hfac)₂, there would be ferromagnetic interactions between the Cu(II) ion and the N1 atom of **4**, and there exist antiferromagnetic interactions between the intramolecular organic ligands <2005MI320>.

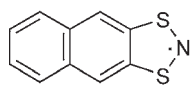
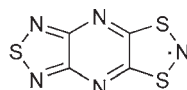
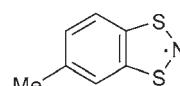
The gyromagnetic tensors of 1,3,2-dithiazolyl radicals **3** and **4** were computed by the coupled-perturbed Kohn–Sham hybrid density functional techniques and were found to be in very good agreement with those determined experimentally <2005CPL382>.

6.02.3 Experimental Structural Methods

The structures of compounds containing a 1,3,2-dithiazole ring (1,3,2-dithiazolidines, 1,3,2-dithiazoles, 1,3,2-dithiazolium cations and radicals) were extensively investigated by X-ray and electron diffraction between 1980 and 1990 <1996CHEC-II(4)433>. Nuclear magnetic resonance (NMR) spectroscopy was found to be very effective for elucidation of the structure of 1,3,2-dioxazoles and 1,3,2-dithiazoles. Electron spin resonance (ESR) spectra of the 1,3,2-dithiazolyl radicals gave important information on their structures.

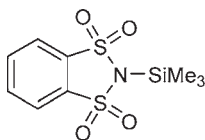
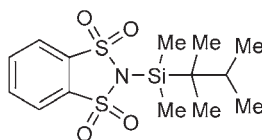
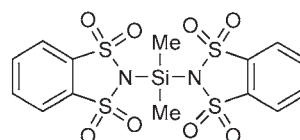
6.02.3.1 X-Ray Diffraction

The crystal structure of naphthalene-**12** and quinoxaline-(**10**)-1,3,2-dithiazolyls consists of discrete molecules of undimerized radicals <1997CC873>. The internal bond lengths of the two heterocyclic rings (mean d (S–N) 1.645 and 1.649 Å, mean d (C–S) 1.748 and 1.736 Å) are typical of those seen in simple dimers. There is no dimerization of these radicals, and the closest intermolecular S··S contacts are well outside the van der Waals separation of 3.6 Å. But, discrete molecules of dithiazolyl **12** are packed in a herringbone fashion, while those of dithiazole **10** adopt a slipped p–p stack motif. A spaced π -stack motif was found in other dithiazolyl radicals such as thiadiazolodithiazolopyrazinyl **13** <1998JA352> and methylbenzodithiazolyl **14** <2000JMC2001>.

**12****13****14**

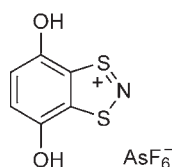
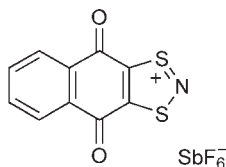
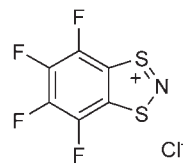
The structure of diradical benzo-bis(1,3,2-dithiazolyl) **7** consists of discrete (undimerized) molecules which lie on a center of inversion; the molecules are planar with the largest deviation from the mean plane being 0.014(3) Å. The molecules form strongly slipped stacks along the χ -direction [\[1997JA2633\]](#). The structure of pyrazinodithiazolyl **9** determined at various (95 and 293 K) temperatures consists of slipped stacks of π -dimers [\[2004JA8256\]](#).

The crystal structure of three *N*-silyl derivatives of dithiazole tetraoxides **15–17** has been determined [\[1998ZFA147\]](#). All molecules display unusually long bonds between the trigonal planar nitrogen and the tetrahedrally coordinated silicon atoms (**15**: 182.6, **16**: 184.1, and **17**: 177.8 and 180.5 pm). The nitrogen–silicon bond lengthening is mainly induced by the π -acceptor character of the SO_2 group.

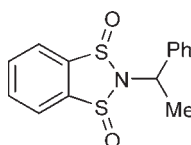
**15****16****17**

X-Ray crystallography has shown that benzofused 1,3,2-dithiazolium **18** consists of discrete planar cations hydrogen-bonded to distorted octahedral AsF_6^- anions [\[2005CC2366\]](#). The shortest hydrogen bond (2.1 Å) is between the hydroxyl proton and the anion, which causes a lengthening of the As–F bond to which it makes closest contact. This suggests that strong hydrogen bonding is responsible for the stability of the potentially reactive substituent group. Notably, there are no N–H contacts.

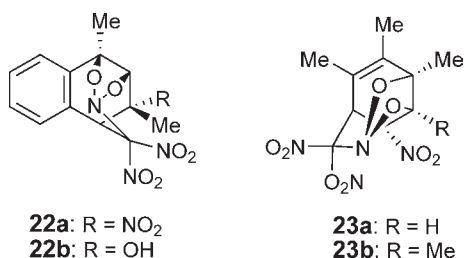
There is a weak hydrogen bonding in naphtha-1,3,2-dithiazolium **19** between SbF_6^- and aromatic protons, but in contrast to cation **18** there are cation–anion S–F contacts [\[2005CC2366\]](#). The structure of tetrafluorobenzo-1,3,2-dithiazolyl chloride **20** has been determined by X-ray crystallography [\[2004PS979\]](#).

**18****19****20**

The absolute configuration of the tricoordinated sulfur atom in the series of oxides was determined via X-ray crystallographic analysis of one of the diastereomeric phenylethyl-1,3,2-benzodithiazole 1,3-dioxide **21** [\[1996ENA13\]](#).

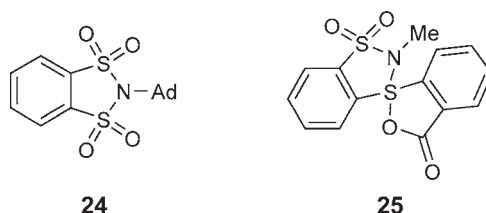
**21**

The structures of four 1,3,2-dioxazoles **22** and **23** have been determined by X-ray crystallography [\[1995ACS482, 1996ACS29, 1996ACS735\]](#). The nitrogen atom of the dioxazole moiety is clearly trigonal pyramidal, and bond length differences are similar to those observed earlier for analogous heterocyclic cage structures.



An exceptionally long N–C bond (1.532 Å) has been found in the structure **24** at the adamantyl bridgehead carbon atom as opposed to the corresponding distance of only 1.48 Å in the *N*-methyl derivative <1999AXC2080>.

The molecular structure of spiro-1,2,3-dithiazole derivative **25** shows a slightly distorted trigonal bipyramidal geometry about the sulfur(IV) atom and similar to other spiro-sulfanes <1995CC1069>. In spiro compound **25**, the S(IV)–N distances (1.79 and 1.75 Å) are near to the sum of the covalent radii (1.74 Å), but show, however, considerable elongation compared to the corresponding distances in the analogous diarylacetyloxycarbonylamino-spirosulfanes (1.71–1.74 Å). S(IV)–O interatomic distances in compound **25** (2.01 and 2.05 Å) are considerably shorter than in the same molecules (2.15 and 2.25 Å) and approach to the hypervalent S(IV)–O bond lengths (1.84 and 1.87 Å).



6.02.3.2 ¹H NMR Spectroscopy

The hydroxyl cycloadduct **22b** was identified by a consideration of its NMR spectra <1995ACS482>. Comparison of the ¹H and ¹³C NMR data for the hydroxyl adduct **22b** and the nitro cycloadduct **22a**, whose structure was established by single X-ray analysis, supports this assignment.

The ¹H NMR spectra of 1,3,2-dithiazoline cations **5** and its methyl derivatives **26–29** are given in Figure 2 <1996JCD1997>. They are consistent with planar ring structures or very rapid equilibrium between the two puckered structures. Resonances attributable to cations **5** and **26–29** are at higher field than those of the corresponding alkene, consistent with higher shielding in the alkane and the effect of the positive charge. The ¹H spectrum of the dithiazole **5** has a singlet at –70 °C with a linewidth similar to that at room temperature showing equivalence of the protons on the NMR timescale down to –70 °C.

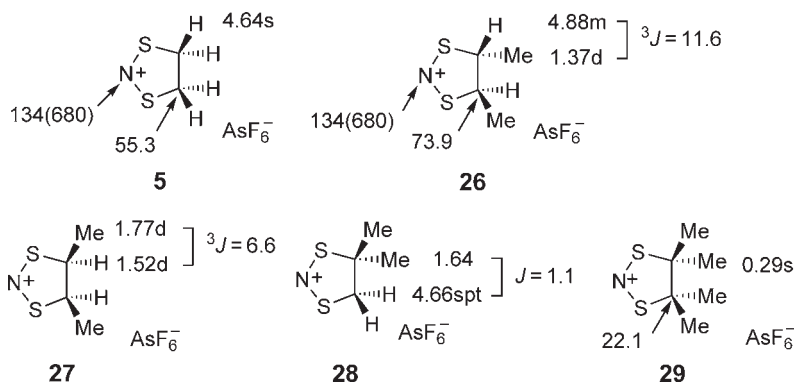
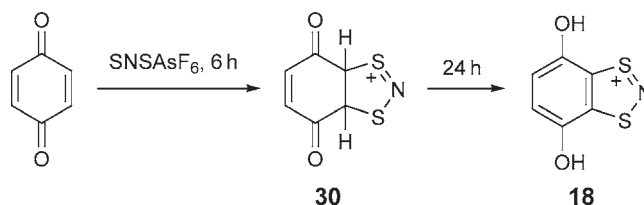


Figure 2 NMR spectra of 1,3,2-dithiazolidine cations.

6.02.3.3 ^{13}C and ^{14}N NMR Spectroscopy

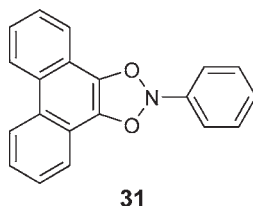
The reaction of 1,4-benzoquinone with SNSAsF_6^- was monitored by ^{13}C NMR spectroscopy <2005CC2366>. The coupled ^{13}C NMR spectrum immediately after mixing the reagents displayed resonances centered at δ 140.7 ppm (J_{CH} 176 Hz) and δ 74.6 ppm (J_{CH} 156 Hz) that are assigned to ethylenic and bridgehead carbons of cation **30**, respectively (Scheme 1). Furthermore, a singlet down-field at δ 186.0 ppm, typical of a carbonyl carbon, was also detected. After 6 h, a new signal emerged in the coupled ^{13}C NMR spectrum at δ 119.5 ppm (J_{CH} 167 Hz) which was assigned to the aromatic C–H in **18**, and two singlets at δ 154.8 ppm and δ 146.5 ppm attributed to the C–S and C–O of cation **18**.



Scheme 1

Unequivocal evidence was also provided by the *in situ* ^{14}N NMR spectrum which showed a broad resonance at δ 122.6 ppm ($\Delta\nu_{1/2} = 1042$ Hz) indicative of cation **30**, and after 6 h only one signal was observed at δ –7.4 ppm ($\Delta\nu_{1/2} = 540$ Hz), attributed to the dithiazolium cation **18** <2005CC2366>.

The structure assigned for phenantro-1,3,2-dioxazole **31** was based on the ^{13}C NMR spectrum which reveals the presence of two signals at δ 142.45 and 142.47 ppm assignable for dioxazole carbons <2002SC2779>.

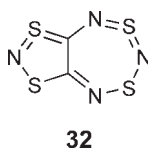


^{13}C and ^{14}N NMR spectra of 1,3,2-dithiazolidine cations **2**, **28**, and **29** are in full agreement with their ^1H NMR spectra (see Figure 2) and are likely to be diagnostic for derivatives of this family of heterocycles <1996JCD1997>.

6.02.3.4 IR, UV, and Photoelectron Spectroscopy

The photoelectron spectrum of benzo-1,3,2-dithiazolyl radical **3** is characterized by a single low-energy band corresponding to ionization from $4b_1$ SOMO radical to the closed shell cation <1997JA2633>. Other high-energy ionization events would give rise to both singlet and triplet cations, but there is no discernible splitting in any of the higher-energy processes. The second, third, and fourth ionization potential values of radical **3** are well separated and can thus be easily assigned to the $2a_2$, $3b_1$, and $1a_2$ orbitals.

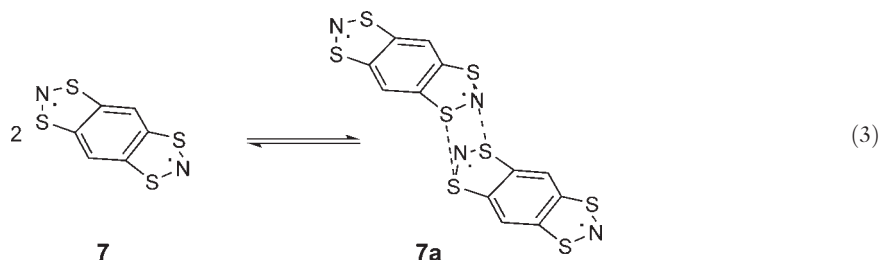
The solution infrared (IR) spectrum of condensed dithiazole **32** is very simple with only four absorptions above 600 cm^{-1} at 1488, 895, 885, and 625 cm^{-1} , and the ultraviolet (UV) spectrum has long wavelength maxima at 322 (log ϵ 3.35) and 492 nm (3.31), suggesting a highly symmetrical and delocalized structure <2000ARK228>.



IR spectra obtained for cations **2** and **26–29** were in good agreement with calculated values, and are assigned as follows: $\nu_{\text{ring vibrations}}$ 1234–1240, 1202–1209, 921–923 cm^{-1} ; $\nu_{\text{asym}}(\text{S–N})$ 886–898 cm^{-1} ; $\nu_{\text{sym}}(\text{S–N})$ 788–791 cm^{-1} , $\delta(\text{SNS})$ 547–552 cm^{-1} <1996JCD997>.

6.02.3.5 ESR Spectroscopy

The ESR spectrum of diradical **7** is both solvent and sample dependent <1997JA2633>. When diradical **7** is dissolved in methylene chloride at room temperature, the ESR spectrum is relatively well resolved as a triplet of triplets (tot) pattern with $a_{\text{N}} = 11.3 \text{ mT}$, $a_{\text{H}} = 0.68 \text{ mT}$, and $g = 2.0067$. The overall intensity of the ESR signal is weak relative to the concentration of the sample. It was concluded that the strong tot signals originate from a partially associated species such as **7a** (Equation 3). In toluene, solvation effects favor free diradical **7** over the open-ended dimer **7a**, and the appearance of the spectrum, that is, a broad quintet, is consistent with that expected for a single diradical for which exchange coupling is much greater than hyperfine coupling a_{N} .

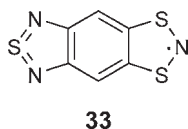


Values of the g -factors and isotropic hyperfine coupling constants a_{N} for 1,3,2-dithiazolyl radicals are provided in Table 1.

Table 1 ESR g -values, hyperfine coupling constants, and half-wave potentials of 1,3,2-dithiazolyl radicals

Structure	g -value	$a_{\text{N}}(\text{MT})$	$a_{\text{H}}(\text{MT})$	$E_{1/2}^{(0/+)}(\text{V})$	$E_{\text{pc}}^{(0/-)}(\text{V})$	Reference
1	2.0071	1.066				1998JA352
3	2.0069	1.101		0.15	-1.2^{a}	1998JA352
4	2.0061	1.115		0.65		2004JA8256
7	2.0069	1.127	0.057, 0.045	0.16	-1.3^{a}	2004JA8256
9	2.0071	1.126		0.53	-0.88^{a}	2004JA8256
10	2.0065	1.089	0.065, 0.023	0.62	-0.73^{a}	1998JA352
12	2.0067	1.140	0.097	0.27	-1.08^{a}	2004JA8256
13	2.0072	0.959		1.06	-0.06	2004JA8256
33	2.0072	1.098	0.16	0.46	-0.76	2004JA8256

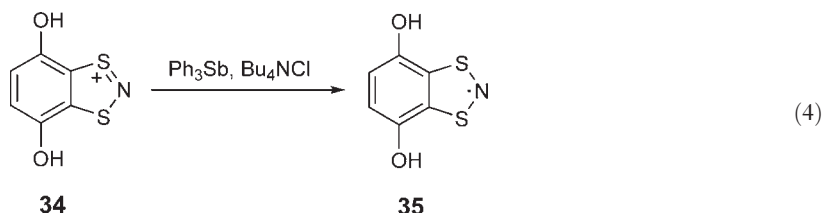
^aIrreversible.



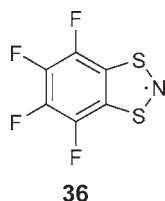
All the radicals show the expected features for 1,3,2-dithiazolyl radicals, that is, a large coupling to the nitrogen within the heterocyclic ring. Taken together, however, the spectra reveal a progressive and significant decrease in this internal a_{N} value along the series **10**, **12**, and **13**. Coupled to this trend is a larger a_{N} value in the pyrazine ring of compound **13** (relative to benzopyrazine **10**) <1998JA352>.

Delocalization of spin density from the 1,3,2-dithiazolyl ring onto the adjacent ring leads to a slight decrease in the value of a_N , and hyperfine coupling to the peripheral benzene protons, or pyrazine/dithiazole nitrogen, is observed. Additional but smaller coupling to the protons (or nitrogens) of the third ring can also be extracted by spectral simulations.

The *in situ* reduction of cation **34** with Ph_3Sb and NBu_4Cl caused it to exhibit a strong and persistent ESR signal ($g = 2.0046$, 1:1:1 triplet due to the nitrogen hyperfine splitting, $a_N = 1.073 \text{ mT}$) (Equation 4). This signal was tentatively assigned to the corresponding 7π 1,3,2-dithiazolyl radical **35** <2005CC2366>.

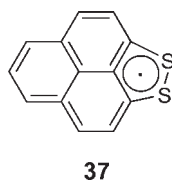


The radical **36** was generated *in situ* by reduction of the salt **20** with Ag powder in dichloromethane <2004PS979>. The ESR spectrum of the radical **36** exhibits a triplet of triplets due to coupling of the unpaired electron to one ^{14}N nuclei and two ^{19}F nuclei ($g = 2.0044$, $a_N = 11.0 \text{ G}$, $a_F = 1.5 \text{ G}$).



6.02.3.6 Cyclic Voltammetry

The solution oxidation potentials for radicals **3** and **7** show that both are powerful electron donors, although not as strong as the neutral dithiopentalenyl radical **37** <1997JA2633>.



For quantitative observations, cyclic voltammetric (CV) measurements were performed over the triad of oxidation states, that is, anion, radical, and cation, available to these systems. The half-wave potentials for reduction and oxidation are summarized in Table 1. For all DTA radicals, oxidation is essentially reversible. Electrochemical reduction of radicals **10** and **12** is, however, almost irreversible, as in the case of radicals **3**, **7**, **10**, and **12**. Only for dithiazoles **13** and **33** <2004JA8256> are both the oxidation and reduction steps reversible.

The radical **33** can be considered as an analog of several previously reported 1,3,2-dithiazolyls, but electrochemically the nearest match is with dithiazolyl **9** <2004JA8256>.

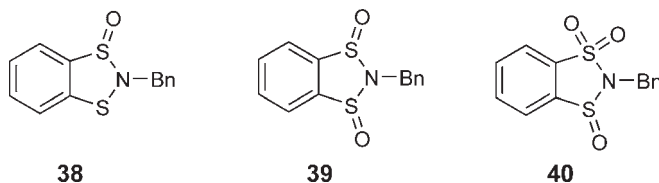
6.02.3.7 Mass Spectrometry

Mass spectrometry was useful to prove the structure of 1,3,2-dioxazole **31** by giving a prominent ion peak for M^+ at m/z 299 (100%) <2002SC2779>.

6.02.4 Thermodynamic Aspects

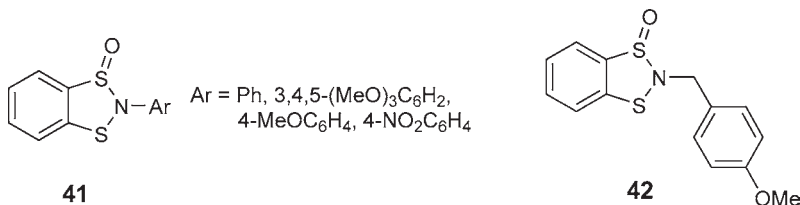
Thermodynamic aspects of 1,3-(oxa/thia)-2-azoles were not covered in CHEC-II(1996).

The optical isomers of the 2-benzyl-1,3,2-benzodithiazole 1-oxide **38**, 1,3-dioxide **39**, and 1,1,3-trioxide **40** have been isolated by chiral liquid chromatography <1996ENA13>. The rate of racemization is much higher for the monooxide as compared to the dioxide and trioxide. The rate of enantiomerization was found to clearly depend on the solvent, for example, enantiomerization of **38** proceeded ca. 10 times faster in hexane than in methanol. This has been attributed to the difference in $\Delta S^\ddagger$ found in the respective solvents <1999JP21587>. A first-order rate constant of $8.65 \times 10^{-5} \text{ s}^{-1}$ was calculated for the racemization of the 1-oxide **38** in acetonitrile at 21 °C. This corresponds to rate constants for the forward and reverse reactions in the enantiomerization process of $4.32 \times 10^{-5} \text{ s}^{-1}$ and a Gibbs' free activation energy of only 96.5 kJ mol^{-1} separating the enantiomers. The presence of a chiral high-performance liquid chromatography (HPLC) stationary phase (Whelk-01) did not affect the rate of enantiomerization to any significant extent.



Free energies of activation for the enantiomerization of a series of *N*-aryl-1,3,2-benzodithiazole 1-oxides **41** have been determined by dynamic high-performance liquid chromatography (DHPLC) on a chiral stationary phase <1999JOC1483>. From a comparison of experimental and computer-simulated chromatograms, the barriers to stereoinversion at sulfur were found to be around 80 kJ mol^{-1} and relatively insensitive to effects from substituents in the *N*-aryl group.

The racemate of 1,3,2-benzodithiazole 1-oxide **42** was separated by supercritical fluid chromatography on the (*R,R*)-Whelk-O1 column with supercritical carbon dioxide containing 20% methanol as a mobile phase. Peak areas of enantiomers prior to and after the separation, used for the calculation of the enantiomerization barrier, were detected by computer-assisted peak deconvolution of peak clusters registered on chromatograms using computer software <2002CH1334>.



6.02.5 Reactivity of Fully Conjugated Rings

The thermolysis and photolysis of mesoionic phenyl-1,3,2-oxathiazolones were extensively investigated during the period 1980–1990 <1996CHEC-II(4)433>. Electrophilic and nucleophilic attack at ring atoms of 1,3,2-dithiazoles (nitrogen, carbon, and sulfur) occurs quite rarely and little attention was paid to it in CHEC-II(1996). A large part of the section was devoted to the transformation of 1,3,2-dithiazolium radicals to corresponding cations and vice versa.

6.02.5.1 Thermal and Photochemical Formally Unimolecular Reactions

No significant developments have been reported in this area since the publication of CHEC-II(1996) <1996CHEC-II(4)433>.

6.02.5.2 Electrophilic Attack at Ring Nitrogen and Carbon

No significant developments have been reported in this area since the publication of CHEC-II(1996) <1996CHEC-II(4)433>.

6.02.5.3 Electrophilic Attack at Ring Sulfur

No significant developments have been reported in this area since the publication of CHEC-II(1996) <1996CHEC-II(4)433>.

6.02.5.4 Nucleophilic Attack at Ring Carbon

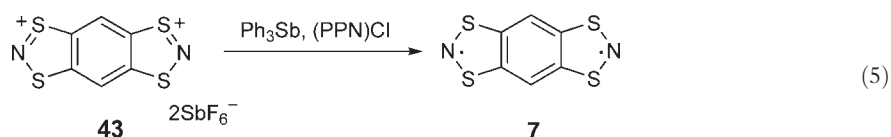
No significant developments have been reported in this area since the publication of CHEC-II(1996) <1996CHEC-II(4)433>.

6.02.5.5 Nucleophilic Attack at Ring Sulfur

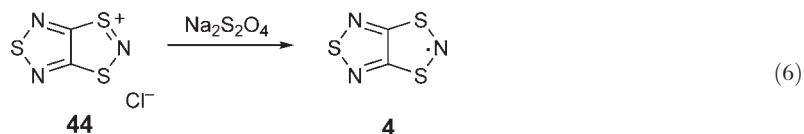
No significant developments have been reported in this area since the publication of CHEC-II(1996) <1996CHEC-II(4)433>.

6.02.5.6 Reactions Involving Radicals, Electron-Deficient Species, Reducing Agents, and at Surfaces

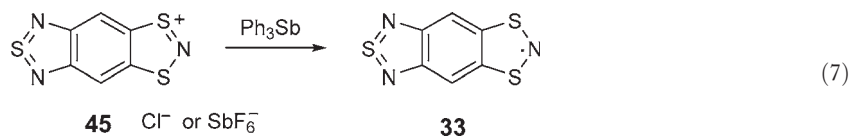
1,3,2-Dithiazolium cations can be readily reduced to the stable mono- and diradicals. Reaction of the disalt **43** could be effected, on a milligram scale, by electrolysis in an acetonitrile solution at 50 μ A onto Pt wire cathode <1997JA2633>. Larger quantities could be obtained by chemical reduction. Attempts to reduce cation **43** directly with silver or zinc powder were unsuccessful. The most successful approach involved the use of triphenylantimony as reducing agent and bis(triphenylphosphine)iminium chloride ((PPN)Cl; Equation (5)). The product obtained (**7**) is remarkably stable in the solid state, in air, and in organic solutions.



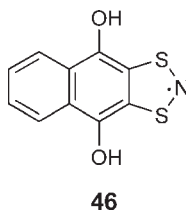
Subsequent reduction of dithiazolium cation **44** with $\text{Na}_2\text{S}_2\text{O}_4$ produced radical **4** in moderate yield (30%) (Equation 6) <2001JMC1992>.



The dithiazolium chloride **45** could be reduced directly with triphenylantimony to the radical **33** (Equation 7). This latter step gave poor yields (<15%) regardless of the choice of solvent (acetonitrile or liquid sulfur dioxide), reductant (Ag, Zn, Ph_3Sb), or starting salt (chloride or hexafluoroantimonate). Radical **33** was best liberated by reduction of the crude salt with triphenylantimony <2004JA8256>. Once isolated, however, radical **33** is relatively air stable in the solid state.



The 1,3,2-dithiazolium radicals **35**, **36**, and **46** generated *in situ* by reduction of corresponding salts with Ph_3Sb and tetrabutylammonium chloride in liquid sulfur dioxide <2005CC2366>, silver powder in dichloromethane <2004PS979>, and Bu_4NCl and $\text{Na}_2\text{S}_2\text{O}_4$ in SO_2 <2005CC2366>, respectively.



6.02.5.7 Cyclic Transition State Reactions with a Second Molecule

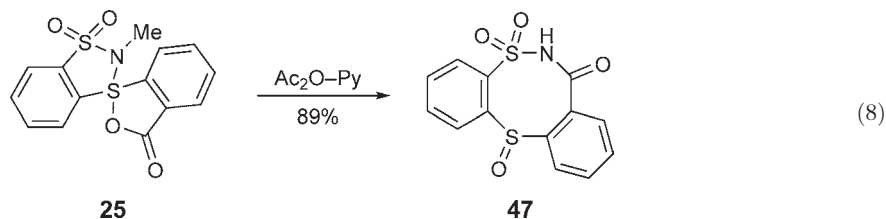
No significant developments have been reported in this area since the publication of CHEC-II(1996) <1996CHEC-II(4)433>.

6.02.6 Reactivity of Nonconjugated Rings

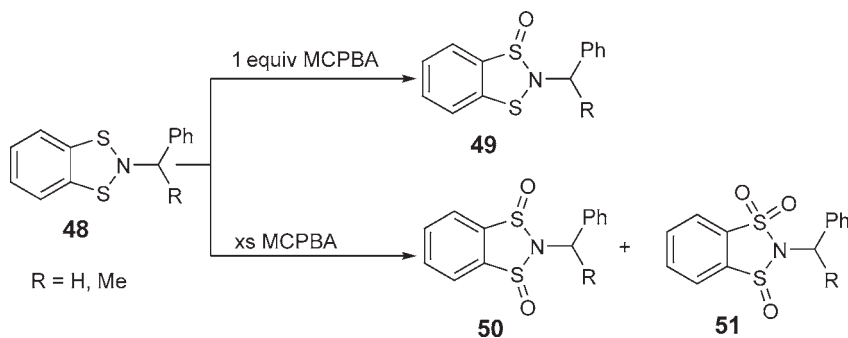
Reactions of hydrogenated derivatives including fluorination of disulfonimides and oxidation 1,3,2-dioxazolidines was an important subject considered in CHEC-II(1996) <1996CHEC-II(4)433>.

6.02.6.1 Reactions of Hydrogenated Derivatives of Fully Conjugated Ring Compounds

Spiro- λ^4 -sulfane **25** was found to transform into cyclic dibenzodithiazocine **47** by refluxing in the mixture of acetic anhydride and pyridine for 3 h (Equation 8) <1995CC1069>. This rearrangement can also be carried out in pyridine, acetic acid, Ac_2O - AcOH , pyridine-*p*-dimethylaminopyridine mixed solvent systems.

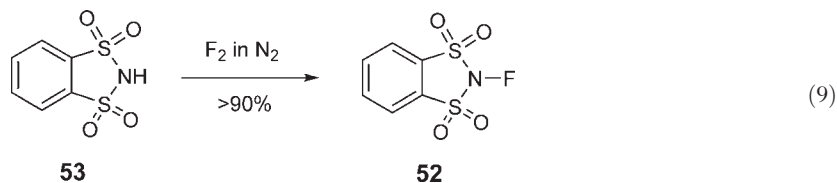


A series of 1,3,2-benzodithiazole *S*-oxides have been prepared by oxidation of 2-benzyl- and 2-phenylethyl-1,3,2-benzodithiazoles **48** <1996ENA13>. One equivalent of MCPBA leads to mono-*S*-oxide **49**, whereas oxidation with an excess of MCPBA yielded a mixture of dioxide **50** and trioxide **51**, which were isolated as optically pure isomers by chiral liquid chromatography (Scheme 2).

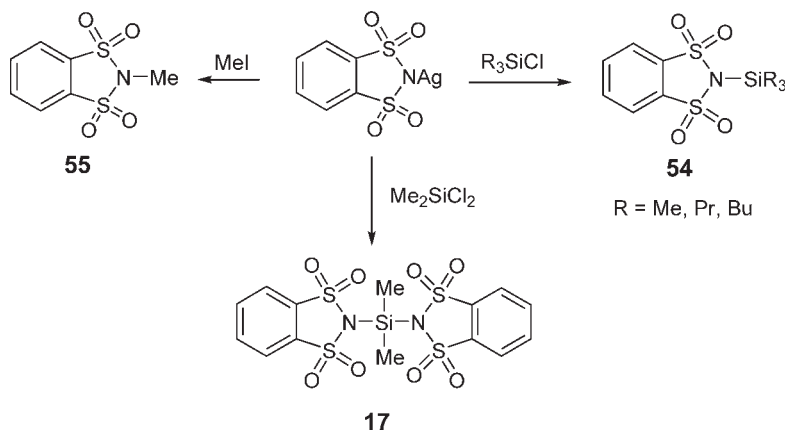


Scheme 2

N-Fluoro-*o*-benzenedisulfonamide **52** was prepared in better than 90% yield by passing 10% molecular fluorine in nitrogen through a solution of *o*-benzenedisulfonamide **53** in a chloroform–CFCl₃ mixture (Equation 9) <1995JOC4730>. The *N*-fluoro derivative **52**, which is perfectly stable at room temperature, is a reagent of choice for the electrophilic fluorination of nucleophilic substrates, carbanions, enolates, enols, and silyl enol esters.

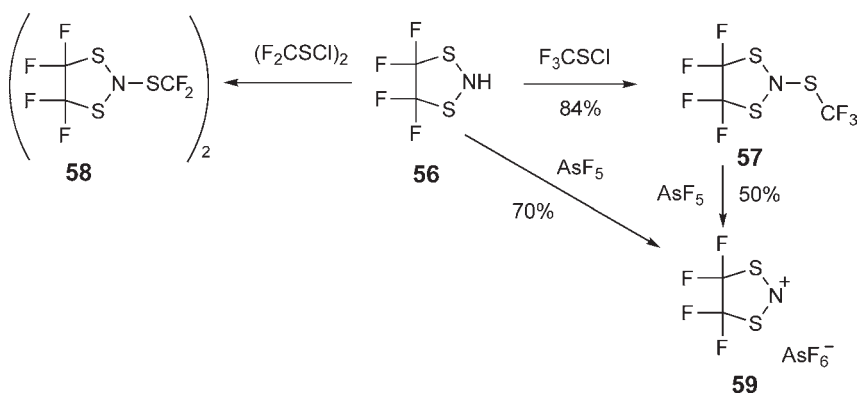


The silver salt of sulfonamide **53** can be effectively silylated with trialkylchlorosilanes to *N*-substituted derivatives **54** <1998ZFA147> or alkylated with methyl iodide giving *N*-methyl benzenedisulfonamide **55** <1995PS91>. Bis(benzenedisulfonamide) silane **17** was obtained from dichlorodimethylsilane (Scheme 3).



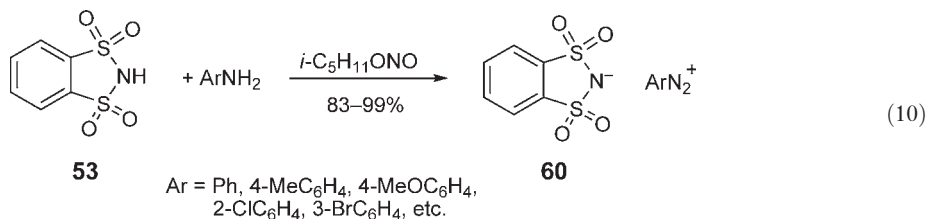
Scheme 3

The perfluorodisulfonamide **56** has been sulfinated with CF₃SCl or (F₂CSCl)₂ to form compound **57** or **58** <1995CB429>, both of which are stable at ambient temperatures and decompose near 100 °C. Oxidation of *N*-sulfinated derivative **57** with AsF₅ yields salt **59** and by-products, which suggests formation of the corresponding cation radical as an intermediate in this reaction. Pure salt **59** is more cleanly accessible by the reaction of 1,3,2-dithiazolidine **56** with AsF₅ (Scheme 4).



Scheme 4

o-Benzenesulfonamide **53** is used in the preparation of arenediazonium *o*-benzenesulfonamides **60** in the dry state by diazotization of aromatic amines with *i*-pentyl nitrite in acetic or formic acid (Equation 10) <1998S1171>. Unlike most diazonium salts in the dry state, salts **60** are very stable.



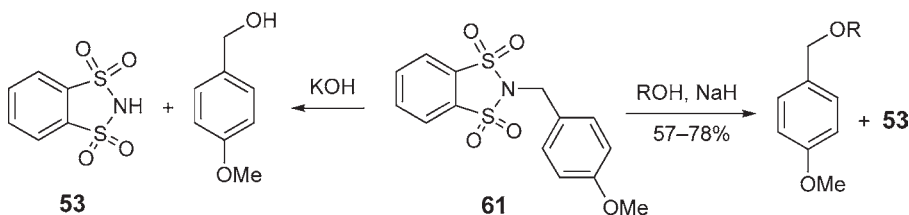
6.02.7 Reactivity of Substituents Attached to Ring Carbon Atoms

Reactivity of the 1,2,5-thiadiazole ring as a substituent to the 1,3,2-dithiazole ring led to unexpected ring transformations that were reported in CHEC-II(1996) <1996CHEC-II(4)433>. No significant developments have been reported in this area since the publication of CHEC-II(1996).

6.02.8 Reactivity of Substituents Attached to Ring Heteroatoms

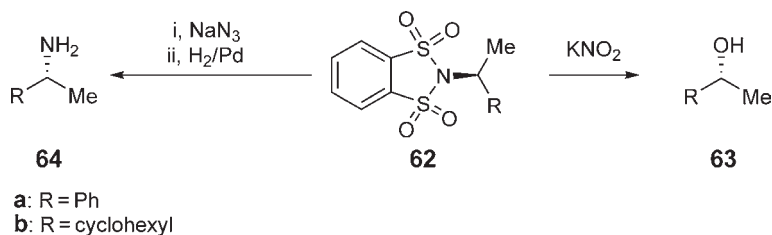
Synthesis of unsubstituted derivatives by hydrolysis of N-substituted 1,3,2-dioxazolidines has been the main subject for investigation in this area <1996CHEC-II(4)433>.

Substituted *o*-benzenesulfonamide **61** was found to be a good source for the synthesis of 4-methoxybenzyl esters by the reaction with alcohols and phenols in the presence of sodium hydride at room temperature <1998TL1799>. Treatment of cyclic sulfonamide **61** with aqueous KOH in dimethylformamide (DMF) yielded 4-methoxybenzyl alcohol together with benzenesulfonamide **53** (Scheme 5).



Scheme 5

N,N-1,2-Benzene **62** and naphthalene disulfonamides were found to be new leaving groups for the stereoselective nucleophilic substitution of amines <1998TA681, 1999TA2627>. Nucleophilic attack of KNO₂ afforded the respective alcohols **63** with 83–90% inversion of configuration. Reaction with sodium azide gave the corresponding azides which were reduced to the inverted amines **64** (70–98.5% inversion) (Scheme 6).



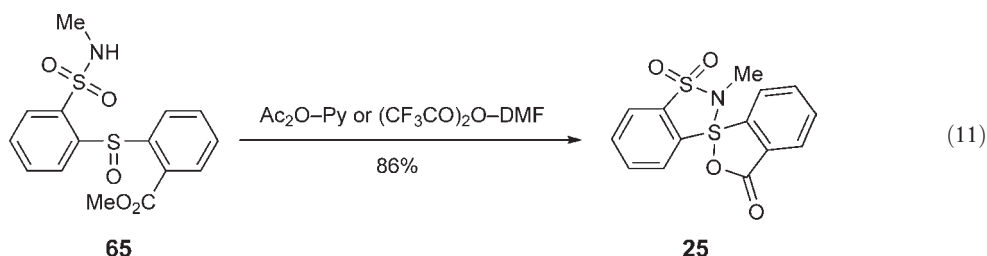
Scheme 6

6.02.9 Ring Syntheses from Acyclic Compounds Classified by Number of Ring Atoms Contributed by Each Component

Acyclic compounds were found to be important precursors for 1,3-oxa/thia-2-azole preparation <1996CHEC-II(4)433>. 1,3,2-Dioxazolidines were synthesized by cyclization of *N,N*-dialkoxyamines and *N*-chloro-*N*-alkoxyamines. The formation of the 1,3,2-oxathiazolidine ring has been performed by nitroization of thiomandelic and thiolactic acids. Aromatic *o*-bis(sulfonylchlorides) and aliphatic ethane 1,2-disulfonyl dichlorides are easily cyclized by reaction with nitrogen-containing substrates: trimethylsilyl azide, bis(trimethylsilyl)sulfur diimide, *N,N'*-bis(trimethylsilyl)amines, and *N,N'*-dichlorosulfonamides. 1,3,2-Dithiazolium cations are accessible by the cycloaddition of dithionitronium (S_2N^+) or dichlorodithionitronium ($ClSN_2SCl^+$) cations to a multiple bond. Most of these processes were developed in the 1990s.

6.02.9.1 Formation of One Bond between Two Heteroatoms

Spiro(benzoxathiazolonbenzothiazole) **25** was easily prepared by intramolecular cyclization of sulfonamide **65** with acetic anhydride–pyridine at 20 °C or with trifluoroacetic anhydride–DMF at 0–5 °C <1995CC1069>. The yield may reach 86% (Equation 11).

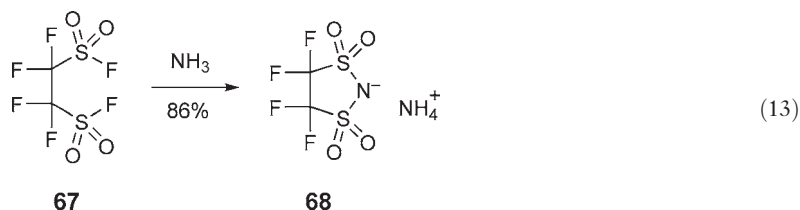
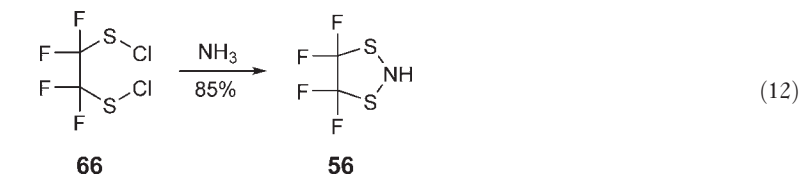


6.02.9.2 Formation of One Bond Adjacent to a Heteroatom

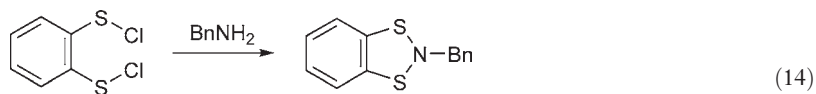
No significant developments have been reported in this area since the publication of CHEC-II(1996) <1996CHEC-2(4)433>.

6.02.9.3 Formation of Two Bonds from Four-Atom Fragment and Nitrogen

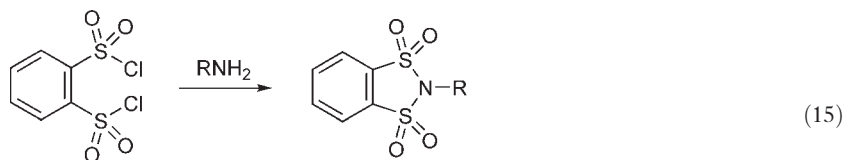
Tetrafluoro-1,2-ethanedisulfonyl dichloride **66** with ammonia easily undergoes a cyclization reaction to give tetrafluoro-1,3,2-dithiazolidine **56** in high yield (Equation 12) <1995CB429>. Structurally similar bis(sulfonylfluoride) **67** affords tetrafluoro-1,3,2-dithiazolidine ammonium salt **68** in practically the same yield under the same conditions with an excess of ammonia (Equation 13) <1997ZNB359>.



Benzene-(disulfonyl) dichloride and bis(sulfonylchlorides) are readily transformed to the 1,3,2-benzodithiazole **49** (R = H) and their tetraoxides **53** and **61** by reaction with ammonia <1998OPP107> or aliphatic amines (Equations 14 and 15) <1996ENA13, 1998TL1799>.



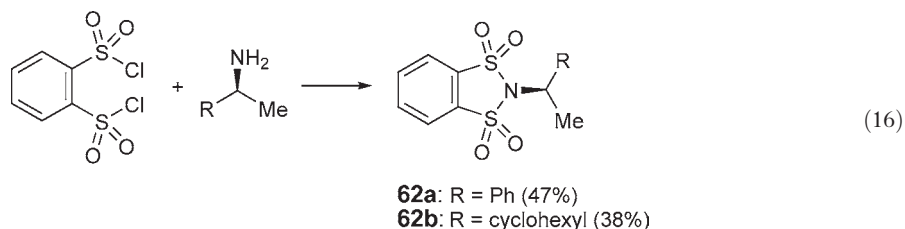
49: R = H



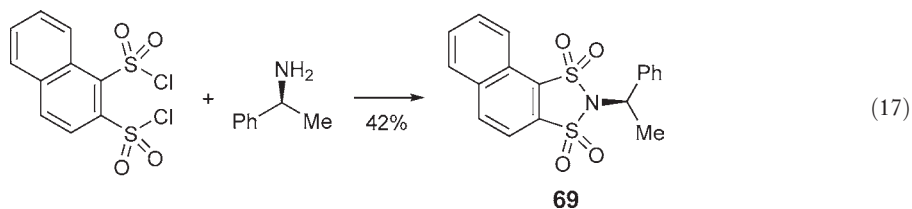
53: R = H

61: R = CH₂C₆H₄-4-OMe

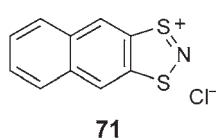
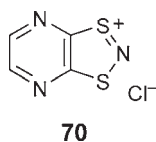
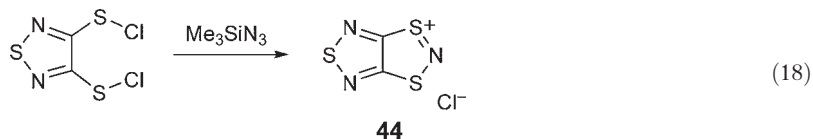
The reaction of chiral amines with benzene-bis(sulfonylchloride) is stereoselective, and fused disulfonylimides **62** retain configuration (Equation 16) <1998TA681>.



Similar results were obtained for naphthalene disulfonylimide derivative **69** (Equation 17) <1999TA2627>.

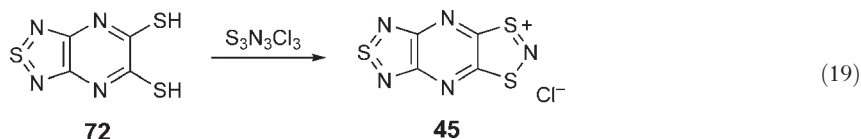


A range of condensed 1,3,2-dithiazolium mono- and bis-salts **43–45**, **70**, and **71** are formed in the ring-closure reaction of *o*-bis(sulfenylchloride)heteroarenes with trimethylsilyl azide (Equation 18) <1997JA2633, 2001JMC1992, 2004JA8256, 1998JA352>.

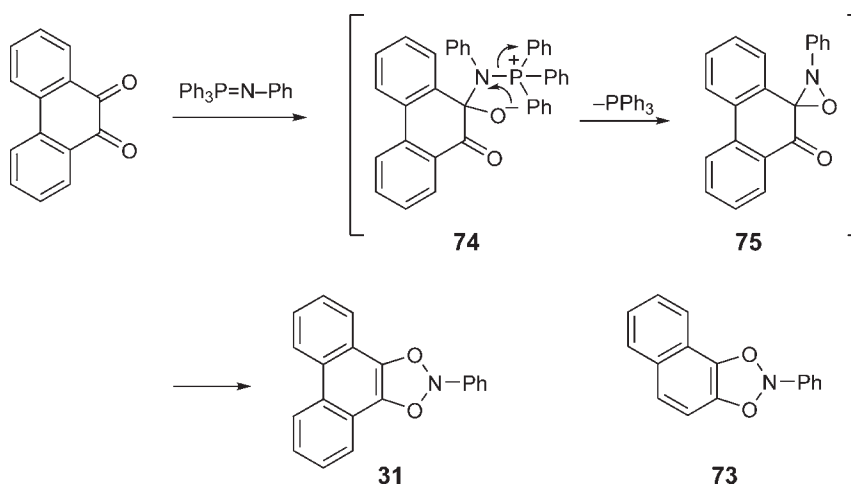


o-Bis(sulfenylchloride)heteroarenes are usually prepared from corresponding *o*-dimercapto derivatives and phenyliodoso dichloride (PhICl₂), but their synthesis requires sometimes stringent control of the oxidation conditions (an excess of PhICl₂), and the use of more vigorous oxidants, for example, chlorine, leads to

chlorination of the aromatic ring. It was discovered that the 1,3,2-dithiazolium cation **45** can be prepared in one step by treatment of the dimercapto derivative **72** with trithiazyl trichloride ($S_3N_3Cl_3$) (Equation 19) <1998JA352>.



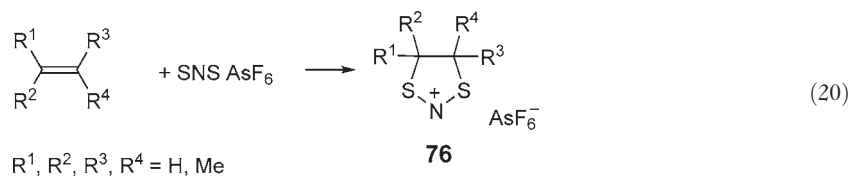
N-Phenyliminophosphorane reacts with 9,10-phenanthrenoquinone and 1,2-naphthoquinone to give condensed 1,3,2-dioxazoles **31** and **73** <2002SC2779>. The reaction mechanism includes nitrogen attack on the carbonyl carbon with formation of betaine **74** followed by subsequent elimination of triphenylphosphine and formation of oxaziridine **75**, which isomerizes to the compound **31** that has a stable dioxazole ring (Scheme 7).



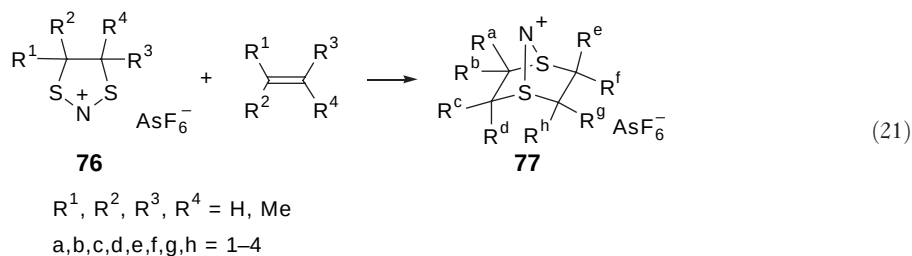
Scheme 7

6.02.9.4 Formation of Two Bonds: [3+2] Atom Fragment by Cycloaddition

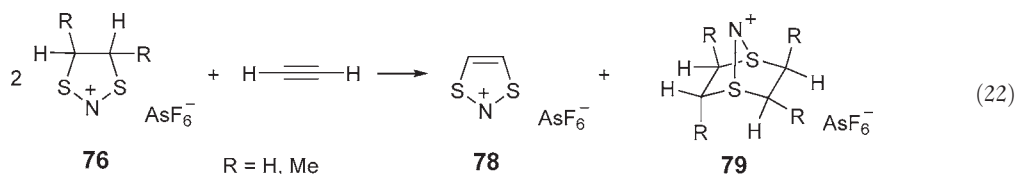
The dithionitronium cation SNS^+ (as the AsF_6^- salt) underwent quantitative concerted symmetry-allowed cycloaddition reactions with alkenes (ethylene, methylethylene, *trans*- and *cis*-1,2-dimethylethylene, 1,1-dimethylethylene, tetramethylethylene, and norbornene) to give 1,3,2-dithiazolidine cations **76** (Equation 20) <1996JCD1997>.



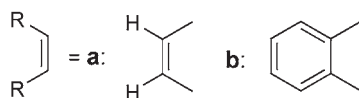
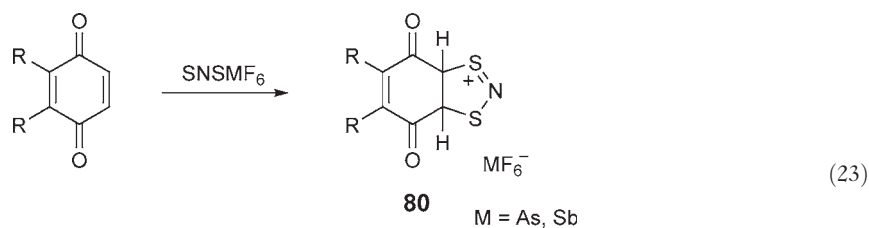
These compounds gave, in a second quantitative symmetry-allowed cycloaddition reaction with another alkene molecule, dithiaazabicyclo[2.2.1]heptene cations **77** (with the exception of tetramethylethylene because of steric effects) (Equation 21). The preparation of cations **76** and **77** from the above reactions provides an apparently general route to the two ring families.



Cations **76** underwent quantitative reactions with acetylene to give 1,3,2-dithiazole cations **78** and **79** (Equation 22). The results are consistent with the expectation that the lower energy of the completely delocalized 6π HCSNSCH⁺ **78** (relative to that of the partially delocalized 4π **76**) renders reaction thermodynamically favorable. Cations **76** did not react with MeCN (ionization potential (MeCN) = 12.2 eV, (acetylene) = 10.5 eV) probably due to a higher kinetic barrier, although the reaction is thermodynamically favorable.



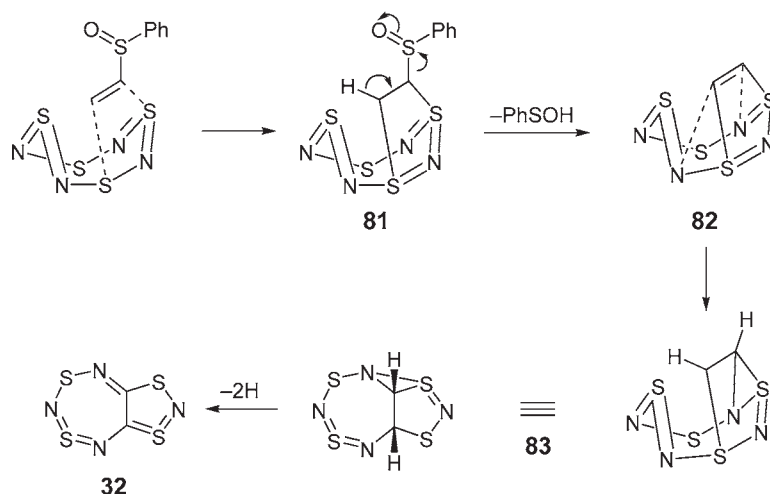
The reaction of the 2,3-ethylenic bond of 1,4-benzo- and naphthoquinones yields the cycloadducts **80** (Equation 23) <2005CCC2366>. The ionization potential of 1,4-naphthoquinone (9.5 eV) is lower than that of 1,4-benzoquinone (10.11 eV), and therefore the cycloaddition reaction of 1,4-naphthoquinone proceeds faster.



The photochemical reaction of tetranitromethane with aromatic compounds leads in low yields to 1,3,2-dioxazoles, as products of the nitroalkene cycloaddition of the trinitromethyl intermediate <1995ACS482, 1996ACS29, 1996ACS735>. The cycloaddition products **22a** and **22b** (0.2–1.8%) were isolated from 1,3-dimethylnaphthalene <1995ACS482>, compound **23a** (20%) from 1,2,3-trimethylbenzene <1996ACS29>, and compound **23b** (3%) from 1,2,3,4-tetramethylbenzene <1996ACS735>. The structure of all these compounds has been proved by single crystal X-ray analysis (see Section 6.02.3.1).

6.02.9.5 Formation of Two Bonds: [3+2] Atom Fragment by Other Processes

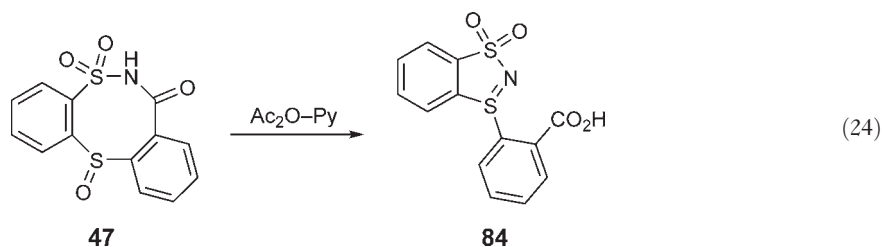
Tetrasulfur tetranitride (S_4N_4) reacts with phenyl vinyl sulfoxide to give an entirely new and unexpected 14π electron aromatic system, tetrathia-2,4,6,8-tetraazaazulene **32** <2000ARK228>. A possible mechanism for the conversion of S_4N_4 into product **32** includes 1,3-dipolar cycloaddition of the alkene across the S(1)–S(3) to afford intermediate **81** followed by thermal elimination of phenylsulfenic acid giving the bicyclic structure **82** in which the S_4N_4 cage is opened up and the five-membered ring of the final dithiazole **32** generated. The seven-membered ring of dithiazole **32** can then be formed by an electrocyclic process, and the tricyclic species **83** so produced is dehydrogenated with concomitant aromatizing valence isomerization to give tetrathiatetraazaazulene **32** (Scheme 8).



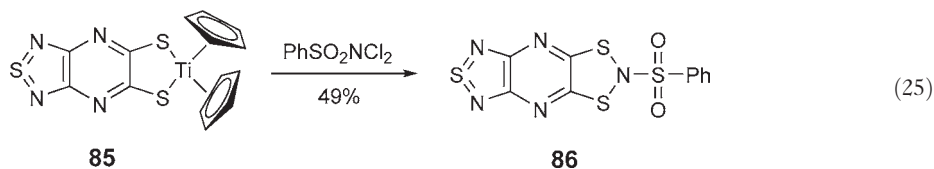
Scheme 8

6.02.10 Ring Syntheses by Transformation of Another Ring

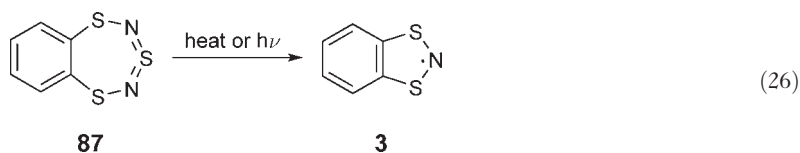
Dibenzodithiazocin **47** can be transformed into cyclic sulfilimine **84** by reaction with a mixture of acetic anhydride–pyridine at 100 °C (Equation 24) <1995CC1069>. No mechanism is given for this transformation.



The titanocene derivative **85** condensed with benzene-*N,N*-dichlorosulfonamide to afford *N*-phenylsulfonyl-1,3,2-dithiazole **86** (Equation 25) <1998JA352>.



The thermolysis and photolysis of dilute (10^{-3} M) solutions of benzotrithiadiazepine **87** in hydrocarbons afforded 1,3,2-benzodithiazolyl radical **3**, which was unambiguously identified by a comparison of its ESR spectra parameters (Equation 26) <2003MC178>. The yield of the thermal transformation was $85 \pm 15\%$, and the photochemical reaction $25 \pm 5\%$. The transformation of diazepine **87** into dithiazolyl radical **3** requires a ring contraction with the loss of the SN radical which decomposed rapidly under experimental conditions.



6.02.11 Synthesis of Particular Classes of Compounds and Critical Comparison of the Various Routes Available

Synthesis of 1,3,2-dithiazoles has been the most extensively studied. Various structural types of these compounds have been synthesized in 1990s from *vic*-dithiols, bis(sulfonylchlorides), and alkynes <1996CHEC-II(4)433>. Much attention has been paid to the preparation of stable 1,3,2-dithiazolyl radicals and, especially, cations. The synthetic potential of 1,3,2-oxathiazoles and 1,3,2-dioxazoles is restricted by several uncommon procedures including nitrosation of thiolcarboxylic acids and photochemical addition of nitrobenzene to alkenes <1996CHEC-II(4)433>.

The synthesis of 1,3,2-dithiazolidines from bis(sulfonylchlorides) and amines has been developed in the 1990s and 2000s (Equations 12 and 14). Trimethylsilyl azide confirmed its important role in the preparation of fused mono- and bis-1,3,2-dithiazolium cations (Equation 18). Oakley and co-workers showed that *o*-dimercapto derivatives can be used in the synthesis of these compounds if treated with trithiazyl trichloride (Equation 19). Synthesis of *N*-substituted 1,3,2-benzodithiazole tetraoxide has been successfully carried out from benzene-bis(sulfonylchloride) and aliphatic amines (Equation 15). An important feature in this reaction is the preparation of chiral derivatives from optically pure amines (Equations 16 and 17).

The Passmore group has developed a synthesis of 1,3,2-dithiazolium cations from alkenes and dithionitronium cation (Equations 20–22). The 2,3-ethylenic bond of 1,4-benzo- and naphthoquinones was also involved in this reaction.

1,3,2-Dithiazoles and their cations can be successfully obtained by ring transformation of dithiazocin 47, titanocene 85, and trithiadiazepine 87.

Condensed 1,3,2-dioxazoles are produced by the reaction of *N*-phenyliminophosphorane and 9,10-phenanthreno- and 1,2-naphthoquinones (Scheme 7). Photochemical addition of tetranitromethane to aromatic compounds is still in use for the preparation of 1,3,2-dioxazolidines 22 and 23 but in low yields.

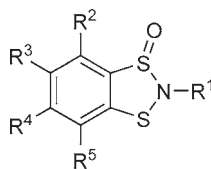
6.02.12 Important Compounds and Application

The most important ability of 1,3,2-dithiazoles is to form stable cations and radicals; therefore, they have been considered as promising conducting charge-transfer complexes and ferromagnetic materials <1996CHEC-II(4)433>. 1,3,2-Dithiazolidines have been claimed to have use in photographic materials.

The interest in magnetic properties and conductivity of stable 1,3,2-dithiazolium radicals has grown in the 1990s and 2000s. Magnetic susceptibility for a range of fused 1,3,2-dithiazolium radicals 4, 7, 9–12, 14, and 33 has been measured at various temperatures <1997CC873, 1997JA2633, 1998JA352, 2000JMC2001, 2004JA8256>. Analysis of susceptibility data for these compounds indicated that they are essentially paramagnetic above 200 K. The room-temperature conductivities for sole 1,3,2-dithiazolium radicals are low, $<10^{-6} \text{ S cm}^{-1}$. But, dithiazolium radical 9 is essentially diamagnetic as expected from the dimeric association observed in the 293 and 95 K crystal structures <2004JA8256>. The bistability of radicals 4, 9, and 33 can lead to their potential application in magnetothermal switching and information storage devices <2004JA14692>. Following this idea, thin films of compound 4 were prepared on gold surfaces and their properties were investigated <2005SM457>.

The complex of dithiazole 4 and bis(hexafluoroacetylacetonato)copper(II) was investigated <2001POL1517>. Its magnetic measurements reveal a ferromagnetic property that suggests that this compound can be a building block for supramolecular magnets.

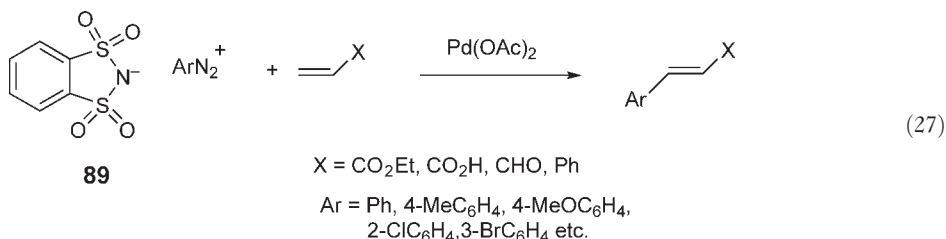
N-Fluorobenzenesulfonimide 52 has been proved as deconjugative electrophilic fluorinating agent <1995JOC4730, 2000T5303>. Substituted 1,3,2-benzodithiazole *S*-oxides 88 have been proposed as microbiocides against *Aspergillus niger* <1995DEP4403838>.



88

6.02.13 Further Developments

Arenediazonium *o*-benzenesulfonamide **89** was found to be a new and efficient reagent for the Heck-type arylation reactions of some common substrates containing C–C multiple bonds, i.e., ethyl acrylate, acrylic acid, acroleine, styrene, and cyclopentene <2006T3146>. The reactions are carried out in the presence of Pd(OAc)₂ and afford arylated products, for example ethyl cinnamates, cinnamic acids, cinnamic aldehydes, and stilbenes, possessing an (*E*)-configuration, and 1-arylcyclopentenes, in good to excellent yields (Equation 27).



Preparation, crystal structures, and magnetic properties of 3-cyanobenzo-1,3,2-dithiazolyl radical were recently reported <2006IC1903>. The crystal structure and magnetic properties of thiazyl radicals and related materials have been reviewed <2006BCJ25>.

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6.03

1,2-Oxa/thia-4-azoles

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6.03.1	Introduction	62
6.03.2	Theoretical Methods	62
6.03.3	Experimental Structural Methods	64
6.03.3.1	X-Ray Diffraction	64
6.03.3.2	Proton NMR Spectroscopy	66
6.03.3.3	Carbon-13 Spectroscopy	67
6.03.3.4	UV Spectroscopy	68
6.03.3.5	IR Spectroscopy	69
6.03.3.6	Mass Spectrometry	69
6.03.4	Thermodynamic Aspects	71
6.03.4.1	Stability and Stabilization	71
6.03.4.2	Isomerization Equilibrium	71
6.03.5	Reactivity of Fully Conjugated Rings	72
6.03.5.1	Thermal and Photochemical Unimolecular Reactions	72
6.03.5.2	Nucleophilic Attack at Ring Carbon	73
6.03.5.3	Attack at Ring Sulfur	75
6.03.5.4	Reactions Involving Radicals, Electron-Deficient Species, Reducing Agents, and Surface Reactions	77
6.03.5.5	Cyclic Transition State Reactions with a Second Molecule	78
6.03.5.6	Other Reactions	79
6.03.6	Reactivity of Nonconjugated Rings	79
6.03.6.1	Reactions of Isomers of Fully Conjugated Ring Compounds	80
6.03.6.1.1	Thermal mononuclear reactions	80
6.03.6.1.2	Attack at ring carbon and nitrogen	80
6.03.6.1.3	Nucleophilic attack at ring sulfur	81
6.03.6.1.4	Cyclic transition state reactions with a second molecule	83
6.03.6.2	Reaction of Hydrogenated Derivatives of Fully Conjugated Ring Compounds	83
6.03.7	Reactivity of Substituents Attached to Ring Carbon and Nitrogen Atoms	86
6.03.8	Ring Synthesis Classified by Number of Ring Atoms in Each Component	86
6.03.8.1	Formation of One Bond between Two Heteroatoms	86
6.03.8.2	Formation of One Bond Adjacent to a Heteroatom	88
6.03.8.3	Formation of Two Bonds: Four-Atom Fragment and Sulfur	89
6.03.8.4	Formation of Two Bonds: [3+2] Atom Fragment by Cycloaddition	90
6.03.8.5	Formation of Two Bonds: [3+2] Atom Fragments by Other Processes	92
6.03.8.6	Formation of Three Bonds	95
6.03.8.7	Formation of Four Bonds	95
6.03.9	Ring Synthesis by Transformation of Another Ring	96
6.03.10	Survey of Ring Synthesis	97
6.03.10.1	1,2,4-Dithiazoles, 1,2,4-Dithiazolines, and 1,2,4-Dithiazolidines	97

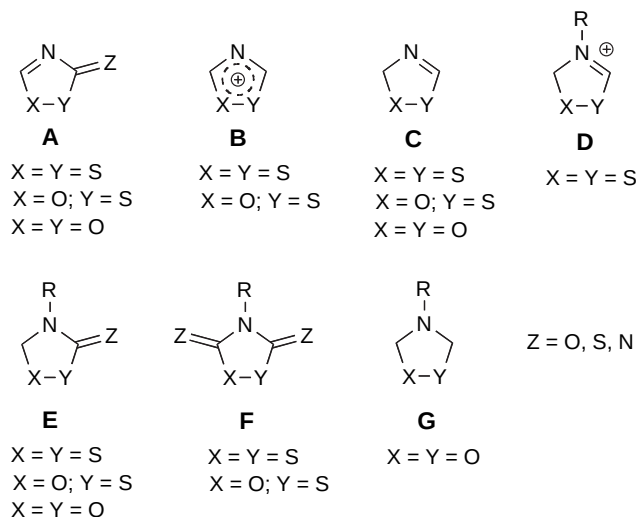
6.03.10.2	1,2,4-Oxathiazolines and 1,2,4-Oxathiazolidines	98
6.03.10.3	1,2,4-Dioxazolines and 1,2,4-Dioxazolidines	98
6.03.11	Important Compounds and Applications	98
6.03.12	Further Developments	99
	References	101

6.03.1 Introduction

For the last 10 years, the investigations focused on the synthesis and chemical transformation of 1,2-oxa/thia-4-azoles continued to develop intensively, although the number of publications has slightly decreased compared to 1984–96 (about 150 instead of 170). As before, most of publications have been devoted to 1,2,4-dithiazole derivatives. The investigations related to the [3+2] cycloaddition reactions and Dimroth rearrangements have dramatically reduced in number. At the same time, the works dealing with the utilization of 1,2,4-dithiazole derivatives as sulfur-transfer reagents and the introduction of the dithiosuccinoyl (Dts) protection of NH_2 groups and its removal in organic and bioorganic chemistry have gained a new impetus. 1,2,4-Dithiazolidine-3,5-dione appears to be very useful as a nucleophilic isocyanate ‘building block’.

New approaches to the synthesis of 1,2,4-oxathiazole derivatives have been found and the previously unknown derivatives of this heterocycle (1,2,4-oxathiazolines, their *S*-monooxides and 1,2,4-oxathiazolium structures) have been synthesized. In addition to the chapters in CHEC(1984) and CHEC-II(1996) <1984CHEC(6)897, 1996CHEC-II(4)453>, only one review covering the whole aspect of 1,2-oxa/thia-4-azoles chemistry has been published <2004HOU29>, but the majority of references cited in this chapter relate to work dating back to 1995.

All synthesized types of 1,2-oxa/thia-4-azole structures can be classified into two major groups: (1) fully conjugated compounds (i.e., not containing sp^3 -hybridized carbon and nitrogen atoms), including azolium systems (structures **A** and **B**); and (2) nonconjugated structures (isomers and hydrogenated derivatives of fully conjugated compounds), including azolines (structures **C** and **D**) and azolidines (structures **E–G**).



6.03.2 Theoretical Methods

A significant part of the theoretical investigations within the 1,2,4-dithiazole series is devoted to 3,4-diaza-1,6,6 α λ^4 -trithiapentalene derivatives <1984CHEC(6)897, 1996CHEC-II(4)453>. A comparison of their enthalpy of formation with that of 1-aza-1,6 α λ^4 -dithia- and 1,6-diaza-6 α λ^4 -thia analogs shows that the 3,4-diaza-1,6,6 α λ^4 -trithiapentalene system is the most thermodynamically favorable <1996CHEC-II(4)453>. The molecular geometry and electronic structure of the still-unknown 3,4-diaza-1,6,6 α λ^4 -trithiapentalene parent compound **1** (R = H) has

been examined in more detail in conjunction with known nitrogen-free 1,6,6 α λ^4 -trithiapentalene **2** (R=H) <1998PS35, 1997PCA4475>. Whereas Hartree–Fock calculations predict **1** and **2** as valence isomers in equilibrium **3a/3b**, density functional theory (DFT) (B3LYP) as well as *ab initio* MP2 calculations result in a single minimum structures of C_{2v} symmetry (Table 1).

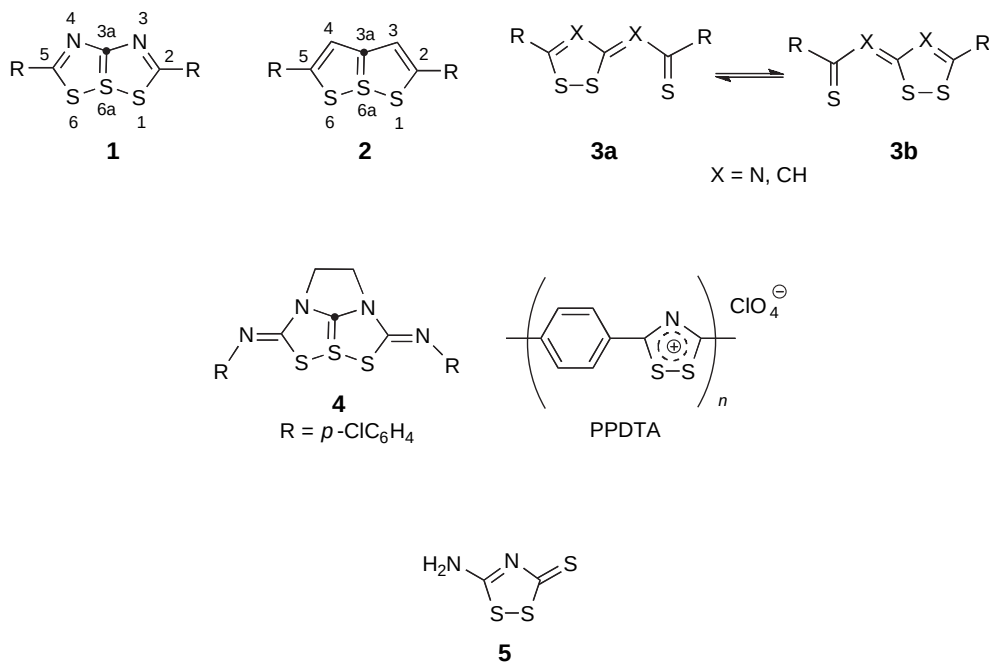


Table 1 Selected theoretical bond lengths and bond angles

Compound	Bonds	Angles	Bond lengths (Å), bond angles (deg)		
			B3LYP 6-31G(d)	B3LYP 6-311 + G(3df,3pd)	Ab initio MP2(frozen) 6-31G(d)
1 R = H	S ₁ –S _{6a}		2.385	2.355	2.336
	C _{3a} –S _{6a}		1.809	1.789	1.779
	C ₂ –S ₁		1.699	1.686	1.681
	C ₂ –N ₃		1.313	1.307	1.320
	C _{3a} –N ₃		1.341	1.337	1.347
	S ₁ C ₂ C ₃	124.4	123.8	123.9	123.9
	C ₂ C ₃ C _{3a}	118.4	118.4	117.0	117.0
	C ₃ C _{3a} S _{6a}	120.6	120.6	121.2	121.2
	C _{3a} S _{6a} S ₁	87.1	87.3	87.6	87.6
	S _{6a} S ₁ C ₂	89.4	90.0	90.3	90.3
	S ₁ S _{6a} S ₆	174.2	174.6	175.2	175.2
	S ₁ –S _{6a}		2.423	2.386	2.368
	C _{3a} –S _{6a}		1.758	1.743	1.739
	C ₂ –S ₁		1.699	1.688	1.686
2 R = H	C ₂ –N ₃		1.373	1.366	1.374
	C _{3a} –N ₃		1.415	1.414	1.413
	S ₁ C ₂ C ₃	120.5	119.9	119.6	119.6
	C ₂ C ₃ C _{3a}	120.6	120.4	119.9	119.9
	C ₃ C _{3a} S _{6a}	118.9	118.9	119.0	119.0
	C _{3a} S _{6a} S ₁	88.9	89.0	89.3	89.3
	S _{6a} S ₁ C ₂	91.1	91.8	92.2	92.2
	S ₁ S _{6a} S ₆	177.9	178.0	170.6	170.6

The calculated and experimental <1973ACS411, 1974JA289> data on ^1H and ^{13}C chemical shifts and nucleus-independent chemical shifts (NICSs) for compounds **1** and **2** ($\text{R} = \text{H}$) were calculated by gauge-independent atomic orbital self-consistent field (GIAO-SCF) <1998PS35>. The calculated values of ^{13}C chemical shifts for compound **2** ($\text{R} = \text{H}$) vary in the same order as those observed experimentally. The numerical agreement between theory and experiment is better for the ^1H chemical shifts. The chemical shifts for compound **1** ($\text{R} = \text{H}$) were predicted at lower fields than for compounds **2** ($\text{R} = \text{H}$). Deshielding of ring protons suggests a strong ring current. The calculated NICS values for five-member rings of compounds **1** and **2** ($\text{R} = \text{H}$) indicate aromatic bond delocalization. These compounds are iso- π -electronic with naphthalene ($\text{NICS} = -9.9$ ppm) (Table 2).

Table 2 Calculated and experimental <1993HOU470> chemical shifts and NICS

Compound	Atoms	^1H NMR calc. (exp.) (ppm)	^{13}C NMR calc. (exp.) (ppm)	NICS (ppm)
1 ($\text{R} = \text{H}$)	H (C_2/C_5)	10.56		
	C_2/C_5		197.87	-7.7
	C_{3a}		202.92	
2 ($\text{R} = \text{H}$)	H (C_2/C_5)	9.23 (9.18)		-8.28
	H (C_3/C_4)	7.80 (7.96)		
	C_2/C_5		174.87 (161.69)	
	C_3/C_4		130.50 (128.64)	
	C_{3a}		191.19 (177.45)	

According to the computational results, the substitution of methine groups by nitrogen atoms in the 3- and 4-positions and introduction of amino groups in 2- and 5-positions of 1,6,6 α λ^4 -trithiapentalene (**1**: $\text{R} = \text{NR}^1$) stabilizes the heterocyclic compound through forming the polymethine-type substructure. Equilibrium geometries for 2,5-diaminosubstituted compounds **1** ($\text{R} = \text{NH}_2$, NMe_2 , and piperidyl) calculated by DFT (B3LYP/6-31G(d)) and *ab initio* (MP2/6-31G *) are in good agreement with the results of X-ray diffraction study of 2,5-bis(piperidyl)-3,4-diaza-1,6,6 α λ^4 -trithiapentalene (**1**: $\text{R} = \text{piperidyl}$) <1998PS35>.

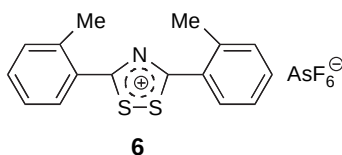
The molecular orbital (MO) calculations within the PM3 method, using a MOPAC package, provided an explanation of the advantages of a new redox system, poly(1,4-phenylene-1,2,4-dithiazolium-3',5'-yl) (PPDTA), as a cathode material for high-capacity lithium secondary batteries in comparison with three typical polymer conductors (poly-*p*-phenylene, polypyrrole, and polythiophene). The MO calculation revealed that the S-S bond in the 1,2,4-dithiazolium moiety of PPDTA caused gap narrowing and a downshift of HOMO and LUMO levels, which is consistent with the electrochemical experiment (HOMO = highest occupied molecular orbital; LUMO = lowest unoccupied molecular orbital) <2001MI2305>.

A computer system for the recognition and prediction of the acute toxicity (LD_{50}) for different heteroorganic compounds is based on two predicted complexes (for hetero- and carbocyclic compounds) and includes about 30 mathematical models. The prediction accuracy is 70–88%. The LD_{50} values, calculated by this method and experimental, for the 5-amino-1,2,4-dithiazole-3-thione **5** are in good agreement <2005MI58, 1999MI54>.

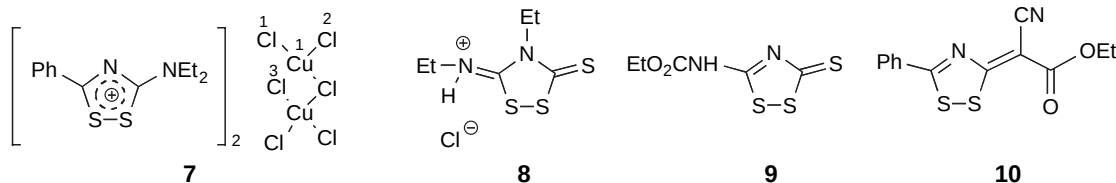
6.03.3 Experimental Structural Methods

6.03.3.1 X-Ray Diffraction

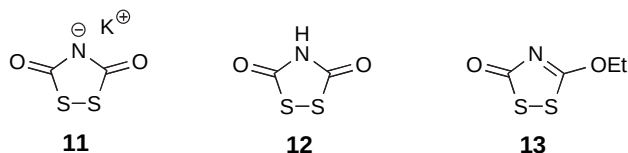
1,2-Oxa/thia-4-azole derivatives, especially 1,2,4-dithiazole derivatives, have been extensively investigated by the X-ray diffraction method. In particular, the dithiazolium cation moiety in all structures has been found to possess a fully delocalized π -electron system <1996CHEC-II(4)453, 1996AXC2148, 1996ZNB175>. The 1,2,4-dithiazolium ring is planar in these structures and ring bonds are shorter relative to those in the uncharged 1,2,4-dithiazole ring <1999AXC260>. The substituents at carbon atoms 3 and 5 are usually coplanar with the central ring. The opposite *o*-tolyl substituents in 3,5-ditolyl-1,2,3-dithiazolium hexafluoroarsenate **6** lie outside of the plane (dihedral angle 29.11°) because of the steric hindrance of the methyl groups. Interionic interactions include short $\text{S} \cdots \text{F}$ and $\text{N} \cdots \text{F}$ contacts <1996AXC2148>.



Bis(3-diethylamino-5-phenyl-1,2,4-dithiazolium) hexachloro dicuprate **7** shows reversible thermochromism: above 210 K it is brown and below 210 K it is gold-yellow <1996ZNB175>. The comparison of crystal structure **7** at room temperature <1991ZNB1113> and at 120 K reveals a difference in the Cl(3)–Cu(1)–Cl(2) angle. At room temperature it is 146.5° and at 120 K–143.29°, which indicates the deformation of the copper atom tetrahedral environment. Therefore, such thermochromism of coordinating compounds may be attributed to the changes in the coordination geometry of the metal ion. The 1,2,4-dithiazolidine ring in hydrochloride **8** is essentially planar (maximum deviation 0.025 Å) and the proton is located on the imino group <1999AXC260>. The bond lengths indicate that the molecule is stabilized through some π -orbital delocalization. However, this delocalization is less pronounced in the disulfide function. The S–S distance (2.069 Å) in compound **8** is even longer than in the previously studied uncharged compound **9** (2.052 Å <1963ACS2575>). An analogous picture is observed for other 1,2,4-dithiazole derivatives with 3(5)-ammonium substituents <1996CHEC-II(4)453> and for compound **5** <1996OM2125>. A specific feature of structure **10** with the 3-ylidene substituent is shortening of the distance between the S-2 ring atom and carbonyl oxygen atom (2.526 Å) <2003H(60)2273>, which implies a presence of the polar interaction between these atoms and is in agreement with the structures of analogous compounds <1988PS55, 1992J(P1)3377, 1997ZNB323, 1996CHEC-II(4)453>.

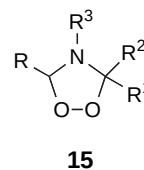
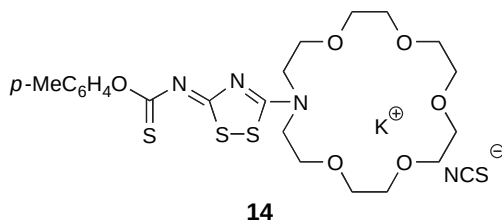


X-Ray crystallographic analysis has been carried out on 1,2,4-dithiazolidine-3,5-dione potassium salt **11** <2003OBC3015> for a structural comparison with parent heterocycle **12** <1996JOC6639>. Significant shortening of the C–N bonds and a concomitant increase in the length of the C–O bonds occurs during the formation of potassium salt **11**. This is consistent with the changes in the bond order that could be assumed to accompany the expected delocalization of the negative charge in the conjugate base across the imide moiety. No other significant bond/angle changes that could point to the stabilization of other interactions in the conjugate base were observed. Interestingly, the C–S bonds are, however, elongated in the conjugate base, which allows a tentative suggestion that the sulfur atom might not be involved in the stabilization. The X-ray study of 3-ethoxy-1,2,4-dithiazole-5-one **13** showed that it also has the planar aromatic structure, the imino nitrogen being coplanar with the ethoxy group <1996JOC6639>.



The molecular structure of 2,5-disubstituted diazatrithiapentalene **1** (R = piperidyl) is closely related to the structures of other trithiapentalenes <1996CHEC-II(4)453>. The central bicyclic system in this structure is planar and the two S–S bonds are unequal in length (2.328 and 2.346 Å) and longer than a standard S–S single bond (2.08 Å), which indicates the hypervalent nature of this bond (a typical hypervalent S–S length is 2.40 Å). In addition, due to H-bonding of *o*-CH groups of piperidyl substituents with S-1, S-6, N-3, and N-4 ring atoms, a closer examination of the structure revealed unusually short CH···N and CH···S interatomic distances with 2.314 and 2.333 Å and 2.513 and 2.501 Å, respectively, which are shorter than the sum of the corresponding van der Waals radii <1998PS35>. Similarly, in the trithiapentalene derivative **4**, the central ring, with maximum deviation 0.111 Å, and the perhydroimidazole ring are also planar and the S–S distances are 2.488 and 2.314 Å <1997BCJ1267>. The structure of complex **14** has no trithiapentalene character that is connected with the unsymmetrical substitution: the S(1)–S(2) length is 2.16 Å and another S–S bond length is 2.54 Å <1994PS81>. The cation K⁺ is located inside the macrocycle near one of the oxygen atoms and the NCS[–] anion is outside the molecule.

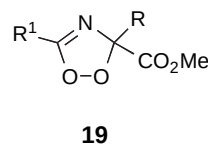
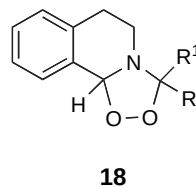
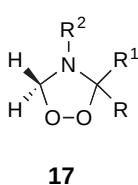
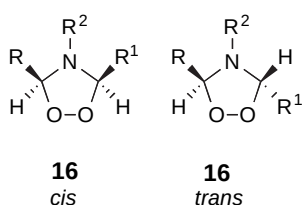
The 1,2,4-oxathiazolidine and the 1,2,4-dioxazolidine rings are not planar and have the envelope conformation, with the bond lengths being close to single bond lengths <1996CHEC-II(4)453>. The central ring of 1,2,4-dioxazolidine **15** also has the envelope conformation where the oxygen atom O-1, distal from the geminal phenyl groups at the C-3 atom, lies out of plane (deviation is 0.703 Å). The geometry at the ring nitrogen atom is pyramidal. The O-O bond length is 1.477 Å <1995J(P1)41>.



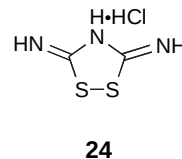
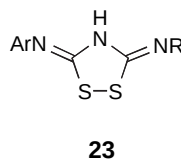
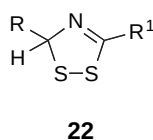
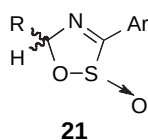
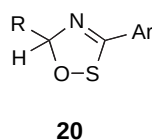
a: R = R¹ = R² = R³ = Ph

6.03.3.2 Proton NMR Spectroscopy

¹H nuclear magnetic resonance (NMR) spectroscopy was used for estimating the structure of 1,2,4-dioxazolidine derivatives **16** obtained as a mixture of *cis*- and *trans*-isomers using the protons positions at carbons atoms 3 and 5. In the *cis*-isomers, these protons were found to exhibit higher field resonance in the ¹H NMR spectrum (two singlets at 5.32–5.58 and 4.10–5.0 ppm) than in the *trans*-isomers (singlets at 5.58–6.00 ppm). The diastereotopic CH₂ groups of 4-benzyl substituents were present as AB quartets at ~3.70 and 3.80 ppm (*J* 13 Hz) in both *cis*- and *trans*-isomers <1995J(P1)41, 1994J(P1)2449, 1996CHEC-II(4)453>. Two protons at 5-carbon atoms of structures **17** were displayed as singlets at 4.99–5.39 ppm, if R = R¹, and as two singlets (4.80 and 5.05 ppm), if these substituents are different. The NH-proton chemical shift in 3,3,5-triphenyl-1,2,4-dioxazolidine is 3.79 ppm, and chemical shifts of the protons at the C-3 atom of 3,4,5,5-tetrasubstituted 1,2,4-dioxazolidines **15** are at 6.62 ppm. The analogous protons in structures **18** exhibited singlets at 5.81–5.92 ppm <1995J(P1)41>. 3-Me groups in the ¹H NMR spectra of 1,2,4-dioxazolines **19** exhibited singlets at 1.98–2.01 ppm and 5-Me groups show singlets at 1.62–1.66 ppm <2005PPS205>.



Protons at the 5-carbon atoms in 3,5-disubstituted 1,2,4-oxathiazolines **20** have characteristic chemical shifts at 5.85–6.06 ppm. These are shifted to lower field upon their transformation into *S*-oxide derivatives **21**, which are a mixture of isomers <2004HAC175, 2003TL2517>. The ratios of major and minor isomers (3:1) in structures **21** were determined by integrating the ¹H NMR spectra; chemical shifts of protons at 5-carbon atoms of major isomers were detected at a lower field (6.59–6.77 ppm) versus minor isomers (6.27–6.50 ppm) <2004HAC175>. Chemical shifts of protons connected with C-3 carbon atoms of 3,5-disubstituted 1,2,4-dithiazolines **22** have similar values in the range 6.26–6.49 ppm <2004HAC208>. Protons of cyclic NH groups in 1,2,4-dithiazolidines **23** and **24** are of acidic character and exhibit within the range 6.10–6.65 ppm for structures **23** <2001IJH311, 2003IJH391, 2004MI189>, regardless of the substituents on imine nitrogen atoms, and in the range 10.3–10.5 ppm for hydrochloride **24** <2003H(60)1401>.

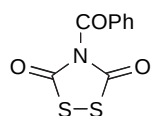


6.03.3.3 Carbon-13 Spectroscopy

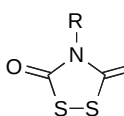
Typical ^{13}C chemical shifts of C-3 and C-5 ring carbon atoms for compounds **19–22** are given in [Table 3](#), and for the compounds **12**, **13**, and **25–29** in [Table 4](#).

Table 3 Carbon ^{13}C data for structures **19–22**

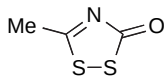
	Structure	Chemical shifts δ of ring carbon (CDCl_3) (ppm)		Reference
		C-R ⁱ (Ar)	C-R	
19	R = R ⁱ = Me	164.9	106.0	2005PPS205
	R = Bu ^t ; R ⁱ = Me	168.6	105.9	
	R = Et; R ⁱ = Pr ⁱ	164.3	111.0	
20	Ar = Ph; R = Bu ^t	168.2	132.0	2004HAC175
	Ar = 4-MeOC ₆ H ₄ ; R = Pr ⁱ	167.4	129.7	
	Ar = naphthyl; R = Bu ^t	168.4	132.0	
21	Two epimers 3:1			2004HAC175
	Ar = Ph; R = Bu ^t	168.2	132.6	
		167.2	131.0	
	Ar = 4-MeOC ₆ H ₄ ; R = Pr ⁱ	163.1	131.7	
		168.2	131.8	
	Ar = naphthyl; R = Bu ^t	168.9	132.7	
22		166.0	132.6	2004HAC208
	R = Ph; R ⁱ = Bu ^t	165.1	104.1	
	R = naphthyl; R ⁱ = Bu ^t	164.3	105.3	
	R = Me; R ⁱ = Bu ^t	162.6	104.5	



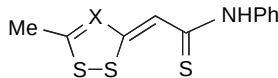
25



26

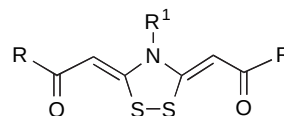


27



28

X = N, CH



29

Table 4 Carbon ^{13}C data for structures **12**, **13**, and **25–29**

	Structure	Chemical shifts δ of ring carbon (CDCl_3) (ppm)		Reference
		C(3/5) [C=O]	C=N	
12		168.7		1996JOC6639
13		[187.3]	179.6	1996JOC6639
25		164.8		2003OBC3015
26	R = C ₆ H ₁₃	167.6		2003OBC3015
	R = CH ₂ CH=CH ₂	167.1		
	R = CH ₂ C≡CH	166.5		
	R = (S)-C(OH)(Me)CO ₂ Me	168.4		
	R = (S)-CH(Me)C ₆ H ₁₃	167.7		
27		[92.7]	188.0	2002J(P1)2046
28	(X=N) ^a	180.45 ^a	184.86 ^a	2005T2141
29	R = Me; R ⁱ = Ph	162.9		1996JOC6639
	R = Ph; R ⁱ = 4-ClC ₆ H ₄	167.3		2003TL7087
				1996SC4165

^a(CD₃)₂SO.

^{13}C NMR was applied in the investigation of the 2,5-bis(aryloxy)-1,6,6 α λ^4 -trithiapentalenes **1** ($\text{R} = \text{ArO}$) aminolysis with different amines, including coronane amines <1994PS81, 1994CB2209>. Characteristic chemical shifts in the ^{13}C NMR spectra for C-5 carbon atoms of monoamino-substituted structures **30** are ~ 181.0 ppm for C-2, ~ 188.0 ppm for C-3a and ~ 196.0 ppm for C-5, and for the diamino-substituted products **31** and **32** ~ 181.0 ppm for C(2,5) and ~ 185.0 ppm for C-3a. Several signals appearing in the ^{13}C NMR spectra at 30°C for each carbon atom of macrocyclic compounds **32**, indicate the presence of conformers. For compound **32b**, it was shown that at 120°C in CDBr_3 these signals coalesced and only three signals were observed – for C-3a, C-2, and C-5 carbon atoms. The most characteristic signal in the ^{13}C NMR spectra for aminolysis products, as well as for structures **33** and **34**, are presented in Table 5.

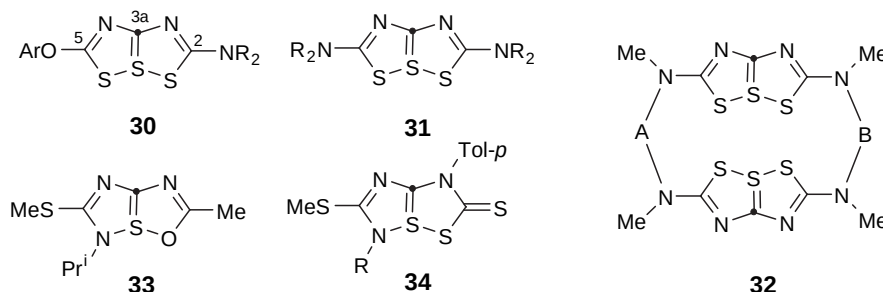


Table 5 Carbon ^{13}C data for the structures **30–34**

		Chemical shifts δ of ring carbon ($(\text{CD}_3)_2\text{SO}$) (ppm)			Reference
Structure		C-2	C-5	C-3a	
1	$\text{R} = \text{Ph}$	195.0	195.0	190.0	1990JPR208
30	$\text{Ar} = 4\text{-MeOC}_6\text{H}_4$ $\text{R} = \text{N}(\text{CH}_2\text{CH}=\text{CH}_2)_2$	181.5	195.8	187.9	1994PS81
	$\text{Ar} = \text{Ph}$ $\text{R} = \text{N}(\text{Et})\text{CH}_2\text{CH}_2\text{OH}$	181.5	196.4	188.5	
	$\text{R} = \text{N}(\text{Me})\text{CH}_2\text{CH}_2\text{OH}$				
31	25°C	184.6	184.7	184.8	1994CB2209
	65°C	182.3	182.3	184.9	
	$\text{R} = \text{N}(\text{CH}_2\text{CH}_2\text{OH})_2$	181.9	181.9	184.9	
32a	$\text{A} = (\text{CH}_2\text{CH}_2\text{O})_3\text{CH}_2\text{CH}_2$ $\text{B} = (\text{CH}_2)_4$	182.6 ^a	183.6 ^a	186.1–186.3 ^a	
32b	$\text{A} = (\text{CH}_2\text{CH}_2\text{O})_4\text{CH}_2\text{CH}_2$ $\text{B} = (\text{CH}_2)_4$ 30°C	179.9–181.4 ^b		183.3–184.0 ^b	
	$\text{A} = (\text{CH}_2\text{CH}_2\text{O})_4\text{CH}_2\text{CH}_2$ $\text{B} = (\text{CH}_2)_4$ 120°C	182.1 ^b	182.2 ^b	184.9 ^b	
33		182.5 ^a	165.5 ^a	177.5 ^a	2003HAC95
34	$\text{R} = \text{Pr}^i$	203.1 ^a	162.1 ^a	169.6 ^a	2003HAC95
	$\text{R} = \text{Bu}^t$	201.9 ^a	159.9 ^a	167.5 ^a	

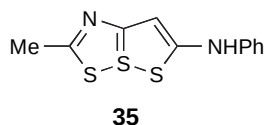
^a CDCl_3 .

^b CDBr_3 .

6.03.3.4 UV Spectroscopy

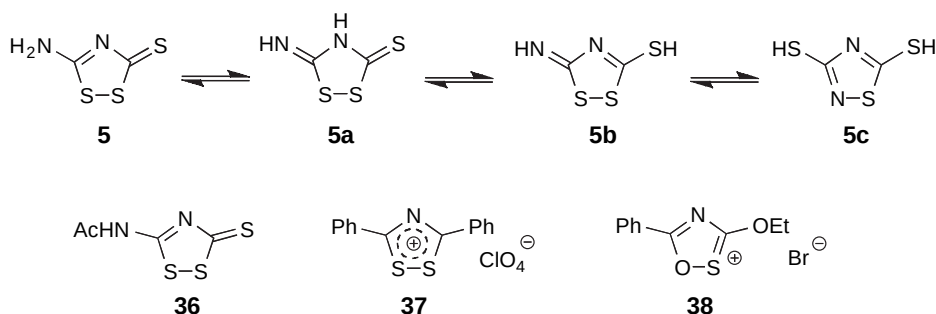
Rather limited data on ultraviolet (UV) spectra of 1,2-oxa/thia-4-azoles have been published. A comparison of λ_{max} values for 3,5-disubstituted 1,2,4-dithiazolium cations showed that all bands in the UV spectra were strongly influenced by the nature of aryl *para*-substituents <1984CHEC(6)897>. A similarity between the UV spectra of

structure **5** and its dialkylamino derivative confirms that the latter is in the amino rather than in the imino form in solution <1984CHEC(6)897>. The UV spectrum of structure **9** is pH dependent, 50% dissociation occurring at pH 7 <1984CHEC(6)897>. Absorption bands for 3,5-bis(dialkylamino)-1,2,4-dithiazolium cations are markedly shifted relative to the bands of the nonsubstituted diamino analog in ethanol <1996CHEC-II(4)453>. The presence of two strong absorption bands at λ_{max} 345 and 435 nm in the UV spectrum of compounds **28** ($X = N$) suggests the 1,6,6 α -trithiamonoazapentalene structure **35**, implying a predominant contribution of structure **28** ($X = N$) to the ground state of the system <2003TL7087>.



6.03.3.5 IR Spectroscopy

Infrared (IR) spectroscopy was employed to identify tautomers **5a–c** of ligand **5** coexisting in the solid state. Structure **5** coordinated with bivalent ions Cd, Co, and Hg stabilizes polymeric complexes, involving initial and thiol tautomers **5** and **5c**, accordingly. Similar results were obtained for *N*-acetyl derivative **36** and its complexes with the same metal cations <1996SPL477>. The IR spectra of structures **29** show strong absorption of the carbonyl group at 1594 cm^{-1} , being very characteristic of compounds with the donor–acceptor $S \cdots O$ intramolecular interaction <1996SC4165>. Model monomer **37** was studied by IR and Raman spectroscopy to support the identification of the structure of weakly soluble PPDTA (see Section 6.03.2). Their IR and Raman spectra data appeared equal or close <2001MI2305>. The IR spectrum of compound **33** shows that it has a polyheterapentalene structure. It does not display the normal carbonyl vibration of *N*-acetylimidates in the $1650\text{--}1660\text{ cm}^{-1}$ range, but shows a weak band at 1635 cm^{-1} together with two bands in the $1500\text{--}1530\text{ cm}^{-1}$ region <2003HAC95>. Some typical bands in the IR spectra for these compounds, as well as for some other 1,2,4-dithiazole and 1,2,4-oxathiazole derivatives, are shown in Table 6. The IR spectroscopy data for 1,2,4-dioxazolidines **15–18** are described in <1995J(P1)41> and for 1,2,4-dioxazolines **19** in <2005PPS205> but without reference to specific bands.



6.03.3.6 Mass Spectrometry

Molecular mass peaks are present in the mass spectra of the majority of 1,2,4-dithiazole and 1,2,4-oxathiazole derivatives, including structures **20**, **21** <2004HAC175>, **22** <2004HAC208>, **25**, **26** <2003OBC3015, 2002J(P1)2046, 2005T2141>, **29** <1996SC4165>, **33** <2003HAC95>, and **37** <2001MI2305>. The fragmentation of 1,2,4-dithiazole derivatives begins with a loss of one or two sulfur atoms <1996CHEC-II(4)453, 2005T2141, 2003OBC3015> and the mode of further fragmentation as a rule depends on the substituents' structures. Thus, alkylisocyanates appear to be fragmentation products in the mass spectra of *N*-alkylated 1,2,4-dithiazolidine-3,5-diones **26** <2005T2141, 2003OBC3015>. The main fragmentation direction of *N*-benzoyl-1,2,4-dithiazolidine-3,5-dione **25** is the formation of the *N*-benzoyl isocyanate fragment ion, in addition to the $(M^+ - S)$ ion <2005T2141>. Basic fragment ions in the mass spectra of compounds **10** ($\text{Ar} = \text{Ph}$, $4\text{-ClC}_6\text{H}_4$) are $[\text{ArC}\equiv\text{NH}^+]$ and $[\text{ArC}\equiv\text{S}^+]$ <2003H(60)2273> and for 5-aryl-3-Bu^t(Prⁱ)-1,2,4-dithiazolines **22** are $[M^+ - \text{Bu}^t(\text{Pr}^i)]$ <2004HAC208>.

Table 6 IR stretching vibrations (cm^{-1}) for some 1,2,4-dithiazole and 1,2,4-oxathiazole derivatives

Structure	IR Absorptions (cm^{-1})				Reference
	$\nu(\text{C}=\text{O})$	$\nu(\text{C}=\text{S})$	$\nu(\text{C}=\text{N})$	Other	
5		1003	1516	3250 (NH), 1629, 1314, 1083 (NH), 1450, 1230 (C–N), 536, 507 (S–S)	1996SPL477
12	1735, 1700, 1683			3360 (NH)	1996JOC6639
13	1705		1541	2990 (CH)	1996JOC6639
20	Ar = Ph; R = Bu ^t		1477	2959 (CH), 1450 (C–N)	2004HAC175
21	Ar = Ph; R = Bu ^t		1450	2967 (CH), 1130 (C–O), 1367 (S → O)	2004HAC175
23	Ar = Ph; R = tetra- <i>O</i> -Bz- β -D-glucopyranozyl	1730	1489	3428 (NH), 1269 (C–N), 489 (S–S)	2003IJH391
29	R = R ¹ = Ar	1594		1567 (C=C)	1996SC4165
33			1500–1530	1635 (C–O)	2003HAC95
34		1040	1530		2003HAC95
36		1692	1022	1509	1996SPL477
37				3500, 3213 (NH), 1440, 1235 (C–N), 540 (S–S) 1590 (C–C), 1500 (Ar), 1400 (C–N), 1100–1200 (ClO ₄); Raman: 568 (S–S), 697 (C–S)	2001MI2305
38			1530	3345 (NH)	1997IJB216
PPDTA				1590 (C–C), 1500 (Ar), 1400 (C–N), 1100–1200 (ClO ₄); Raman: 541 (S–S), 688 (C–S)	2001MI2305

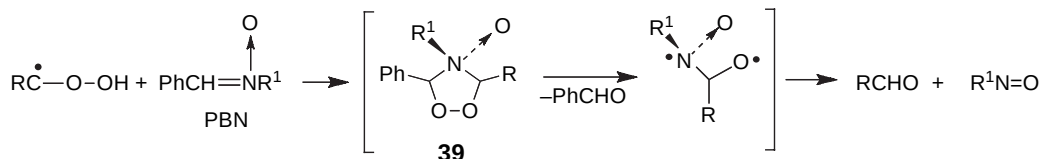
6.03.4 Thermodynamic Aspects

6.03.4.1 Stability and Stabilization

Some complexes of 3-dialkylamino-5-phenyl-1,2,4-dithiazolidinium cations (such as **7**), and their 3,5-diamino analogs with divalent metal halogenides, decompose in protic solvents (H_2O , AlkOH) and strongly coordinating solvents (dimethylformamide (DMF), dimethyl sulfoxide (DMSO), MeCN) in which they are soluble <1996CHEC-II(4)453>. 1,2,4-Oxathiazolines **20** are labile toward storage, so some deviation in their elemental analysis data relative to the calculated ones is observed <2003TL2517, 2004HAC175>. The main products of their decomposition are ArCN. This process is especially appreciable where $\text{Ar} = 4\text{-MeOC}_6\text{H}_4$. The authors assume that the push-pull-type substituent effect of the electron-donating 4-methoxyphenyl group might accelerate the C–S bond cleavage. Some stabilization of compounds **20** was reached after their oxidation into *S*-oxides **21**. These compounds are relatively more stable toward storage at room temperature and upon contact with silica gel <2004HAC175>.

To study the stability of 5-methyl-1,2,4-dithiazole-3-one **27** in solution at room temperature, the sulfurization efficiency of the freshly prepared compound was compared with a 3-week solution in the synthesis of 25-mer oligodeoxyribonucleotide phosphorothioate <1999TL2095>. The result obtained showed that in both cases the same sulfur transfer efficiency (>99.5%) was achieved.

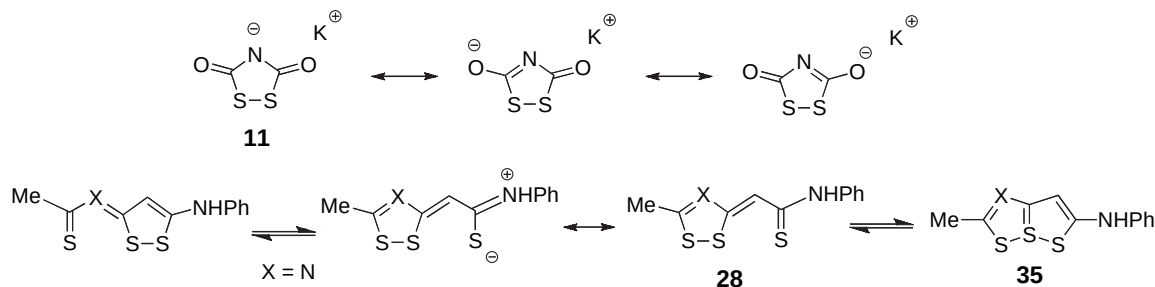
A mixture of PhCHO, RCHO, and $\text{R}^1\text{N}=\text{O}$ was obtained in an attempt to perform the cyclocondensation of carbonyl oxide with α -phenyl-*tert*-butyl nitron PBN <2002JPC3917>. The authors believe that a preferable pathway for this reaction is the formation of 1,2,4-dioxazolidine *N*-oxide **39** as an unstable intermediate (Scheme 1).



Scheme 1

6.03.4.2 Isomerization Equilibrium

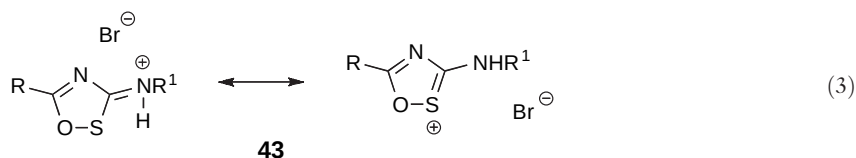
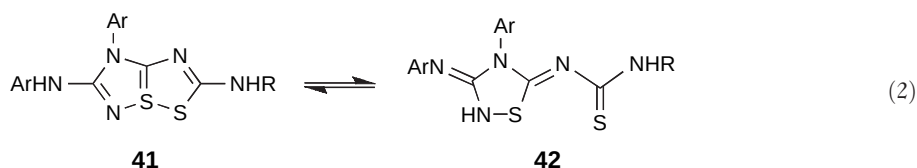
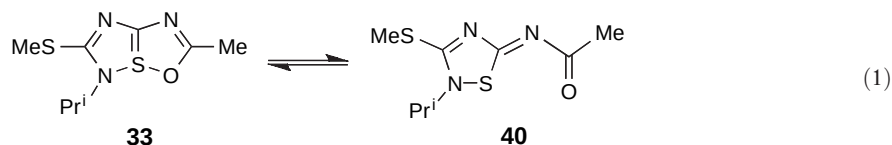
Among reversible processes in the 1,2,4-dithiazole series is the Dimroth rearrangement <1996CHEC-II(4)453>. Possible tautomers of 5-amino-1,2,4-dithiazole-3-thione **5** are represented by structures **5a–c** (see Section 6.03.3.5); the coordination with divalent ions Cd, Co, and Hg stabilizes two of them <1996SPL477, 2000OPD194>. The resonance stabilization of the conjugate base of potassium salt **11** (Scheme 2) was demonstrated by X-ray diffraction (see Section 6.03.3.1) <2003OBC3015>. The spectral characteristics of compound **28** ($\text{X} = \text{N}$) suggest an equilibrium between structures of this kind and the 4-aza-1,6,6 α λ^4 -trithiapentalene structure **35** (Scheme 2) <2003TL7087>.



Scheme 2

The analogous equilibrium was assumed for pentalene derivative **33** and its monocyclic form **40** (Equation 1) <2003HAC95> as well as for structure **41** and its open form **42** (Equation 2) <1997IJB399>. There are two

resonance forms in which hydrobromide **43** can exist. So far there has been no evidence to conclude which of the two forms is more stable (Equation 3) <1997IJB216>.



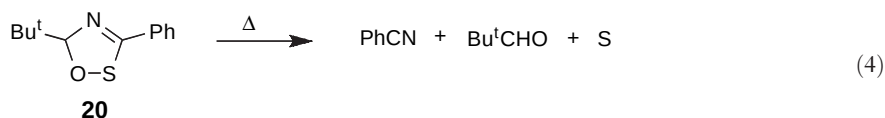
6.03.5 Reactivity of Fully Conjugated Rings

The chemical transformation of fully conjugated 1,2-oxa/thia-4-azoles has been described mainly for 1,2,4-dithiazoles. Most general for such compounds are ring-opening reactions under the action of various dipolarophiles and nucleophilic reagents. 1,3-Cycloaddition reactions with dipolarophiles leading to new heterocycles are characteristic for 1,2,4-dithiazoles containing S-C=O, S-C=S, or S-C=N fragments (see <1996CHEC-II(4)453>; Section 6.03.5.5). The generation of thioacyliso(isothio)cyanates under the action of Ph₃P or (AlkO)₃P under mild conditions is a common reaction for 5-(*R*)-1,2,4-dithiazole-3-ones(thiones) (see Section 6.03.5.3). A capacity of these compounds to donate a cyclic sulfur atom to P-nucleophiles is the basis of their use as sulfur-transfer reagents for the synthesis of oligodeoxyribonucleotide phosphorothioates and they may beneficially replace Beacage reagents (see Section 6.03.5.3).

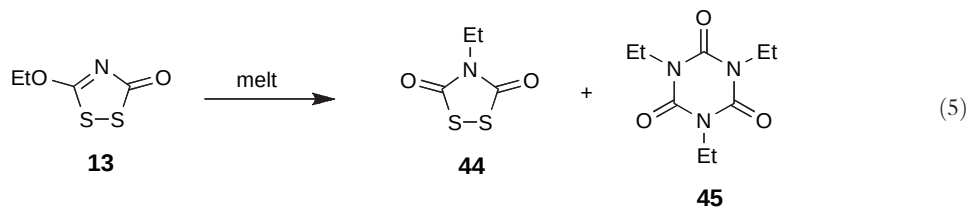
The ring-opening reactions initiated by a nucleophilic attack at cyclic carbon atoms to form new heterocycles are very common reactions of 1,2,4-dithiazolium salts that do not contain good leaving groups at 3,5-positions. Good leaving groups at 3,5-positions of 1,2,4-dithiazolium salt, as well as of uncharged 1,2,4-dithiazole derivatives, are susceptible to replacement with the ring preservation (see Section 6.03.5.2). The thermolysis of 1,2,4-dithiazoles leads to the ring rupture and generation of different products depending on the substituents; in particular, substituted nitriles or nitrile sulfides can be formed with sulfur extrusion. The thermolysis of 5-phenyl-3-*tert*-butyl-1,2,4-oxathiazoline affords a 1:1 mixture of benzonitrile and pivaldehyde (see <1996CHEC-II(4)453>; Section 6.03.5.1). 1,2,4-Dioxazoles are deoxygenated by Ph₃P with opening of the ring <1984CHEC(6)897>.

6.03.5.1 Thermal and Photochemical Unimolecular Reactions

The thermolysis of 5-Ph-1,2,4-dithiazole-3-one(thione) results in benzonitrile sulfide and 5-amino-1,2,4-dithiazole-3-thione **5** loses CS₂ at 184 °C <1996CHEC-II(4)453>. When a CDCl₃ solution of 1,2,4-oxathiazoline **20** (Ar = Ph, R = Bu^t) was heated at 100 °C for 12 h in a sealed NMR tube, a 1:1 mixture of benzonitrile and pivaldehyde along with elemental sulfur were formed (Equation 4) <2003TL2517, 2004HAC175>.



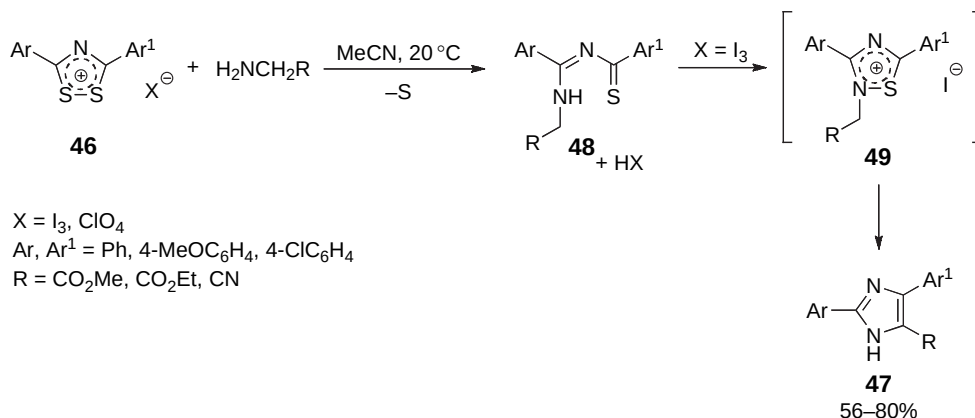
When compound **13** is heated above the melting point, it undergoes rearrangement to give *N*-ethyl-1,2,4-dithiazolidine-3,5-dione **44** as the main product and triethyl isocyanurate **45**, an ethyl isocyanate trimer, as the minor product (Equation 5) <1996JOC6639>.



6.03.5.2 Nucleophilic Attack at Ring Carbon

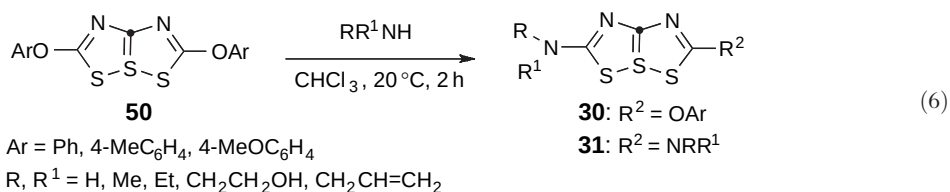
1,2,4-Dithiazolium salts that do not contain good leaving groups at positions 3 or 5 (e.g., 3,5-diaryl derivatives) are prone to ring opening under the action of N-, C-, O-, and S-nucleophiles with the extrusion of sulfur and formation of the ring-opened intermediate at the first reaction step. Depending on the nucleophile nature and reaction conditions, this intermediate transforms into five- or six-member heterocycles (oxadiazoles, triazoles, thiadiazoles, thiazoles, pirimidines, triazines, thiadiazines) as well as into open-chain products, in particular, thioacylamidines <1984CHEC(6)897, 1996CHEC-II(4)453>. The latter can be oxidized into ring compounds (thiadiazoles) by heating with sulfur <1984CHEC(6)897>.

A short synthesis of imidazoles **47** was discovered on the basis of the reaction of 3,5-diaryl-1,2,4-dithiazolium triiodides **46** ($X = I_3$) with glycines or aminoacetonitrile. Intermediate (thiocarbonyl)amidines **48** were oxidized *in situ* to 1,2,4-thiadiazolium salts **49** by the triiodide anion resulting in imidazoles **47**. The same reaction with 3,5-diaryl-1,2,4-dithiazolium perchlorates **46** ($X = ClO_4$) stops at the formation of amidines **48** due to the lack of an oxidizing counterion (Scheme 3) <1997JOC3480>.

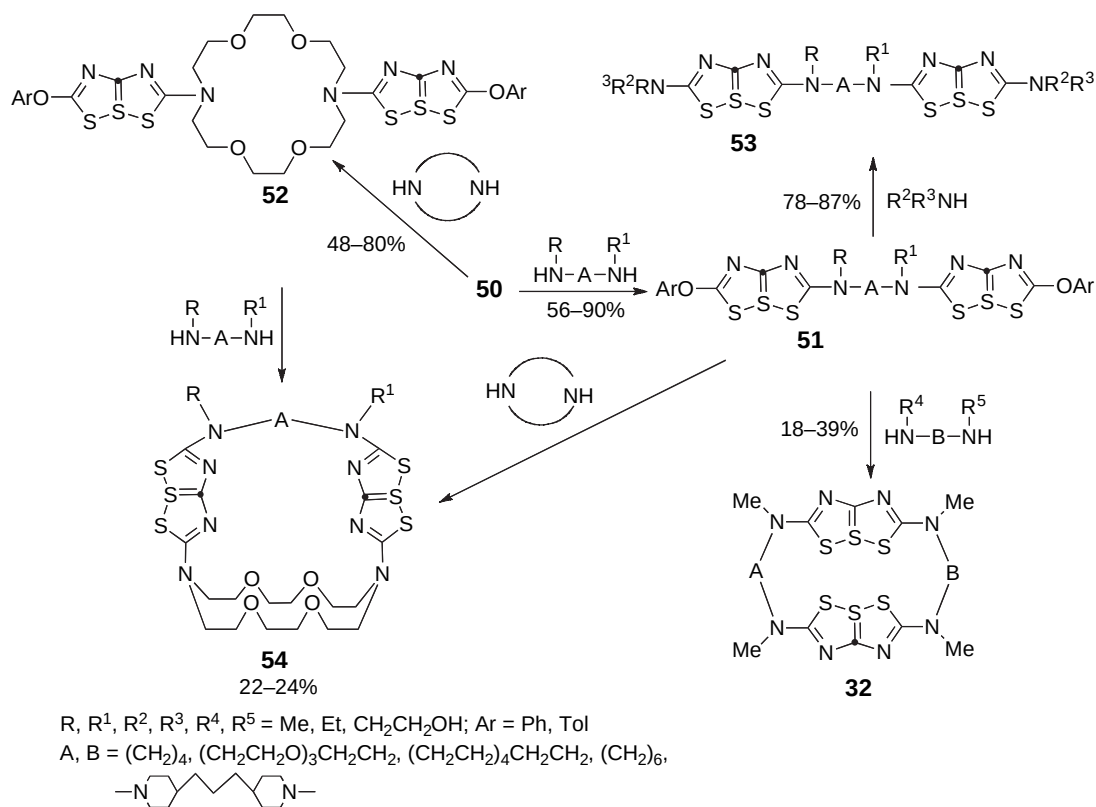


Scheme 3

1,2,4-Dithiazolium salts containing substituents susceptible to displacement by nucleophiles (e.g., OAr) give the products where the ring remains intact <1996CHEC-II(4)453>. The uncharged 1,2,4-dithiazole derivatives can also be subjected to a nucleophilic attack at carbon atoms. For example, aryloxy groups in 2,5-bis(aryloxy)-3,4-diaza-1,6,6 λ^4 -trithiapentalenes **50** can be substituted with amino groups under the action of primary aromatic and secondary aliphatic amines resulting in mono-**30** or disubstituted **31** products depending on the molar ratio of compound **50** and the amine (Equation 6) <1996CHEC-II(4)453, 1994PS81, 1994CB2209>.

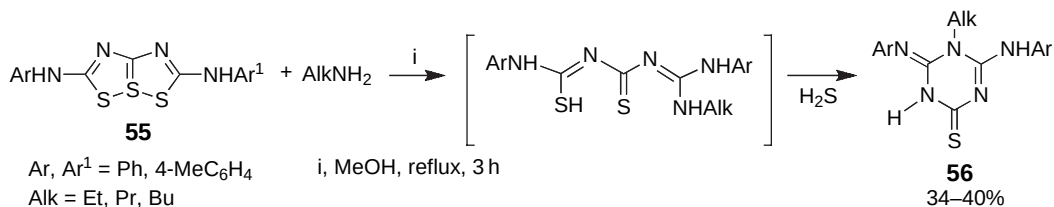


The aminolysis of pentalenes **50** with aliphatic diamines or azacrown ethers, which play the role of diamines, results in *N,N'*-bis(diazatrithiapentalenyl)diamines **51** and azacrown ether derivatives **52**. Aryloxy groups in diamines **51** can be also substituted by NR^2R^3 fragments. A combination of azacrown ethers and different diamines results in compounds **32**, **53**, and **54** (Scheme 4) <1994CB2209, 1994PS81>.



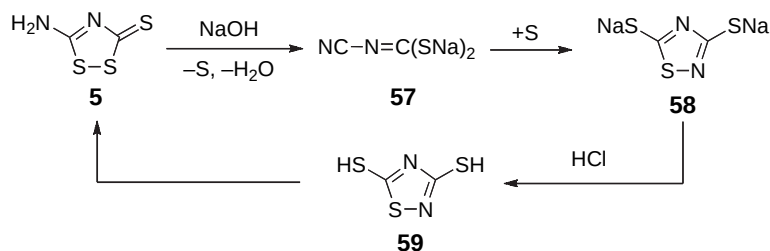
Scheme 4

2,5-Bis(arylamino)trithiapentalenes **55** transform into tetrahydro-1,3,5-triazin-4-thiones **56** under the action of primary aliphatic amines (Scheme 5) <1996IJB246>.



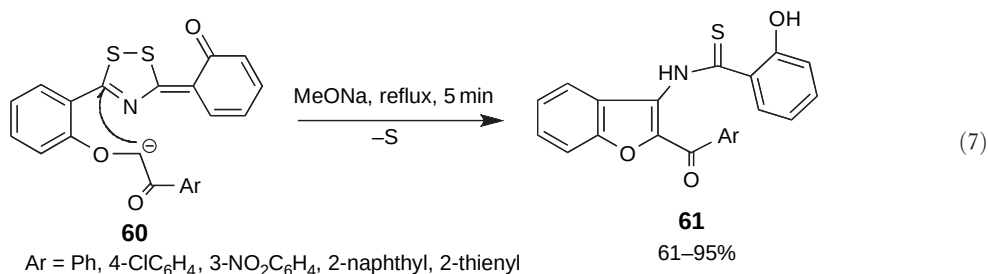
Scheme 5

5-Amino-1,2,4-dithiazole-3-thione **5** gives disodium salts **57** with sulfur extrusion in NaOH aqueous solution. Subsequently compound **57** reacts with sulfur to form the disodium salt of 1,2,4-thiadiazole **58**, which is stable in alkaline solution. After acidification, the salt **58** transforms into the initial dithiazole **5** via the unstable bithiole **59** (**Scheme 6**) <2002RJC1439, 1997JIC676, 1982ZFA111, 2001MI5>. Dianion **57** is used as a bridging ligand for the synthesis of dinuclear ruthenium(II) complexes <1995SRI663>.



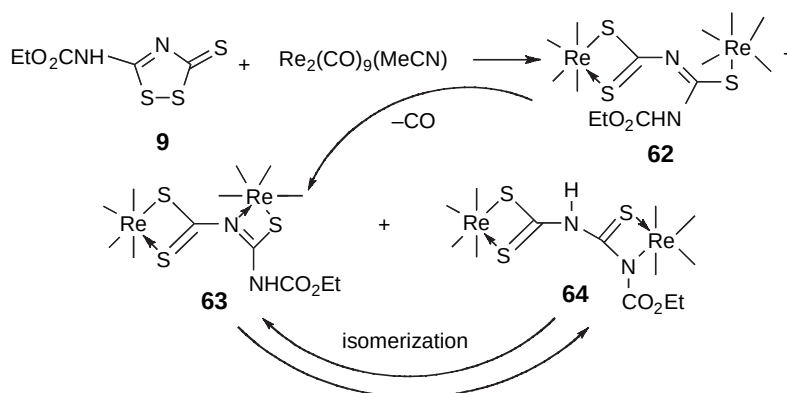
Scheme 6

Intramolecular nucleophilic attack of the acidic methylene moiety at the dithiazole C-5 carbon atom of compounds **60** is carried out in the presence of sodium methoxide. After the ring opening and extrusion of one sulfur atom, products **61** are formed (**Equation 7**) <2005H(65)1295>.



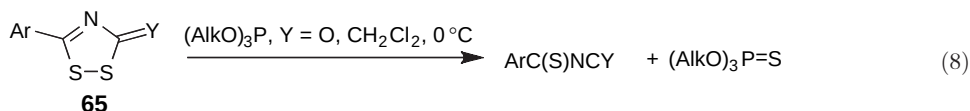
6.03.5.3 Attack at Ring Sulfur

Only a few examples of an electrophilic attack at the ring sulfur atom in 1,2,4-dithiazole derivatives are known, and, in particular, these are chlorination and methylation <1984CHEC(6)897>. The ring-opening insertion of 5-(ethoxycarbonylamino)-1,2,4-dithiazole-3-thione **9** into the Re–Re bond of the dirhenium carbonyl complex $\text{Re}_2(\text{CO})_9(\text{MeCN})$ can also be regarded as an electrophilic attack at the ring sulfur atom since a driving force of this reaction is the donation of a lone electron pair of the sulfur atom into the vacant orbital of Re. A series of complexes (mainly **62–64**) were isolated and characterized as a result of this insertion (**Scheme 7**) <1996OM2125>.

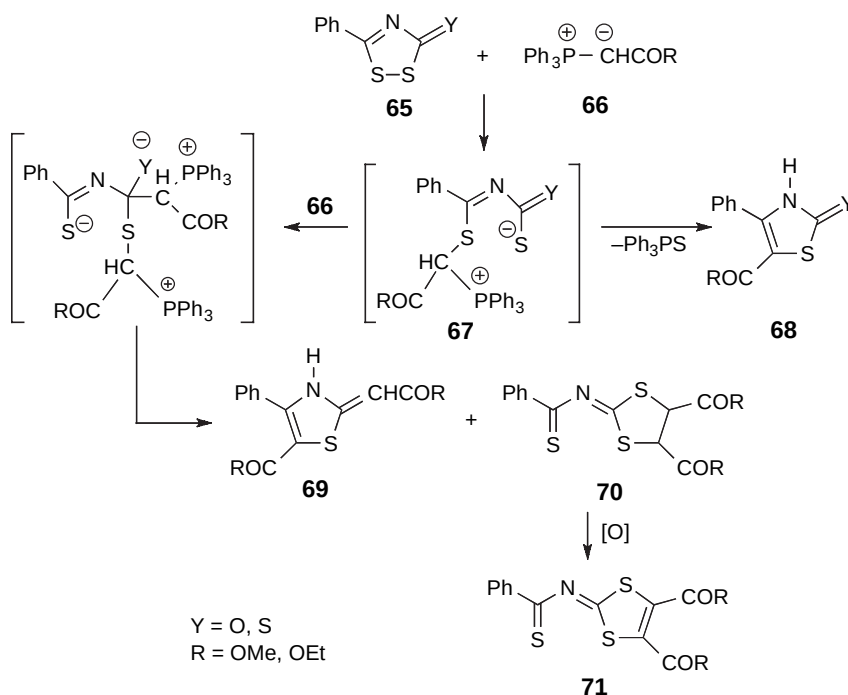


Scheme 7

Triphenylphosphine attacks the ring sulfur atom adjacent to 3-one or 3-thione groups in 1,2,4-dithiazole-3-ones(thiones) with the formation of thioacyl isocyanates or the corresponding thioacyl isothiocyantes. In the reaction with 1,2,4-dioxazole-3-ones, triphenylphosphine attacks the ring oxygen atom [1984CHEC\(6\)897](#). *O*-Ethyl cyanate is generated in the reaction of 5-ethoxy-1,2,4-dithiazole-3-one **13** with different phosphines [1996JOC6639](#). 5-Ar(Het)-1,2,4-dithiazole-3-ones (**65**; Y = O) react in a similar manner with trialkyl phosphites at 0 °C to give the corresponding thioacyl isocyanate (Equation 8) [1981CB549](#).



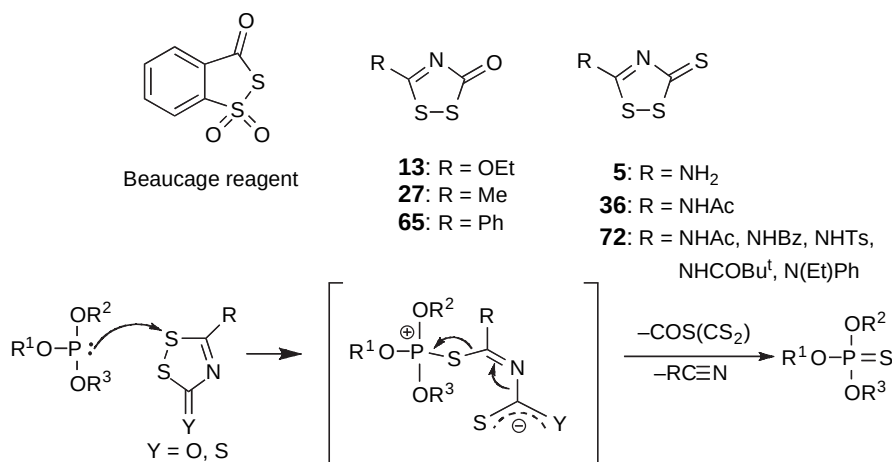
Phosphonium ylides **66** attack 1,2,4-dithiazole derivatives **65** (Y = O, S) mainly at the S–S bond to give intermediates **67**, which can either afford thiazoline derivatives **68** or react further, with a second ylide molecule **66** at the C=Y bond, to finally yield new thiazole and dithiole derivatives **69** and **70**. Compounds **70** are predominant in this mixture (yields > 50%). They are oxidized into known dithiole derivatives **71** (Scheme 8) [1993MI33](#), [1994PS105](#), [1995PS63](#), [1999PS393](#).



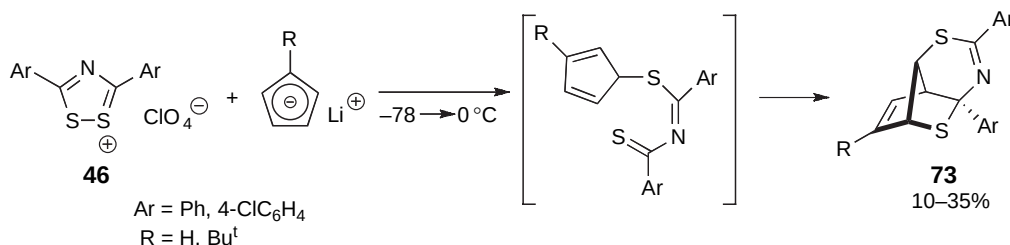
Scheme 8

The chemistry of dithiazole derivatives has received a new impetus due to their sulfur-transfer applications in the solid-phase synthesis of oligodeoxyribonucleotide phosphorothioates via the phosphoroamidite method (including a large-scale synthesis): they are advantageous alternatives to the previously used Beaucage reagent [1990JOC4693](#), [1998TL2467](#), [1999TL2095](#). For this purpose, the following 5-R-substituted 1,2,4-dithiazole-3-ones and 5-R-substituted 1,2,4-dithiazole-3-thiones have been used: **12** [1997WO41130](#), **13** [1999TL2095](#), [1999USP9903873](#), [1996NAR1602](#), [1996NAR3643](#), [1997NAR3590](#), **27** [1999TL2095](#), [2002TL4347](#), [2005USP097817](#), **65** [1999WO03873](#), **5** [2000OPD194](#), [2002TL4347](#), [2004GBPP085454](#), **36** [1998WO54198](#), and **72** [2000EPP992506](#), [1998WO54198](#). The general mechanism of the sulfur-transfer reaction is presented in Scheme 9 [2000OPD194](#), [2002TL4347](#).

Condensation of 3,5-diaryl-1,2,4-dithiazolium salts **46** with lithium cyclopentadienides affords tricyclic azadithia heterocycles **73** (Scheme 10) [1994TL3893](#), [1997LA221](#).



Scheme 9

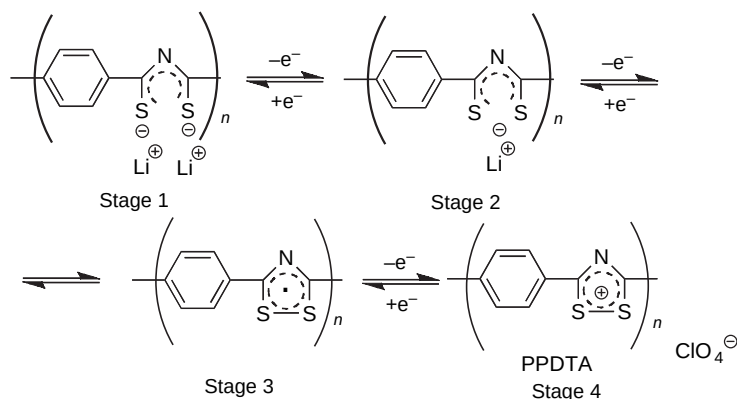


Scheme 10

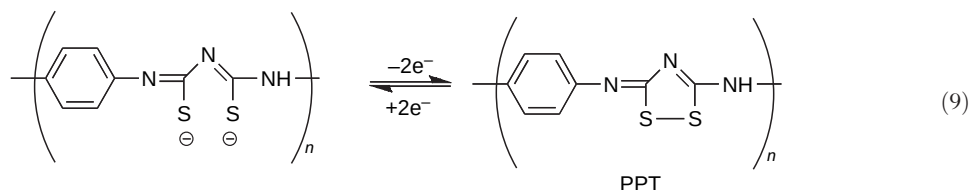
6.03.5.4 Reactions Involving Radicals, Electron-Deficient Species, Reducing Agents, and Surface Reactions

Use of Ph₃P and (AlkO)₃P for the transformation of 1,2,4-dithiazole derivatives is described in [Section 6.03.5.3](#) and in CHEC(1984) <1984CHEC(6)897>. In addition to structures containing trivalent phosphorus, other reductive reagents (e.g., NaBH₄) are also employed for the 1,2,4-dithiazole ring transformation <1996CHEC-II(4)453>.

Two new redox copolymers (PPDTA <2001MI2305> and PPT <2000CL946>) containing alternating aromatic and 1,2,4-dithiazole rings were investigated by cyclic voltammetry as potential cathode materials for high-capacity lithium secondary batteries. PPDTA provides a three-electron process due to successive redox reactions of the S–S bond and the 7π-electron unsaturated ring. At the highest oxidized stage (stage 4), the five-membered ring transforms to a 6π-aromatic cation (Scheme 11). The oxidative–reductive interconversion of covalent PPT is a two-electron process (Equation 9).

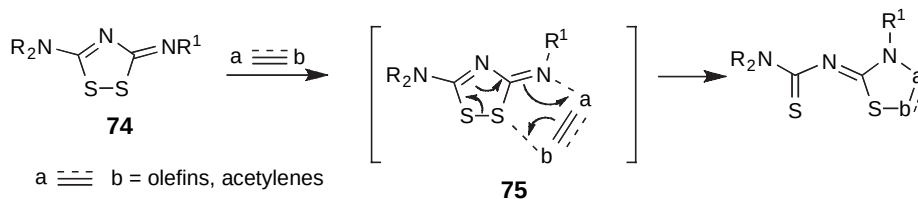


Scheme 11



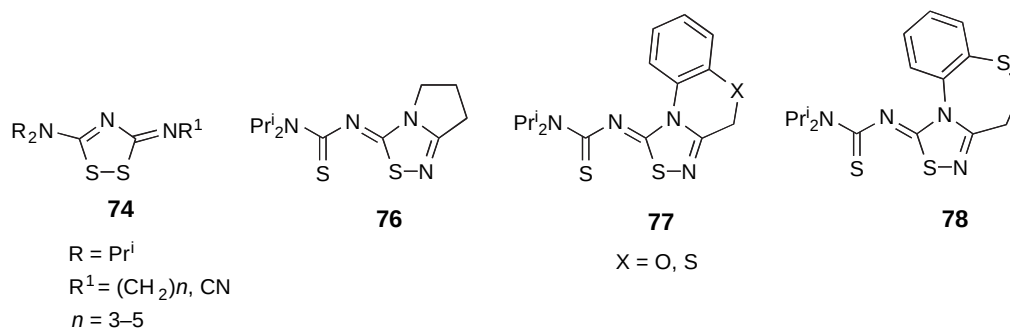
6.03.5.5 Cyclic Transition State Reactions with a Second Molecule

5-Substituted-1,2,4-dithiazole-3-ones(thiones) contain S-C=O (S-C=S) fragments capable of reacting with different dipolarophiles as 1,3-dipoles. These reactions occur with S-S bond cleavage and result in the formation of other heterocycles (1,3-thiazoles, 1,3-oxazoles, 1,2,4-thiadiazoles) [<1996CHEC-II\(4\)453>](#). 5-Amino-3-imino-1,2,4-dithiazole derivatives **74** display analogous reactivity. Thus, they undergo cycloaddition–ring-opening reactions with nitriles, heterocumulenes, activated alkenes, or acetylenes to give a new five-member heterocycles via thia-pentalene intermediates **75** (Scheme 12). These reactions are typical examples of azole–azole rearrangements [<1993AHC\(56\)49, 1993H\(35\)483>](#).

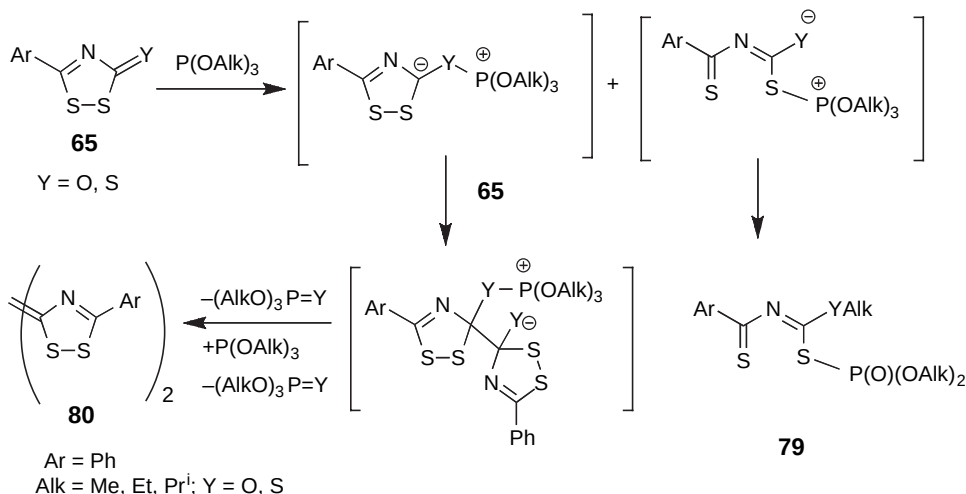


Scheme 12

An interaction of compounds **74** with nitriles can proceed both in an intra- [<1996J\(P1\)225>](#) and intermolecular [<1984CHEC\(6\)897>](#) manner. If the exocyclic imine group in compound **74** is linked with the nitrile fragment through a three-, four-, or five-atom tether, 5/5, 5/6, and 5/7 fused 1,2,4-thiadiazoles **76–78** are formed [<1996J\(P1\)225>](#).



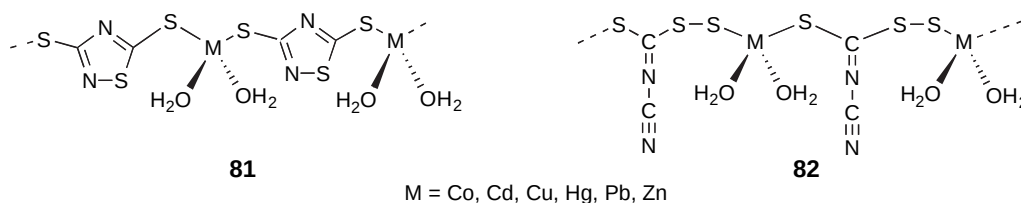
When the reaction of 5-phenyl-1,2,4-dithiazole-3-one(thione) **65** (Ar = Ph, Y = O, S) with trialkylphosphites is carried out under severe conditions (100 °C, 10 h), two different reaction centers in reactant **65** undergo an attack, namely the ring sulfur atom and the exocyclic sulfur or oxygen atom. In the first case, *S*-phosphorothioates **79** are formed. Bicyclic products **80** are the result of the second reaction pathway (Scheme 13) [<1995JRM442, 1996PS557>](#).



Scheme 13

6.03.5.6 Other Reactions

Several types of 1,2,4-dithiazolium cation complexes with metal halides and chelated transition metals were prepared and investigated; in particular, 3,5-diamino- and 5-phenyl-3-R-1,2,4-dithiazolium derivatives [<1996CHEC-II\(4\)453>](#). An interest in complexing of 1,2,4-dithiazole derivatives has been stimulated by their ability to form insoluble compounds with heavy metal salts that can be used for water treatment. 5-Amino-1,2,4-dithiazole-3-thione **5** and its *N*-acetyl derivative **36** forms complexes with Co, Cd, Cu, Hg, Pb, and Zn chlorides by mixing solutions of ligand and the corresponding metal salt in equimolar amounts [<1996SPL477>](#). According to the IR data, the obtained complexes have a polymer structure that is built with tautomeric forms of the initial ligands (both cyclic **81** and open **82**) (see also [Section 6.03.3.5](#)).



6.03.6 Reactivity of Nonconjugated Rings

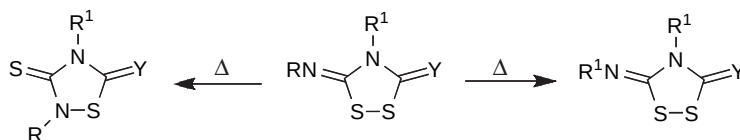
As for fully conjugated systems, most of the research on chemical transformations of the nonconjugated rings has been devoted to 1,2,4-dithiazolidine derivatives. Molecules having imino- or thione groups conjugated with the ring sulfur atom participate in 1,3-cycloaddition with various dipolarophiles to form new five-membered heterocycles (see [<1996CHEC-II\(4\)453>](#); [Section 6.03.6.1.4](#)). The Dimroth rearrangement, which is initiated thermally or by a basic catalysis, is also a general reaction for such compounds [<1984CHEC\(6\)897, 1996CHEC-II\(4\)453>](#). All ring atoms (carbon, nitrogen, and sulfur) can easily undergo a nucleophilic attack that results in a significant transformation of the molecule, mainly with the formation of new heterocyclic systems, either with the sulfur atom or without it. In addition, the ring nitrogen atom in *N*-nonsubstituted 1,2,4-dithiazolidine-2,5-dione is capable of undergoing an electrophilic attack (alkylation, acylation, and Mitsunobu reactions) (see [Section 6.03.6.1.2](#)). The ability of the formed *N*-substituted 1,2,4-dithiazolidine-3,5-diones to donate a ring sulfur atom to different reducing agents (thiols, Ph_3P) is used for removal of the Dts protecting group and for the synthesis of isocyanates, including stereocontrolled synthesis (see [Section 6.03.6.1.3](#)).

1,2,4-Oxathiazolidine-3-ones lose CO₂ and sulfur at room temperature to form open-chain products <1996CHEC-II(4)453>. 3-Aryl-1,2,4-oxathiazolines are oxidized by *m*-chloroperbenzoic acid (MCPBA) to the corresponding cyclic *S*-oxides and decompose thermally, or under the action of amines or Ph₃P, to give ArCN (see Section 6.03.6.2). The most characteristic reaction of 1,2,4-dioxazolidines is thermal rupture of the O–O bond to form acyclic products (see <1984CHEC(6)897, 1996CHEC-II(4)453>; Section 6.03.6.2).

6.03.6.1 Reactions of Isomers of Fully Conjugated Ring Compounds

6.03.6.1.1 Thermal mononuclear reactions

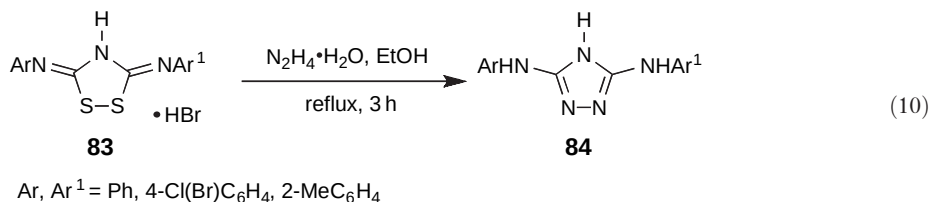
A classic example of this reaction is the Dimroth rearrangement, which is initiated thermally or in the presence of base catalysts and can usually occur with the retention or cleavage of the S–S bond depending on the nature of the substituents. The former pathway is typical of 3,5-diimino- and 5-imino-1,2,4-dithiazolidine-3-one derivatives and involves a rupture of one C–N bond, rotation of the N–C–N moiety around the S–C bond, and formation of a new 1,2,4-dithiazolidine derivative. The second pathway occurs when at least one N-substituent is an alkyl group and involves a rupture of the S–S bond, rotation of the N–C–S moiety around the N–C bond, and formation of the 1,2,4-thiadiazolidine derivative (Scheme 14) <1996CHEC-II(4)453>.



Scheme 14

6.03.6.1.2 Attack at ring carbon and nitrogen

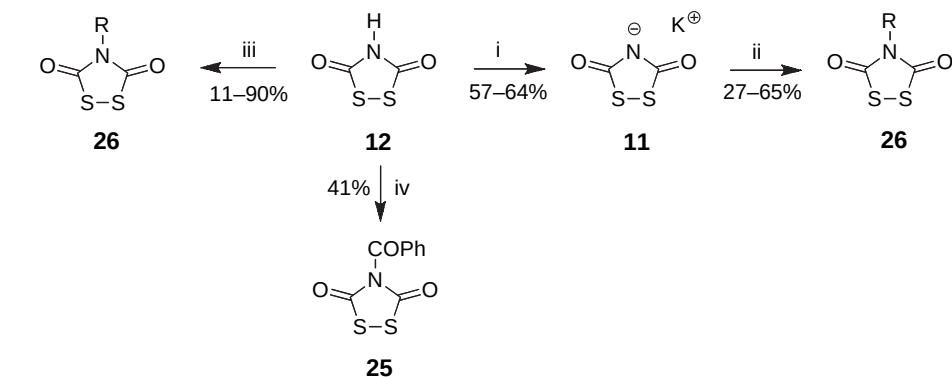
Similar to the conjugated 1,2,4-dithiazole derivatives, 1,2,4-dithiazolidines are disposed toward nucleophilic attacks at carbon and sulfur atoms. Thus, 3,5-bis(arylimino)-1,2,4-dithiazolidine hydrobromides **83** are transformed into 4*H*-3,5-bis(arylimino)-1,2,4-triazoles **84** at reflux with a hydrazine hydrate excess in ethanol (Equation 10) <2004MI534>. Aniline and benzylamine also attack 1,2,4-dithiazolidines **23** at 3,5-carbon atoms <1996CHEC-II(4)453>.



Only a few examples of a nucleophilic attack at the nitrogen atom of 1,2,4-dithiazolidine derivatives are known. 5-Imino-1,2,4-dithiazolidine-3-thione gives tribenzyl-substituted 5-imino-1,2,4-thiadiazolidine-3-thione with an excess of boiling benzylamine <1996CHEC-II(4)453>. 1,2,4-Dithiazolidine-3,5-dione **12** forms the potassium salt **11** under the action of KOH in ethanol or KH in MeCN (Scheme 15) <2000SL1622>.

The unsubstituted nitrogen atom in 1,2,4-dithiazolidines is more prone to electrophilic reactions. Both the potassium salt **11** and the initial product **12** can participate in alkylation and acylation reactions. Alkylation of salt **11** with alkyl halides is carried out in DMF or MeCN and compound **12** can react with alkyl halides in MeCN in the presence of inorganic bases (NaH, Bu⁺OK, AcONa, NaHCO₃, Cs₂CO₃): NaHCO₃ proved to be the base of choice. Yields of alkylation products **26** in some cases reach 85–90%. Compound **12** was acylated by benzoyl chloride in pyridine to form the *N*-benzoyl derivative **25** (Scheme 15) <2000SL1622, 2003OBC3015>.

Another approach to the preparation of *N*-alkyl derivatives **26** is the Mitsunobu reaction. The Mitsunobu procedure is now a well-known method for preparing amines from alcohols using acidic imide derivatives as a nitrogen nucleophile <1981S1, 1996OPP127>. The remarkably high acidity of 1,2,4-dithiazolidine-3,5-dione **12** (p*K*_a = 2.8) <2000SL1622> suggests that it is likely to be a synthetically useful nucleophile in this procedure. The sensitivity of heterocycle **12** to phosphines prevents the application of traditional triphenylphosphine–azodicarboxylate Mitsunobu conditions. Betaine



R = Me, hexyl, Prⁱ, Bn, ($\pm$)CH₂C(H)CO₂Me, allyl, propargyl, prenyl, CH₂CO₂Et, 4-BnOC₆H₄CH₂

i, (a) KOH, EtOH, -5°C , 15 min; (b) KH, MeCN, -20°C , 2 h

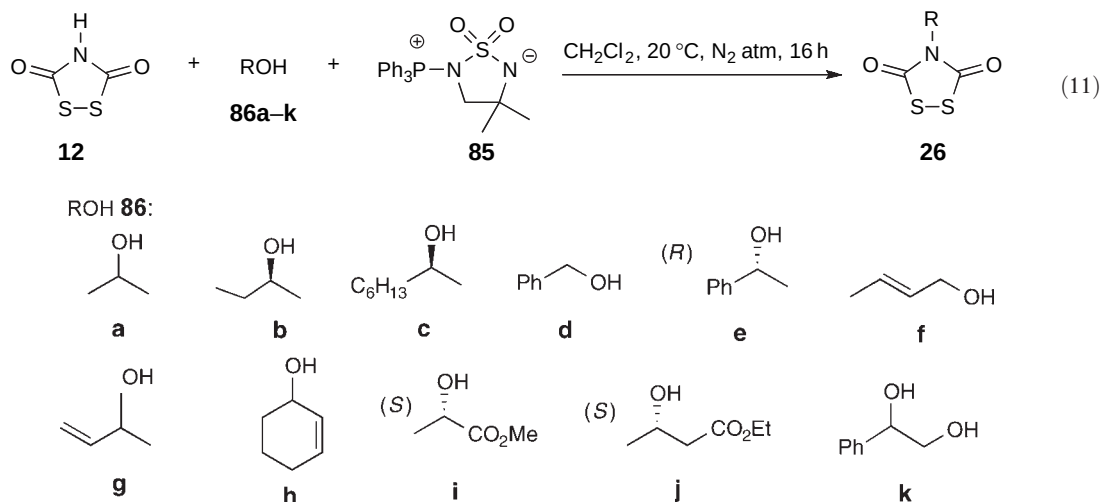
ii, RI (RBr) (1–1.5 mol), DMF or MeCN, 40 °C, 16 h

iii, RBr (RI, RCl + KI), (1–1.6 mol), base (0.5–2 mol), MeCN, rt, 16 h

iv, BzCl (1 mol), pyridine (2.5 mol), 0–20 °C, 72 h

Scheme 15

85 appears to be an effective reagent for introducing compound **12** into the Mitsunobu reaction <2002J(P1)2046, 2005T2141>. A suitable range of alcohol substrates **86a–k** were used to compare the results with the known phthalimide Mitsunobu procedure. Treatment of alcohols **86a–k** with 1,2,4-dithiazolidine-3,5-dione **12** in the presence of 1–1.5 mol betaine **85** in CH₂Cl₂ resulted in formation of the corresponding N-alkylated compounds **26** (Equation 11).



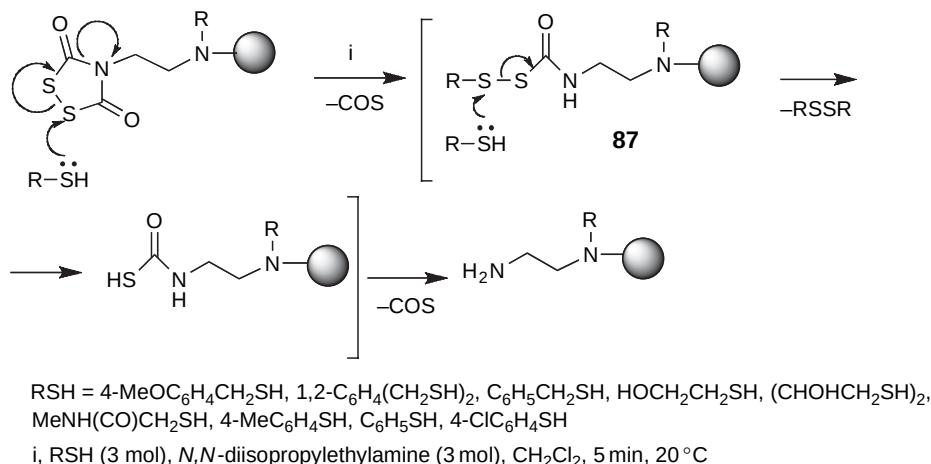
It has been found that the results of this new variant of the Mitsunobu procedure are generally comparable with the results of the traditional Mitsunobu reaction both with respect to the yields and enantiomeric excess (ee) of chiral compounds **26**. Thus, products prepared from alcohol **86e** using both methods had ee 70% and 72%, and from (*S*)-methyl lactate **86i** 92% and 99%, respectively. However the new variant of the Mitsunobu procedure has a significant synthetic advantage over the traditional procedure: imides **26** can be transformed into primary amines under milder conditions in comparison with the deprotection of *N*-alkylphthalimides (see Section 6.03.6.1.3).

6.03.6.1.3 Nucleophilic attack at ring sulfur

1,2,4-Dithiazolidine-3,5-dione **12**, as for 5-R-1,2,4-dithiazole-3-ones(thiones) **5**, **13**, **27**, **36**, **65**, and **72**, is an effective sulfur-transfer reagent for establishing phosphorothioate linkages in oligodeoxyribonucleotides (see [Section 6.03.3.3](#)). Sulfurization promoted by compound **12** as well as by compound **13** occur at low concentrations and short reaction

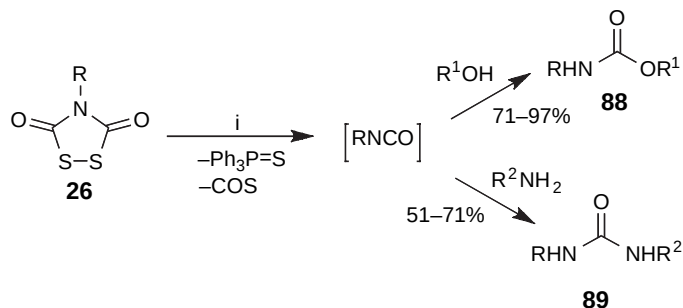
times <1996SPL477, 1997WO41130>. The known susceptibility of the 1,2,4-dithiazolidine ring to S–S bond reduction is extensively used for the removal of the Dts protecting group in the synthesis of peptides, O-glucopptides, protected peptide nucleic acid oligomer (PNA), and 1,2-*trans*-amino sugar glycosides <1995J(P1)405, 1996JA3148, 1996SPL477, 1996J(P1)985, 1997J(P1)871, 1997AGE1976, 1999JOC7281>.

The Dts protecting group is removed by thiols through intermediate open-chain carbamoyl disulfide **87**, which reacts further with a second equivalent of thiol to provide a free amino function (**Scheme 16**). The reaction is driven to completion by a loss of 2 equiv of gaseous carbonyl sulfide and is usually catalyzed by tertiary amines, for example, *N,N*-diisopropylethylamine. Sometimes Zn in AcOH is used to remove the Dts protection; simultaneously, free amine group acylation can be carried out by Ac₂O/pyridine addition to the reaction mixture <1996J(P1)985, 1996JA3148>.



Scheme 16

The successive synthesis of *N*-alkyl-1,2,4-dithiazolidine-3,5-diones **26** by alkylation and especially by the Mitsunobu reaction (see Section 6.03.6.1.2.) of compound **12** has given an opportunity for a simple preparation of different isocyanates (and thus primary aliphatic amines) from corresponding alcohols, including a stereocontrolled route to protected isocyanates. In fact, 1,2,4-dithiazolidine-3,5-dione **12** is a nucleophilic isocyanate 'building block'. The isocyanates are synthesized by heating of compounds **26** with 1 equiv of Ph₃P in benzene or toluene under reflux and trapped as urethanes **88** or ureas **89** by addition of corresponding alcohols or amines to the reaction mixture (**Scheme 17**) <1996JA3148, 2000SL1622, 2002J(P1)2046, 2003OBC3015, 2005T2141>. Importantly, for all isolated urethanes **88**, the ee was determined to be the same as for starting alcohols (see Section 6.03.6.1.2) within experimental error, assuming that the intermediate isocyanates were configurationally stable under the reaction conditions employed <2005T2141>.

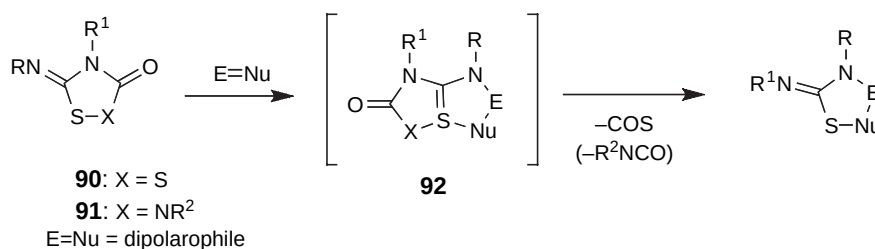


i, Ph₃P (1 mol), R¹OH (R²NH₂), benzene (80 °C), toluene (110 °C), 48 h

Scheme 17

6.03.6.1.4 Cyclic transition state reactions with a second molecule

Sulfur-containing five-membered heterocycles having imino or thione groups conjugated with the ring sulfur atom interact with different dipolarophiles (heterocumulenes, nitriles, ketenes, acetylenes) at the S-C=N or S-C=S fragments (1,3-dipoles) by cycloaddition–elimination through heteropentalene intermediates with the formation of new five-membered heterocycles <1996CHEC-II(4)453>. 5-Imino-1,2,4-dithiazolidine-3-ones **90** and 5-imino-1,2,4-thiadiazolidine-3-ones **91** enter analogous reactions with unsaturated dipolarophiles of the E=Nu type forming new heterocycles via the bicyclic intermediates **92** (Scheme 18) <1990JHC1629, 1991JPR579, 1996CHEC-II(4)453>.



Scheme 18

Both compounds **90** and **91** can react with reagents containing electron-rich double bonds such as enamines **93** and ester enolates **98** <1998EJO515>. It was found that compounds **90** were less reactive than their 1,2,4-thiadiazolidine analogs **91**. Electron-withdrawing substituents attached to nitrogen atoms of compounds **90** accelerate the reaction. Dialkyl-substituted dithiazolidines **90** do not react with enamines under these conditions. In the interaction of diphenyl-substituted 1,2,4-dithiazolidine **90a** (R = R¹ = Ph) with 2 equiv of piperidinocyclopentene **93a** and pyrrolidinocyclohexene **93b**, bicyclic amins **94** and **95** are isolated (Scheme 19). However, when compound **90b** reacted with enamine **93a**, a mixture of two chromatographically inseparable isomers **94a** and **94b** was obtained, with isomer **94b** being the main component. Such behavior of compound **90b** in this reaction can be understood by postulating the intermediate **97**. The reaction of compound **90b** with enamine **93b** resulted in a mixture of isomers **96a** and **96b**, evidently being the products of the deamination of structural analogs of compounds **95a** and **95b** (Scheme 19).

Dithiazolidine **90a** reacts with ketene enolates **98** at the imino group with the formation of new dithiazolidine derivative **99** through a possible bicyclic intermediate containing a β -lactame fragment (Scheme 20) <1998EJO515>.

6.03.6.2 Reaction of Hydrogenated Derivatives of Fully Conjugated Ring Compounds

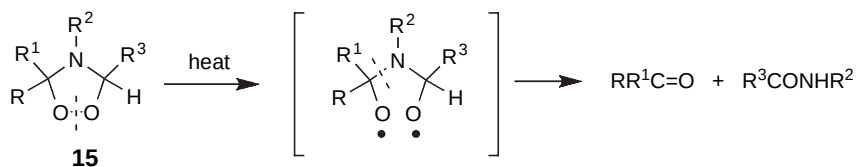
The most characteristic reactions for these compounds are thermolysis and decomposition under the action of both acids and nucleophilic reagents. 1,2,4-Dioxazolidines **15** are thermally stable only below 100 °C. The thermolysis of compound **15a** in solution at 130 °C afforded benzophenone and benzamide in quantitative yields. The formation of these products is consistent with a radical mechanism involving initial O–O homolysis (Scheme 21). The base-catalyzed decomposition of compound **15a** afforded the same products. Similar results were observed for the decomposition of compounds **15b** and **15c**. The interaction of dioxazolidine **15a** with triphenylphosphine resulted in deoxygenation of the system with the concomitant formation of benzophenone and its imine with aniline <1995J(P1)41>.

The treatment of the dioxazolidines **16** with silica gel in CH₂Cl₂ for 1 day afforded a mixture of the corresponding cycloalkenes, benzaldehyde and *N*-benzylformamide (Scheme 22) <1994J(P1)2449>.

The thermolysis of 1,2,4-oxathiazolines **20**, as well as their interaction with benzylamine, produces nitriles of the corresponding benzoic acids. When compounds **20** were treated with Ph₃P, the same nitriles and Ph₃P=S were obtained. Oxidation of compounds **20** with MCPBA gives an inseparable oily epimeric mixture of the corresponding *S*-oxides **21** in the approximate ratio 3:1. 1,2,4-Thiadiazoles **100** were formed through the contact of compounds **20** with silica gel or Lewis acids (Scheme 23) <2003TL2517>.

The reaction of 1,2,4-dithiazolines **22** (R = Bu^t, R¹ = Ph) with Ph₃P in the presence of EtOH in CH₂Cl₂ at room temperature afforded thioamide **102**, which is the 1,4-adduct of heterodiene **101** with EtOH, together with Ph₃P=S (Scheme 24) <2004TL6187>.



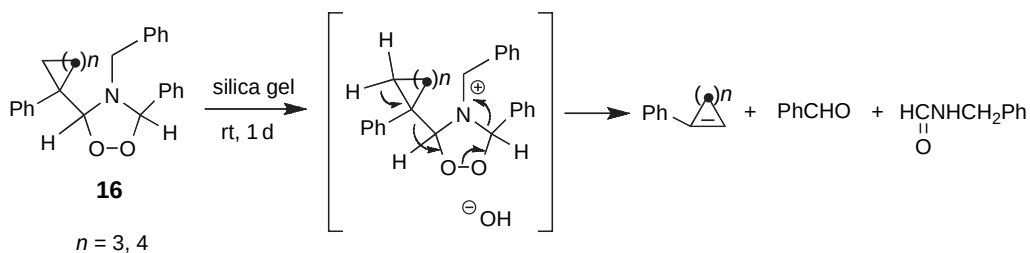


a: $R = R^1 = R^2 = R^3 = \text{Ph}$

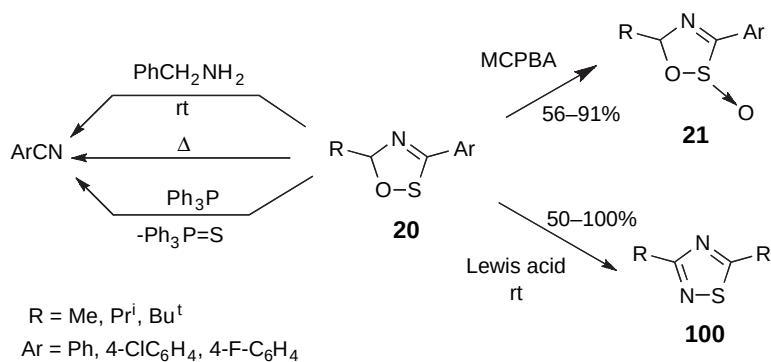
b: $R = \text{Me}; R^1 = R^2 = R^3 = \text{Ph}$

c: $R-R^1 = (\text{CH}_2)_2\text{CHBu}^t(\text{CH}_2)_2; R^2 = R^3 = \text{Ph}$

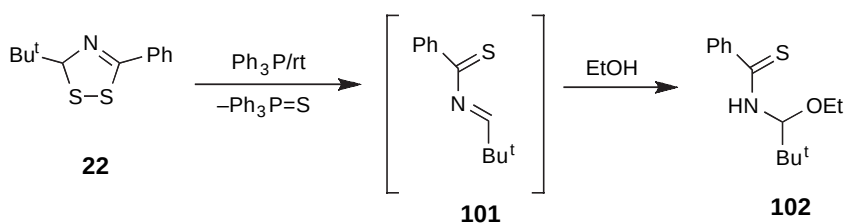
Scheme 21



Scheme 22



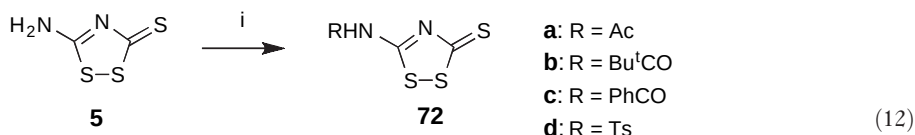
Scheme 23



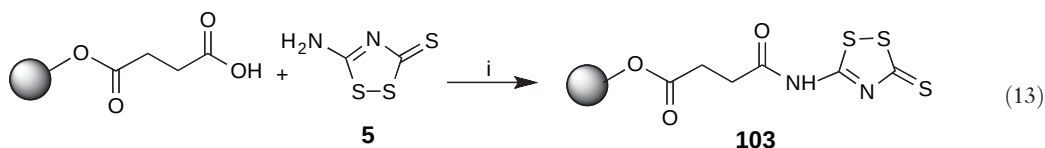
Scheme 24

6.03.7 Reactivity of Substituents Attached to Ring Carbon and Nitrogen Atoms

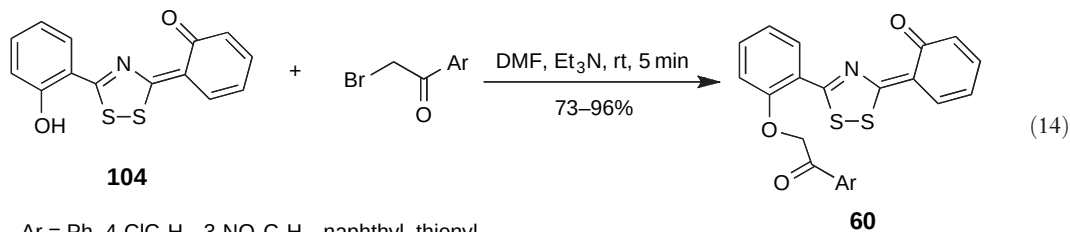
Several new sulfur-transfer reagents **72a–d** were synthesized by acylation of 5-amino-1,2,4-dithiazole-3-thione **5** with acetic anhydride, trimethylacetic anhydride, benzoyl chloride, and *p*-toluenesulfonyl chloride in the presence of tertiary amines in dipolar aprotic solvents (Equation 12) <1998WO54198>. The polymer-supported 5-amino-1,2,4-dithiazole-5-thione **103**, which is an effective sulfur-transfer reagent, was synthesized by the attachment of a hydroxyl resin via a succinic acid linker (Equation 13) <2002TL4347>. The synthesis of structures **60** was performed by alkylation of phenolic hydroxyl groups in 3,5-bis(2-hydroxyphenyl)-1,2,4-dithiazole **104** (Equation 14) <2005H(65)1295>. *N*-Amidino derivatives of 3,5-bis(phenylimino)-1,2,4-dithiazolidines **105** undergo acylation and nitrosylation reactions at the amidine fragments (Equation 15) <2004MI447>.



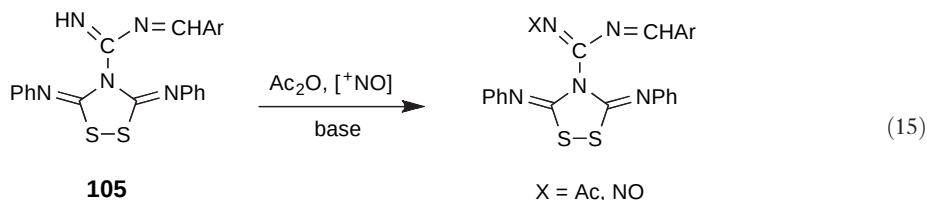
i, Ac₂O [(Bu^tCO)₂O, PhCOCl, TsCl] (1.2 mol),
pyridine (triethylamine) (xs), MeCN (CH₂Cl₂), 25 °C, 1–2 h



i, *N,N*-diisopropylcarbodiimide, pyridine, rt, 12 h



Ar = Ph, 4-ClC₆H₄, 3-NO₂C₆H₄, naphthyl, thienyl

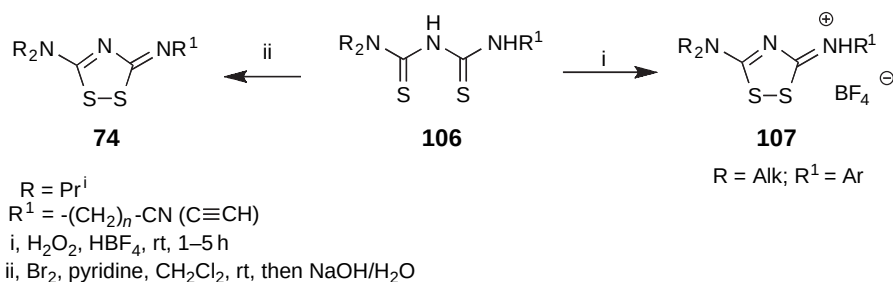


Ar = Ph, 4-ClC₆H₄, 3-MeO-5-HOC₆H₃, 4-MeOC₆H₄, 4-Me₂NC₆H₄

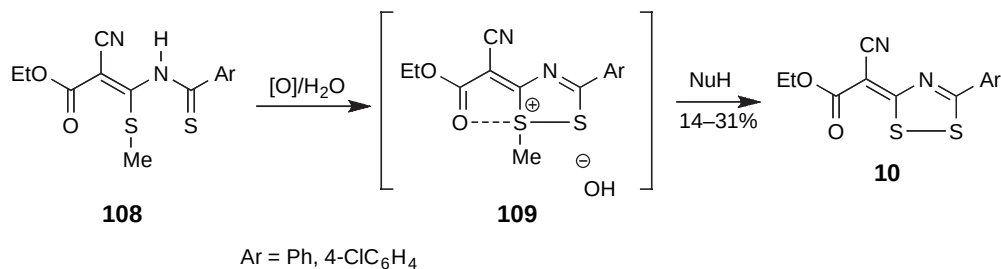
6.03.8 Ring Synthesis Classified by Number of Ring Atoms in Each Component

6.03.8.1 Formation of One Bond between Two Heteroatoms

S–S Bond formation by oxidative cyclization of thioacyl thioureas, dithiobiurets, or isodithiobiurets is one of the best known methods for the preparation of 1,2,4-dithiazole derivatives, and continues to be useful <1996CHEC-II(4)453>. Thus dithiobiurets **106** are cyclized, readily, and in high yields, to dithiazolium salts **107** by treatment with a H₂O₂/HBF₄ mixture <1994JPP08027148>. Where the NH group in compound **106** is intramolecularly bound to CN or C≡CH fragments, cyclization into dithiazoles **74** is performed with Br₂ in pyridine (Scheme 25) <1996J(P1)225>. Thioamide **108** was oxidized into dithiazole **10** by air oxygen via intermediate **109** (Scheme 26) <2003H(60)2273>.

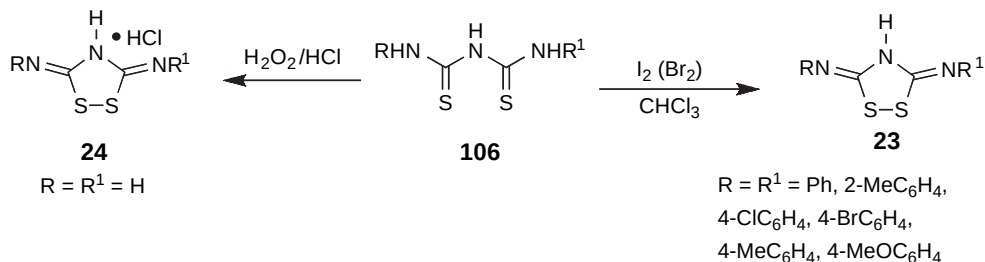


Scheme 25

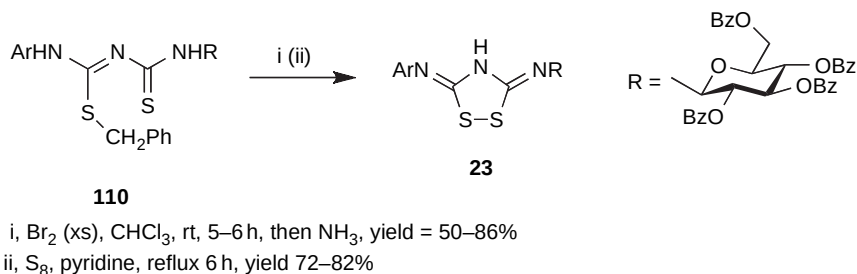


Scheme 26

The treatment of dithiobiurets **106** (R = R¹ = Ar) with I₂ <2002MI103> and **106** (R = H) with H₂O₂ or Br₂ <2004MI534, 2003H(60)1401> results in dithiazolidines **23** and **24**, respectively (Scheme 27). A series of 5-aryl-imino-3-(tetra-*O*-benzoyl-β-D-glucopyranosylimino)-1,2,4-dithiazolidines **23** were synthesized by cyclization with debenzoylation of the corresponding isodithiobiurets **110** under the action of Br₂ <2003IJH391> or elemental sulfur in pyridine (Scheme 28) <1995MI672, 1998MI986>.

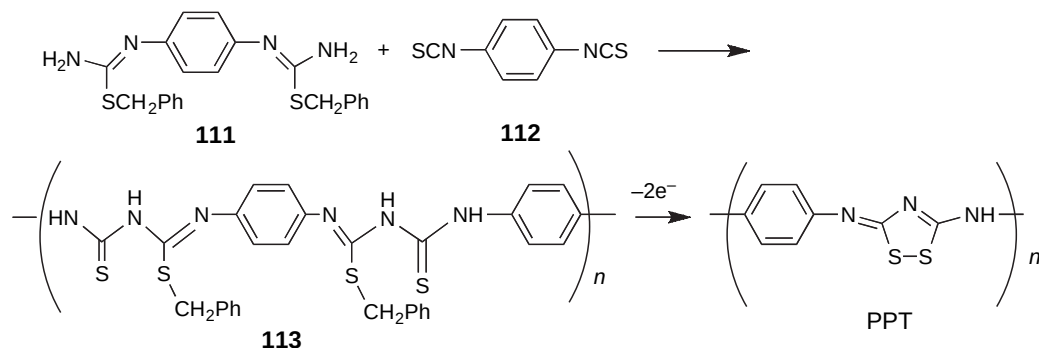


Scheme 27



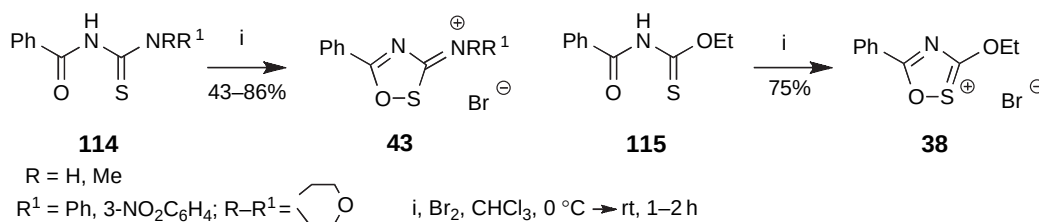
Scheme 28

S-Benzylthiobiuret **113** synthesized by condensation of *N,N'*-1,4-phenylenebis(*S*-benzylthiourea) **111** with 1,4-diisocyanate **112** was transformed into a new redox polymer PPT by electrochemical oxidative debenzylation on the cathode with simultaneous cyclization (Scheme 29) <2000CL946>. An electrochemical reaction is superior to a chemical reaction from the standpoint of generating completely debenzylated PPT in a heterogeneous reaction and estimating the PPT charge capacity.



Scheme 29

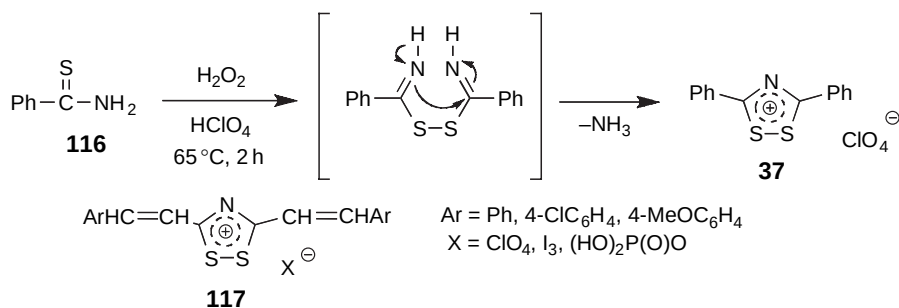
Oxidative cyclization of *N*-acylthiourea derivatives **114** and *N*-acylthiocarbamates **115** also proved to be effective for preparing 1,2,4-oxathiazolium structures **43** and **38**, respectively <1997IJB216>. Hydrogen peroxide and Br₂ were examined as oxidants for this reaction (Scheme 30). Br₂ appeared to be a better oxidant compared to hydrogen peroxide. The latter brought about sulfur atom replacement by oxygen.



Scheme 30

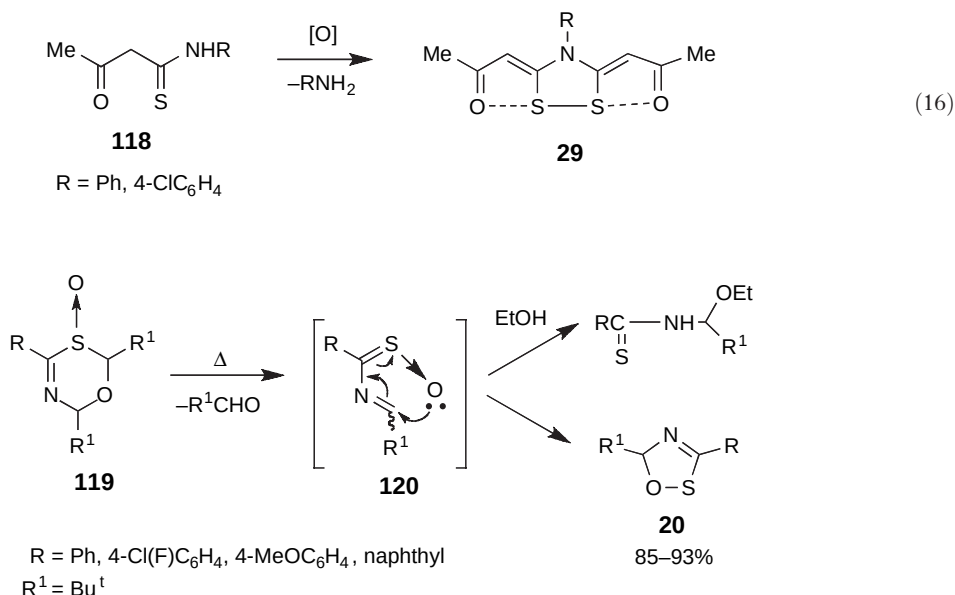
6.03.8.2 Formation of One Bond Adjacent to a Heteroatom

The *N*-acylthioureas <1996CHEC-II(4)453>, thioamides, and thioanilides of 3-oxoacids can be converted into 1,2,4-dithiazole derivatives by reaction with different oxidants. In all the cases, the reaction begins with S-S bond formation followed by cyclization to the target compounds with primary amine or ammonia extrusion. Thus, thiobenzamide **116** gives 3,5-diphenyl-1,2,4-dithiazolium perchlorate **37** in 80% yield upon treatment with H₂O₂ and HClO₄ (Scheme 31) <2001MI2305>. In a similar way, PPDTA <2001MI2305> (see Section 6.03.2), 3,5-bis(α,β-unsaturated)-1,2,4-dithiazolium salts **117**, and 1,2,4-dithiazole **104** <2005H(65)1295> are prepared.



Scheme 31

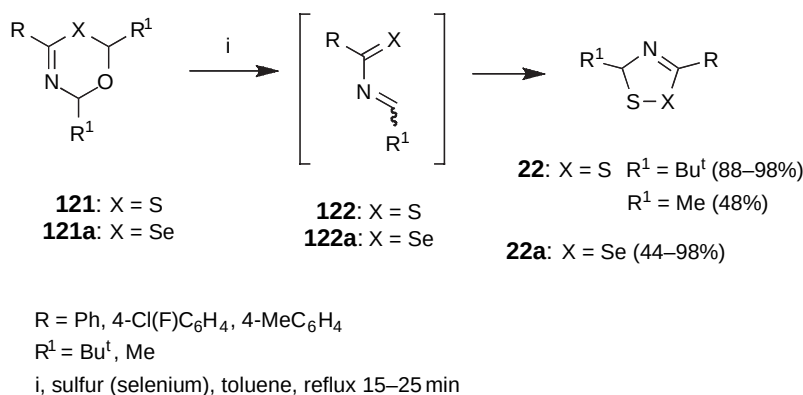
Thioamides of 3-oxoacids **118** are transformed into 1,2,4-dithiazolidines **29** by treatment with cerium ammonium nitrate (CAN) in MeOH or with CF_3SCl in CH_2Cl_2 (Equation 16) <1996SC4165, 2001SC189>. The thermal conversion of 6*H*-1,3,5-oxathiazine *S*-oxides **119** in refluxing benzene results in 1,2,4-oxathiazolines **20** with extrusion of R^1CHO . This reaction involves the heterodiene intermediate **120**, which can be independently trapped by the reaction with EtOH (Scheme 32) <2003TL2517, 2004HAC175>.



Scheme 32

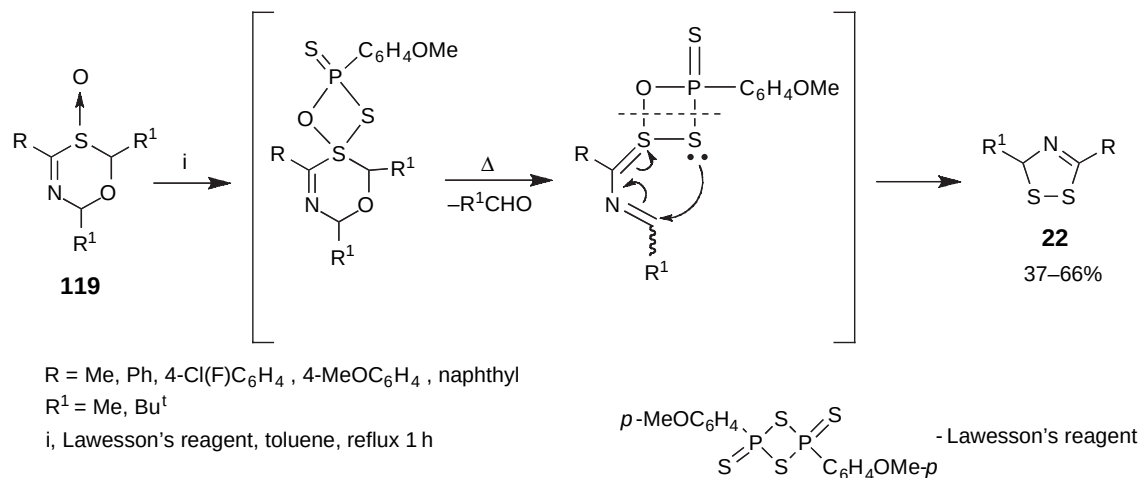
6.03.8.3 Formation of Two Bonds: Four-Atom Fragment and Sulfur

The initial four-atom fragments, that is, heterodienes **122**, can be generated by the thermally induced retro-[4+2] cycloconversion of 6*H*-1,3,5-oxathiazines **121** <2001BCJ511, 2004TL6187, 2004HAC208>. The same transformation takes place with 6*H*-1,3,5-oxaselenazines **121a**. If compounds **121** are heated in the absence of sulfur, only traces of 1,2,4-dithiazolines **22** are formed along with recovery of substrate **122**. Evidently, the intermediate heterodienes **122** upon heating may undergo further fragmentation to give sulfur species. When the thermolysis is performed in the presence of sulfur, 1,2,4-dithiazolines **22** are formed in high yields (Scheme 33).



Scheme 33

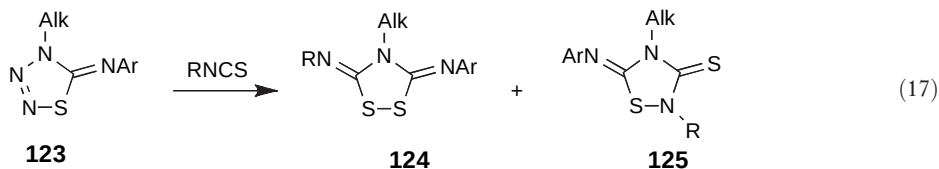
Thiobenzamide can also be used as a thiating reagent in this reaction <2001BCJ511>. However, in this case, 1,2,4-dithiazolines **22** are formed in low yield (14–22%). The latter can be also synthesized by treating 6*H*-1,3,5-oxathiazine *S*-oxides **119** with Lawesson's reagent (LR) or P₂S₅ in refluxing toluene <2004HAC208>. The most probable mechanism of the reaction with LR includes R¹CHO extrusion followed by the deoxygenation and sulfurization steps (Scheme 34).



Scheme 34

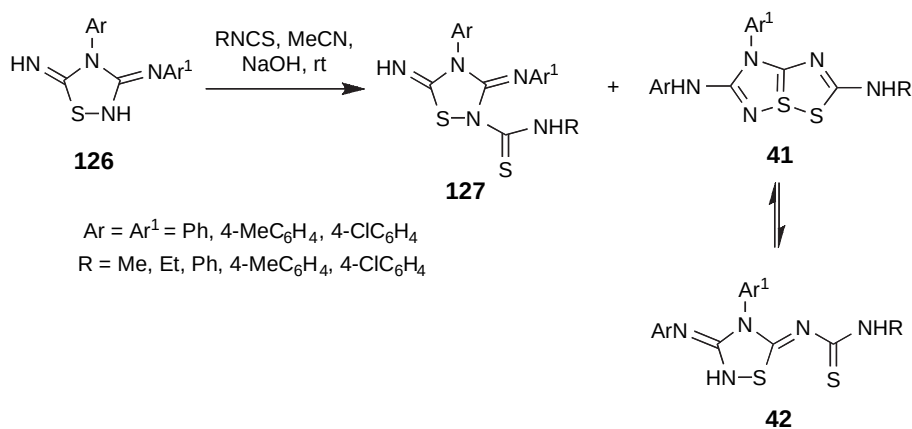
6.03.8.4 Formation of Two Bonds: [3+2] Atom Fragment by Cycloaddition

This approach to 1,2,4-dithiazolidine derivatives **124** was investigated in detail by L'abbe and co-workers on the example of a reaction of 4-alkyl-5-arylimino-1,2,3,4-thiotriazolines **123** and related compounds with isothiocyanates and other heterocumulenes. In these reactions, in addition to compounds **124**, 1,2,4-thiadiazolidine-3-thiones **125** are formed (Equation 17) <1996CHEC-II(4)453>.

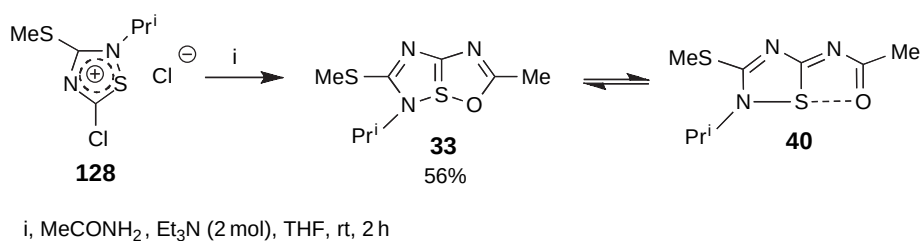


Cyclocondensation of alkyl(aryl)isothiocyanates with 4-aryl-3-arylimino-5-imino-1,2,4-thiadiazolidines (Hector's bases) **126** in the presence of strong bases leads to the formation of the corresponding (1,2,4-thiadiazolidinyl)thioureas **127** and heteropentalene structures **41** (Scheme 35), for which an isomerization equilibrium with the open form **42** was proposed (see Section 6.03.4.2) <1997IJB399>.

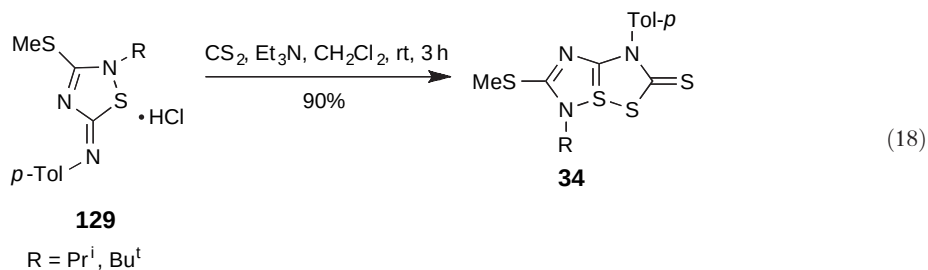
Acetamide enters a cycloaddition reaction with thiadiazolium salts **128** in the presence of triethylamine with the formation of heteropentalene structure **33**, for which an isomerization equilibrium with open form **40** was also proposed (see Section 6.03.4) (Scheme 36) <2003HAC95>. 3-*S*-Methyl-5-(*p*-tolylimino)-1,2,4-thiadiazole hydrochlorides **129** form heteropentalene structures **34** in a cycloaddition reaction with CS₂ in nearly quantitative yields (Equation 18) <2003HAC95>. Similar structures, including selenium containing products, are obtained by the reaction of compounds **129** with iso-, isothio-, and isoselenocyanates <2003HAC95>.



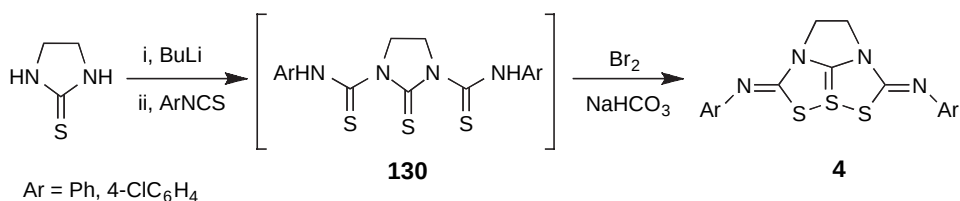
Scheme 35



Scheme 36



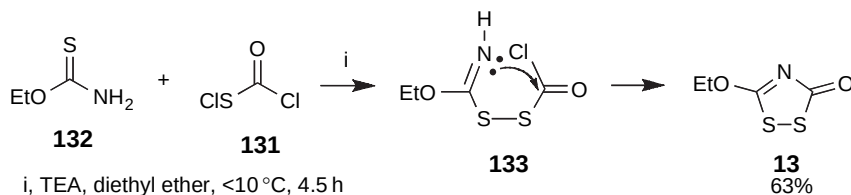
Heteropentalene structures **4** were synthesized by the reaction of imidazolidine-2-thione with ArNCS in the presence of BuLi followed by oxidation of intermediates **130** with Br₂/NaHCO₃ (**Scheme 37**) <1997BCJ1267>.



Scheme 37

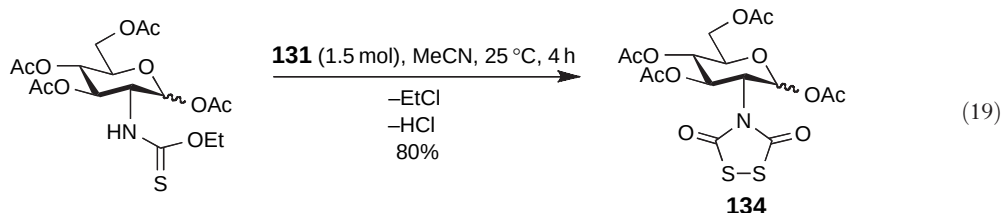
6.03.8.5 Formation of Two Bonds: [3+2] Atom Fragments by Other Processes

The [3+2] reactions of chlorocarbonylsulfonyl chloride **131** and its derivatives at the carbonyl group with thioureas and related compounds have been used for a long time to prepare 1,2,4-dithiazole derivatives <1996CHEC-II(4)453>. Over the last years studies of these reactions have been stimulated by their applications for the Dts protection in the synthesis of peptides and glycosides as well as by the use of 5-ethoxy-1,2,4-dithiazole-3-one **13** and the product of its hydrolysis (1,2,4-dithiazolidine-3,5-dione **12**) as new effective sulfur-transfer reagents (see Section 6.03.6.1.3). The mechanism of formation of compound **13** from sulfonyl chloride **131** and ethylthiocarbamate **132** in the presence of triethylamine was studied and it was found that the first reaction involves S–S bond formation with intermediate **133** being isolated and identified by spectral methods (Scheme 38) <1996JOC6639, 1996NAR1602>. The analogous reaction of compound **131** with thioacetamide gives 5-methyl-1,2,4-dithiazole-3-one **27** <1996JOC6639>.

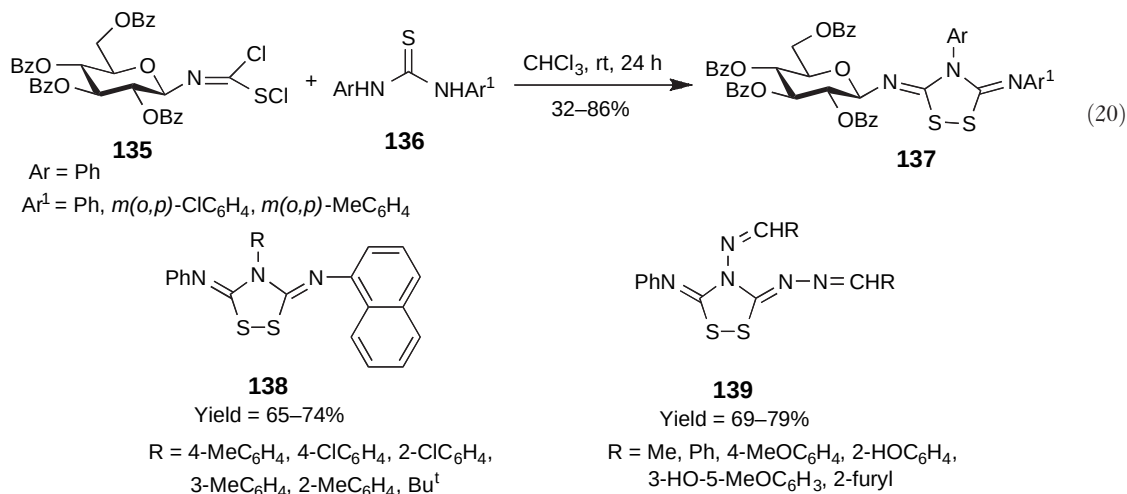


Scheme 38

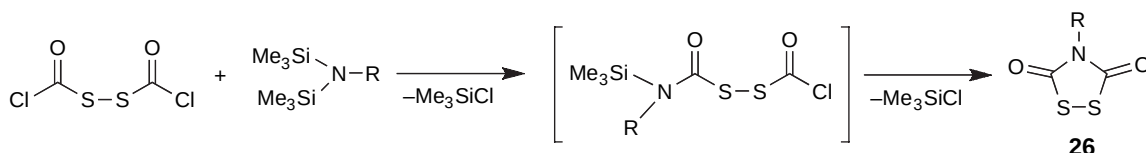
The same approach was used for introducing *N*-Dts protection into the peptide monomer <1995J(P1)405> and glycosyl donor **134** <1996JA3148> (Equation 19). In this case, however, triethylamine was not added and the 1,2,4-dithiazolidine-3,5-dione fragment was formed with extrusion of EtCl and HCl.



The reaction of β -D-glucopyranosyl-*S*-chloroisothiocarbamoyl chloride **135** with 1,3-diarylthioureas **136** affords 3,5-diimino derivatives of 4-aryl-1,2,4-dithiazolidine **137** (Equation 20) <2004JIC155, 2004MI305>. The similar structures **138** <2004MI255, 2005MI495> and **139** <2005MI495> were synthesized in the same manner.

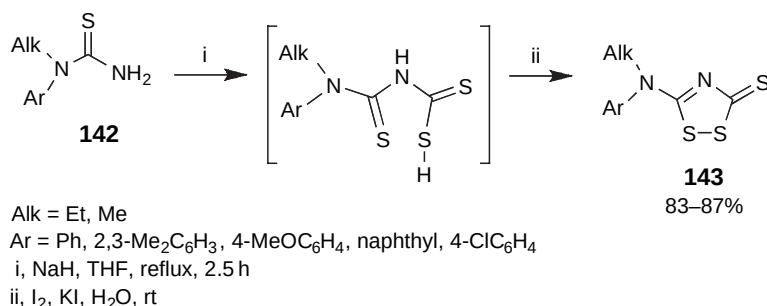
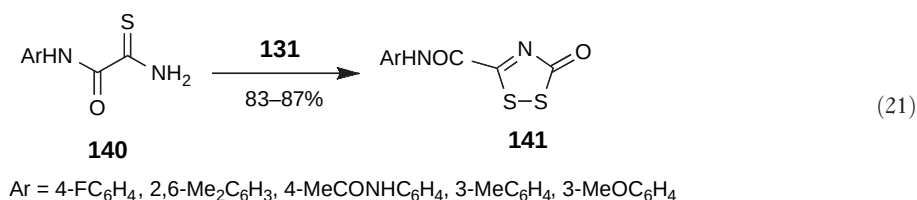


Recently, a new efficient approach for the preparation of 4-alkyl-1,2,4-dithiazolidine-3,5-diones (Dts-amines) **26** was developed by G. Barany and co-workers [<2005JA508>](#). They have shown that Dts-amines **26** can be synthesized directly in a simple and robust reaction of bis(chlorocarbonyl)disulfane with bis(trimethylsilyl)amines that uses the trimethylsilyl group as a 'large proton' to circumvent extant synthetic problems. The reaction occurs in a dry medium with extrusion of two molecules of trimethylchlorosilane (**Scheme 39**). This simplification and improvement in the synthesis of Dts-amines **26** promises to open new avenues for the application of Dts-based protection strategies.



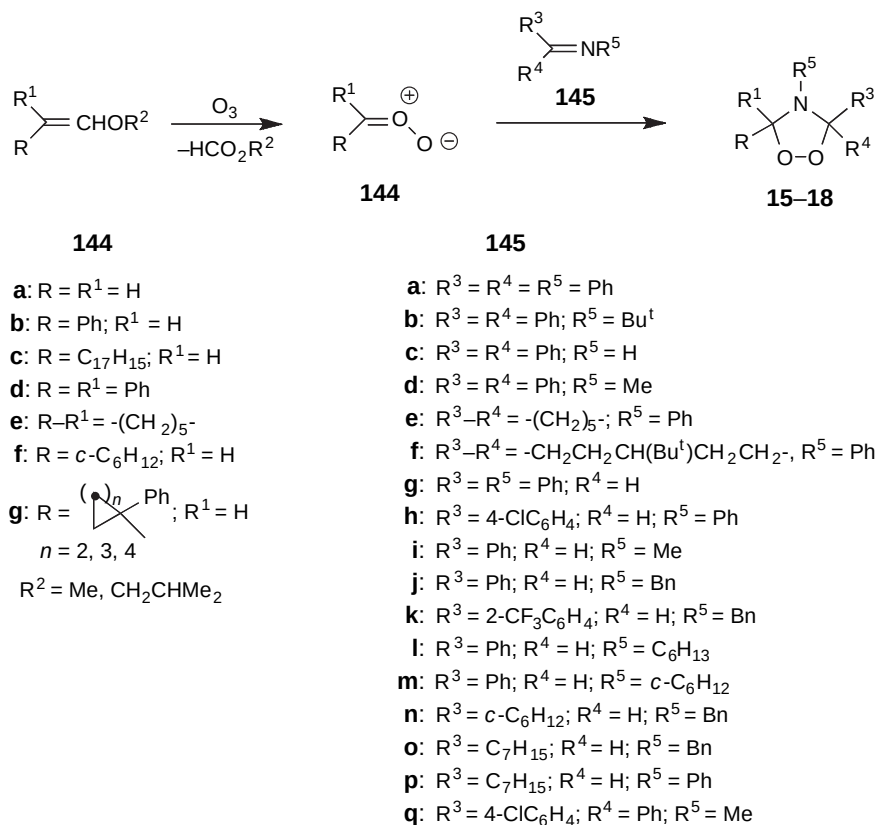
Scheme 39

Refluxing of monothioamides **140** with sulfenyl chloride **131** in toluene results in 5-arylcarbamoyl-1,2,4-dithiazole-3-ones **141** (Equation 21) [<2003PS1283>](#). A series of 5-(*N*-alkyl-*N*-arylthioureas) **142** with CS₂ in the presence of NaH followed by oxidation of the formed intermediate with I₂ (**Scheme 40**) [<2000EPP992506>](#).



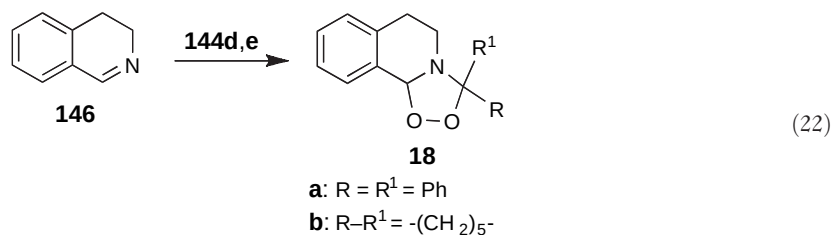
Scheme 40

Carbonyl *O*-oxides **144**, generated *in situ* by the ozonolysis of vinyl ethers at low temperature (−70 °C), readily undergo [3+2] cycloaddition with imines **145** added to the reaction mixture to afford the corresponding 1,2,4-dioxazolidines **15–18** in 14–97% isolated yields (**Scheme 41**) [<1994J\(P1\)2449, 1995J\(P1\)41>](#). The repetition of these reactions in MeOH results in the quantitative recovery of the initial imines **145**. The steric bulk of the α-substituents did not appear to diminish the imines **145** reactivity, because the isolated yields of 1,2,4-dioxazolidines

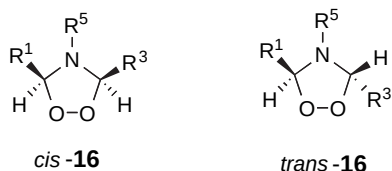


Scheme 41

from trisubstituted imines were generally higher than those from disubstituted imines. In contrast, the reactivities of carbonyl oxides **144** generated from aldehydes and ketones have marked differences. Aldehyde *O*-oxides **144a-c** underwent cycloaddition with a variety of imines yielding the corresponding 1,2,4-dioxazolidines in each case, whereas the sterically more encumbered ketone *O*-oxides **144d** and **144e** were not reactive toward imines **145e**, **145g** and **145o**. This implies that the carbonyl *O*-oxide carbon atom approaching the nitrogen atom of the imine is sensitive to steric hindrance. Nevertheless, benzophenone *O*-oxides **144d** and **144e** react with 3,4-dihydroisoquinoline **146** affording adducts **18a** and **18b** (Equation 22).

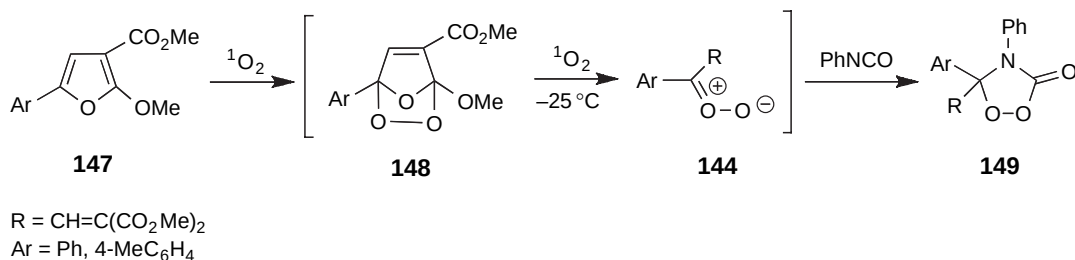


This reaction involving asymmetrically substituted imines and carbonyl *O*-oxides occurs with a high degree of stereoselectivity and only 3,4,5-trisubstituted dioxazolidines **16a-g** were obtained as a mixture of *cis*- and *trans*-isomers with predominance of *cis*-isomers. The structure and ratio of isomers were established by NMR spectroscopy <1995J(P1)41>.



	<i>Ratio of cis:trans</i>
a: R ¹ = R ³ = Ph; R ⁵ = Me	75:25
b: R ¹ = R ³ = Ph; R ⁵ = Bn	63:37
c: R ¹ = Ph; R ³ = 4-ClC ₆ H ₄ ; R ⁵ = Bn	79:21
d: R ¹ = R ³ = Ph; R ⁵ = C ₆ H ₁₃	80:20
e: R ¹ = R ³ = Ph; R ⁵ = cyclohexylmethyl	81:19
f: R ¹ = Ph; R ³ = <i>c</i> -C ₆ H ₁₂ ; R ⁵ = Bn	78:22
g: R ¹ = Ph; R ³ = C ₇ H ₁₅ ; R ⁵ = Bn	74:26

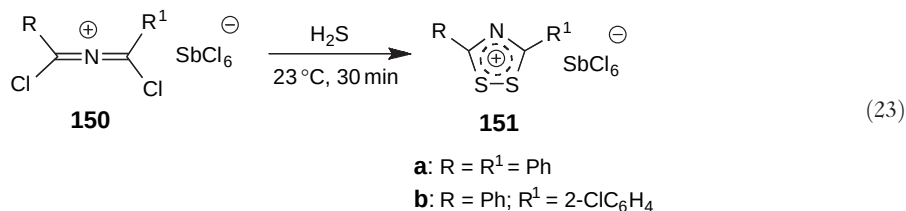
The regioisomers of 3,3,4-trisubstituted 1,2,4-dioxazolidine-3-ones **149** were obtained by the [3+2] reactions of carbonyl oxides **144** with phenylisocyanate, where the latter was used as a solvent. Initial carbonyl oxides **144** were generated by photooxygenation of furan derivatives **147** through peroxide intermediate **148** (Scheme 42) <1994J(P1)3295>.



Scheme 42

6.03.8.6 Formation of Three Bonds

Passing gaseous H₂S through a solution of 1,3-dichloro-2-azoniaallene salts **150** in dichloroethane results in 3,5-diaryl-1,2,4-dithiazolium hexachloroantimonates **151** (Equation 23) <1995JPR274>.

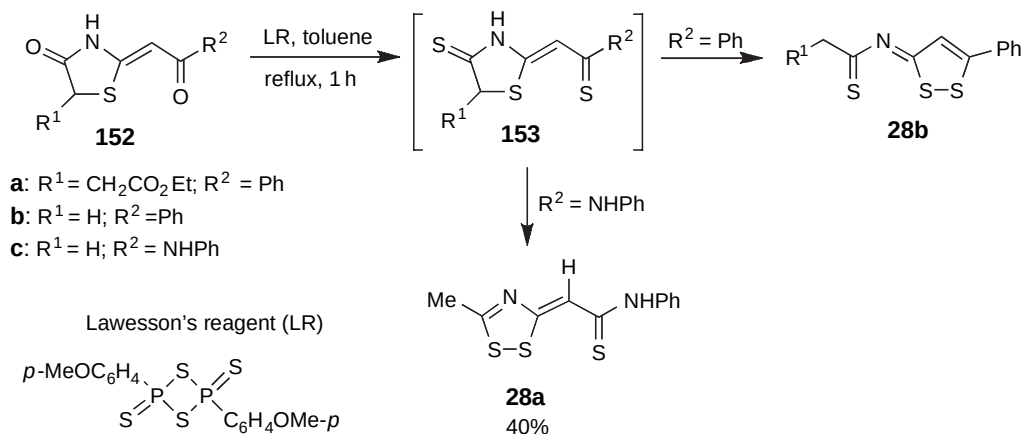


6.03.8.7 Formation of Four Bonds

Several examples of preparing 1,2,4-dithiazole derivatives by this approach are described in CHEC-II(1996) <1996CHEC-II(4)453>.

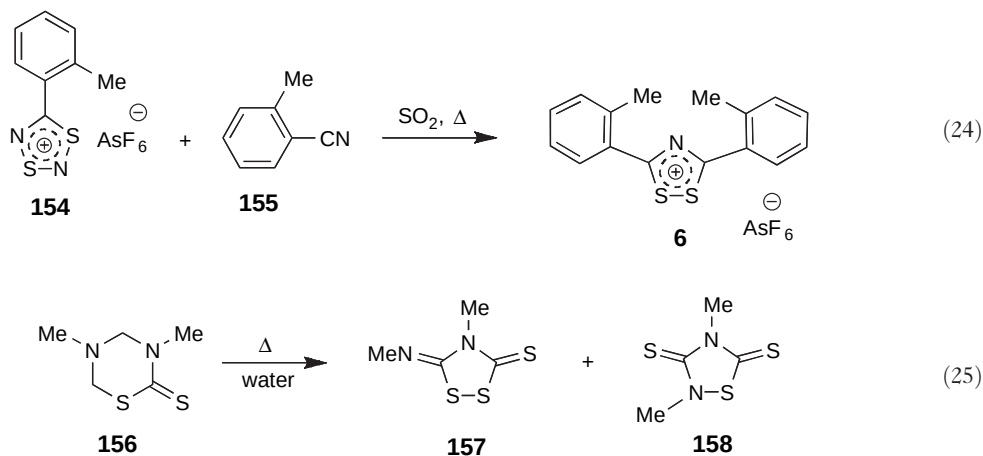
6.03.9 Ring Synthesis by Transformation of Another Ring

The Dimroth rearrangement of 1,2,4-thiadiazole derivatives into 1,2,4-dithiazole derivatives is a typical example of the title transformation <1996CHEC-II(4)453>. The synthesis of 1,2,4-dithiazole **28a** is carried out by ring-closing processes, including the Dimroth rearrangement, and by the thionation of 1,3-thiazol-4-ones **152** with LR <2003TL7087>. When $R^2 = \text{Ph}$, the reaction products are 1,2-dithioles **28b**. Both reactions occur in a highly regioselective fashion. The mechanism of these reactions probably involves the formation of the intermediates **153** (Scheme 43).



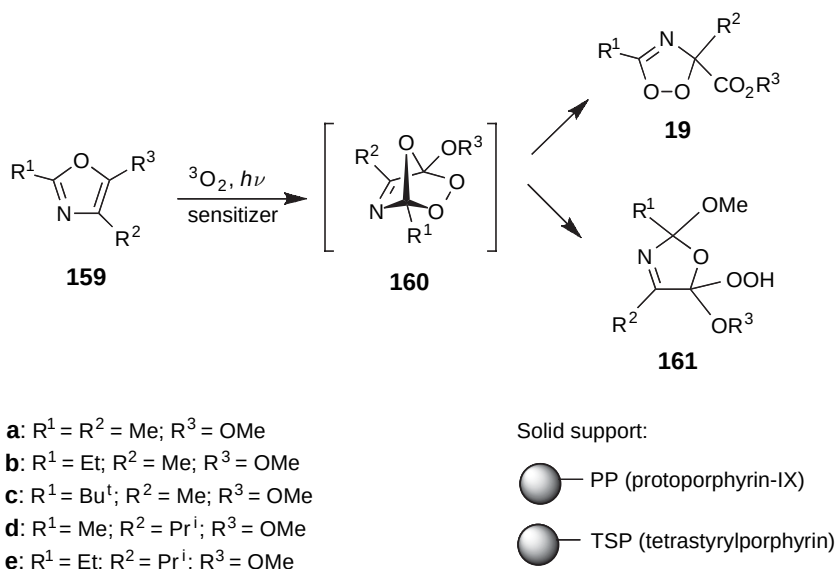
Scheme 43

The heating of 4-*o*-tolyl-1,3-dithia-2,5-diazolium hexafluoroarsenate **154** with a small excess of *o*-tolylcyanide **155** in liquid SO_2 leads to 1,2,4-dithiazolium hexafluoroarsenate **6** in low yield (Equation 24) <1996AXC2148>. The decomposition of the known pesticide, 3,5-dimethyltetrahydro-2*H*-1,3,5-thiadiazine-2-thione **156** (DTTT), in water and in salt solutions was studied in detail. 4-Methyl-5-methylimino-1,2,4-dithiazolidine-3-thione **157** and 2,4-dimethyl-1,2,4-thiadiazolidine-3,5-dithione **158** were isolated by HPLC and identified among the noncyclic decomposition products (Equation 25) <1996MI503>.



The solvent-free photooxygenation of the oxazoles **159** into the 1,2,4-dioxazolines **19** was performed under the action of two singlet oxygen sensitizers with cross-linking properties – the synthetic tetrakis(4-ethylphenyl)porphyrin (or tetrastyrilporphyrin, TSP) and the natural protoporphyrin-IX (PP) as peripheral substituted with unsaturated side chain <2005PPS205>. The cycloaddition of singlet oxygen to oxazoles **159** involves an endoperoxide intermediate

160 which can be rearranged to 1,2,4-dioxazolines **19** or trapped by nucleophiles such as methanol affording 1,3-oxazolines **161** (Scheme 44). This reaction on solid support resulted in 1,2,4-dioxazolines **19** in 74–96% yields. The combination of a microreactor system as the reaction medium and visible light and air as the reagents offers a new and convenient approach toward ‘green’ photooxygenation conditions.



Scheme 44

6.03.10 Survey of Ring Synthesis

6.03.10.1 1,2,4-Dithiazoles, 1,2,4-Dithiazolines, and 1,2,4-Dithiazolidines

One of the oldest methods for the preparation of 1,2,4-dithiazole derivatives is oxidative cyclization of dithioamides <1984CHEC(6)897>, which may be used in the form of thioacyl thioureas <1996CHEC-II(4)453>, *N*-thioacyl dithiocarbamates, dithiobiurets (**106**, Schemes 25 and 27) or *S*-benzyl isodithiobiurets (**110**, **113**, Schemes 28 and 29). Halogens (Cl_2 , Br_2 , I_2), hydrogen peroxide, atmospheric oxygen, or elemental sulfur in pyridine are usually employed as oxidants (see <1996CHEC-II(4)453>; Section 6.03.8.1). Final products of this synthetic option are 1,2,4-dithiazole derivatives with imino- or thione groups in 3- or/and 5-positions (e.g., compounds **10**, **23**, **24**, and **107**).

A general method of preparing 3-amino-1,2,4-dithiazolium cations is oxidative cyclization of metal chelates by Br_2 , SOCl_2 , or electrochemically induced cyclization <1996CHEC-II(4)453>. Another approach to 1,2,4-dithiazole ring formation is based on the creation of the S–S bond by oxidative cyclization of thioamides (e.g., **116**) or thioamides of 3-oxoacids (e.g., **118**) by H_2O_2 or Br_2 . This reaction occurs with extrusion of primary amines or ammonia. The reaction products are 1,2,4-dithiazolium salts (**37**, **117**) or covalent compounds (e.g., **29**) (see <1984CHEC(6)897, 1996CHEC-II(4)453>; Section 6.03.8.2). Passing H_2S through a solution of 1,3-dichloro-2-azaniaallene salts **150** results in 3,5-diaryl-1,2,4-dithiazolium hexachloroantimonates **151** (see Section 6.03.8.6).

The interaction of chlorocarbonyl sulfonyl chloride **131** and its imino derivatives at the carbonyl group with thioureas (**136**, **142**) and related compounds (thioamides, thiosemicarbazones, formamidines <1984CHEC(6)897, 1996CHEC-II(4)453>, thiocarbamates **132**, and monothiooxamides **140**) in the presence of tertiary amines is a general method for the preparation of 1,2,4-dithiazole derivatives. The mechanism of these reactions includes, at the first step, the formation of the S–S bond followed by intramolecular cyclization (see 5-*R*-1,2,4-dithiazole-3-ones(thiones) **13**, **141**, **143** and 3,5-diimino-1,2,4-dithiazolidines **137**, **138**, **139** <1984CHEC(6)897, 1996CHEC-II(4)453>; Section 6.03.8.5). The same method is used to introduce the Dts protection of amino groups. However, in this case, tertiary amines are not added and so the 1,2,4-dithiazolidine-3,5-dione fragment is formed. A new approach

to the preparation of Dts-amines **26** has been reported based on an interaction of *N,N*-bis(trimethylsilyl)amines with bis(chlorocarbonyl)disulfane in dry medium (see [Scheme 39](#)).

The reaction of 4-alkyl-5-imino-1,2,3,4-thiatriazolines with isothiocyanates gives 4-alkyl-3,5-diimino-1,2,4-dithiazolidines and 1,2,4-thiazolidines [<1996CHEC-II\(4\)453>](#). Cyclocondensation of isocyanates with imino derivatives of other heterocycles is a useful method for preparing 1,2,4-dithiazole derivatives (see [Schemes 35](#) and [37](#)). Instead of isocyanates, CS₂ is also used (see [Section 6.03.8.4](#), [Equation \(18\)](#), [<1984CHEC\(6\)897>](#)). Products of the 1,2,4-dithiazole type are also obtained from thiocarbonyl isocyanates by a reaction with Cl₂ [<1984CHEC\(6\)897>](#), PhMgBr, or S₈ and sulfonylisocyanate with dialkylthioketenes [<1996CHEC-II\(4\)453>](#).

Another pathway to the 1,2,4-dithiazolines **22** is an insertion of elemental sulfur into heterodienene intermediate **122** generated by the thermally induced retro-[4+2] cycloconversion of 6*H*-1,3,5-oxathiazines **121**. Thioamide and LR may be also used in this reaction as a thiating reagent (see [Section 6.03.8.3](#)).

6.03.10.2 1,2,4-Oxathiazolines and 1,2,4-Oxathiazolidines

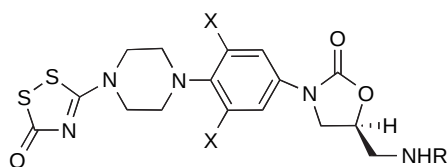
A historic method for 1,2,4-oxathiazolidine synthesis is based on 1,3-cycloaddition reactions, for example, addition of carbonyl compounds across the S=C=N groups of 5-imino-1,2,3,4-thiatriazolines [<1996CHEC-II\(4\)453>](#). The thermally induced conversion of 6*H*-1,3,5-oxathiazine *S*-oxides **119** in refluxing benzene results in 1,2,4-oxathiazolines **20** in high yields by intramolecular cyclization with extrusion of carboxaldehydes (see [Section 6.03.8.2](#)). Oxidative cyclization of *N*-acylthioureas **114** and *N*-acylthiocarbamates **115** by Br₂ gives 1,2,4-oxathiazolium hydrobromides **43** and **38**, respectively (see [Section 6.03.8.1](#)).

6.03.10.3 1,2,4-Dioxazolines and 1,2,4-Dioxazolidines

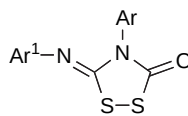
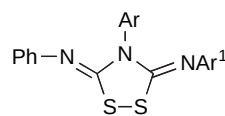
The synthesis of 1,2,4-dioxazolines and 1,2,4-dioxazolidines is based on the use of singlet oxygen, ozone, or peroxides. Thus, photoaddition of O₂ to 2-alkoxyoxazoles followed by a rearrangement leads to unstable 3-acyl-1,2,4-dioxazolines [<1984CHEC\(6\)897>](#). Solvent-free photooxygenation of oxazoles **159** on solid support results in 1,2,4-dioxazolines **19** in 74–96% yield (see [Section 6.03.9](#)). 4-Unsubstituted 1,2,4-dioxazolidines are obtained by a catalytic reaction of aldehydes or ketones with H₂O₂ and NH₃ through the intermediate formation of *N*-(α -hydroperoxyalkyl)imines [<1996CHEC-II\(4\)453>](#). Carbonyl *O*-oxides **144**, generated *in situ* by the ozonolysis of vinyl ethers at low temperature, undergo the [3+2] reaction with imines **145** affording 1,2,4-dioxazolidines **15–18** in good yields (see [Section 6.03.8.5](#); [<1996CHEC-II\(4\)482>](#)). Aldehyde *O*-oxides enter this reaction in all cases, whereas ketone *O*-oxides, sterically more encumbered, may be unreactive toward some imines. This reaction with asymmetrically substituted imines and carbonyl *O*-oxides occurs with a high stereoselectivity degree and *cis*-isomers are predominant (*cis:trans* ratio $\sim$ 3:1). Carbonyl *O*-oxides may be generated *in situ* by photooxygenation of furan derivatives (see [Scheme 42](#)).

6.03.11 Important Compounds and Applications

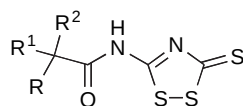
The 1,2,4-dithiazole series compounds were found to possess various valuable properties; for example, they exhibit insecticidal, fungicidal, acaricidal, and antibacterial activities. Some of them display an anticorrosion effect and can be used for silver halide photographic materials [<1984CHEC\(6\)897](#), [1996CHEC-II\(4\)453>](#). Similar types of activity have been found for 1,2,4-dithiazole derivatives in recent years. Thus, 1,2,4-dithiazolynyl piperazine derivative **162** [<1997WO9730981>](#), 4-phenyl-5-phenylimino-1,2,4-dithiazolidine-3-ones **163** [<2002AAC1310](#), [2004AAC3093>](#), 4-aryl-3,5-bis(arylimino)-1,2,4-dithiazolidines **164** [<2004MI189>](#), and compounds **23** [<2003IJH391>](#) displayed antimicrobial activity. Compound **163** is also effective against the protozoan parasites of the genus *Plasmodium* causing malaria [<2003B1160>](#). Compounds **23**, **83**, **137**, and **138** have shown the antifungal activity [<2001IJH311](#), [2004MI534](#), [2004MI255>](#). 1,2,4-Dithiazolidine-3-thiones **165** are used for external skin compositions [<2003JPP064065>](#). 3-Nitro-4-(*N*-dithiasuccinoylimido)methyl benzoic acid **166** is a photoactivatable agent for photolytic delivery of some drugs [<1995USP382212>](#).

**162**

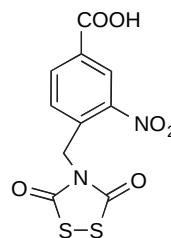
X = H, Cl, F
 R = CHO, COMe, COCHCl₂,
 CO₂Me, SO₂Me, COCH₂OH

**163****164**

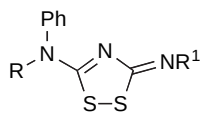
Ar = Ph, *o*-(*m,p*)-MeC₆H₄
 Ar¹ = 2-NH₂C₆H₄, 2-ClC₆H₄

**165**

R, R¹, R² = Alk, Ar, Het

**166**

3,5-Bis(aryimino)-1,2,4-dithiazolidines **164** and 5-(methyphenylamino)-3-imino-1,2,4-dithiazoles **167** are useful as antiwear and antifriction additives for lubrication of automatic and constantly variable transmissions <2000MI37, 2003USPO15346A1>. The similar structures **168** as well as **23** are effective as corrosion inhibitors for mild steel in hydrochloric and sulfuric acids <2002MI103, 2002MI515, 2004MI77, 2004MI171>. The 3,4-diaza-1,6,6αλ⁴-trithiapentalenes, including fused structure **4**, displayed efficiency for chemical sensitization of high-contrast silver halide photographic materials <1997USP5604084, 1999JPP11202439>.

**167**

R = Me; R¹ = H, Me, Bn

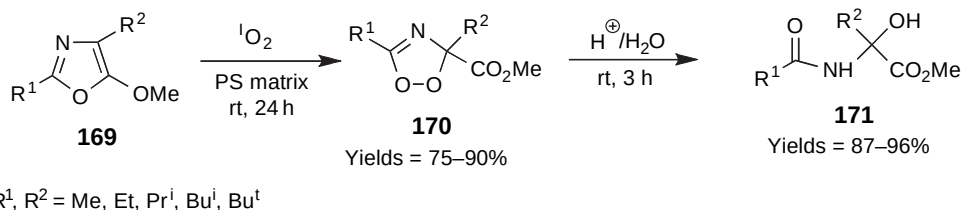
168

R = H; R¹ = Ar

In addition to the above properties, the last decade saw new potential applications of 1,2,4-dithiazole derivatives. Some representatives of this class were found to be extremely useful in organic and bioorganic syntheses. Thus, compounds **5**, **12**, **13**, **27**, **36**, **65**, and **72** are new effective sulfur-transfer reagents having significant advantages over the Beaucage reagent used earlier (see Sections 6.03.5.3 and 6.03.7). They are currently extensively applied for the synthesis of phosphorothioate-containing oligodeoxyribonucleotides. On the other hand, important progress has been made in bioorganic synthesis owing to the Dts protection of amino groups (see Sections 6.03.6.1.3 and 6.03.8.5). And, finally, the readily accessible N-alkylated 1,2,4-dithiazolidine-3,5-diones **26** proved to be new effective 'building blocks' that have paved the way to the synthesis of isocyanates (and primary amines), including stereocontrolled synthesis, from the corresponding alcohols (see Section 6.03.6.1.3).

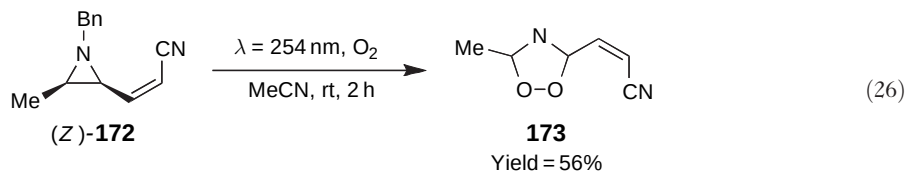
6.03.12 Further Developments

A solvent-free photooxygenation of 5-methoxyoxazoles **169** embedded in porphyrin-loaded polystyrene beaded as solid support resulted in 3*H*-1,2,4-dioxazoles **170** as sole products in good yields. Stereoselective synthesis of α-amino carboxylic acids derivatives **171** was developed by acid catalyzed hydrolysis of compounds **170** (Scheme 45) <2005JCR422>.

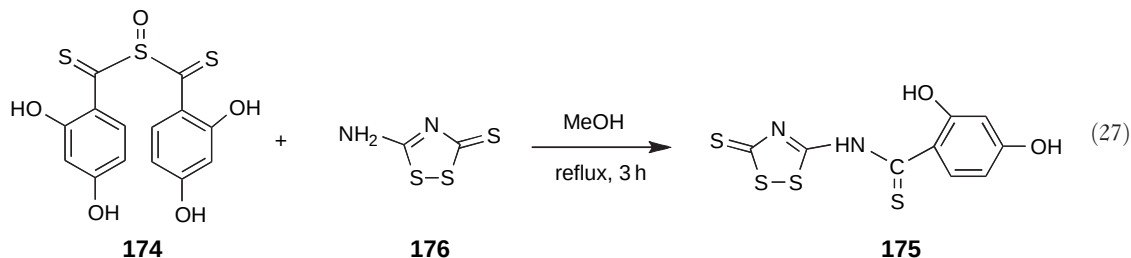


Scheme 45

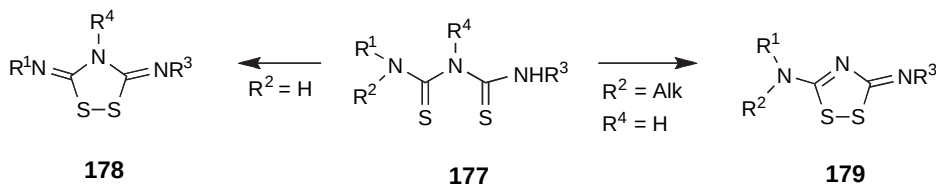
Direct irradiation of the β -aziridinylacrylonitrile (*Z*)-**172** solution in acetonitrile under bubbling oxygen with a low-pressure mercury lamp in a quartz test tube at room temperature afforded dioxazolidine **173** (Equation 26) <2006T10865>.



New thioacylating reagent – sulfinylbis(2,4-dihydroxythiobenzoyl) **174** was applied for the preparation of *N*-(1,2,4-dithiazol-5-thion-3-yl)-2,4-dihydroxythiobenzamide **175** from 3-amino-1,2,4-dithiazole **176** (Equation 27) <2006MI14>. The compound **175** revealed a significant growth-inhibitory effect against several phytopathogenic fungi.



The oxidation of dithiobiuretes **177** with Br_2 in TEA results in the dithiazolidines **178** at $\text{R}^2 = \text{H}$ and dithiazoles **179** at $\text{R}^2 = \text{Alk}$ (Scheme 46). The derivatives **178** and **179** are effective as inducers of glutation-S-transferase (GST) and NADPH quinine oxidoreductase (NQO) and useful for the prophylaxis and treatment of adverse conditions associated with cytotoxicity in general and apoptosis in particular <2006WO084854>.



Scheme 46

1,2,4-Dithiazolodin-3,5-diones with Ph and Bn substituents on nitrogen atom have been revealed as GSK-3-inhibitors <2005JMC7103>.

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Biographical Sketch



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6.04

1,4-Oxa/thia-2-azoles

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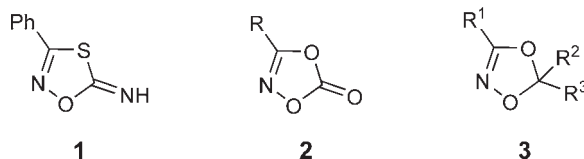
6.04.1	Introduction	106
6.04.1.1	Survey of Possible Structures	106
6.04.2	Theoretical Methods	107
6.04.3	Experimental Structural Methods	108
6.04.3.1	X-Ray Diffraction	108
6.04.3.2	Electron Diffraction and Microwave Spectra	110
6.04.3.3	NMR Spectroscopy	110
6.04.3.3.1	¹ H NMR spectra	110
6.04.3.3.2	¹³ C NMR spectra	111
6.04.3.3.3	¹⁴ N NMR	113
6.04.3.3.4	¹⁹ F NMR	113
6.04.3.4	UV Spectroscopy	113
6.04.3.5	Mass Spectrometry	113
6.04.3.6	IR Spectroscopy	115
6.04.4	Thermodynamic Aspects	115
6.04.4.1	Intermolecular Forces	115
6.04.4.2	Stability and Aromaticity	115
6.04.4.3	Conformation	115
6.04.4.4	Tautomerism	115
6.04.5	Reactivity of Fully Conjugated Rings	116
6.04.5.1	General Survey of Reactivity	116
6.04.5.2	Unimolecular Thermal and Photochemical Reactions	116
6.04.5.2.1	Thermal reactions	116
6.04.5.2.2	Photochemical reactions	117
6.04.5.3	Electrophilic Attack at Carbon, Nitrogen, and Sulfur	117
6.04.5.4	Nucleophilic Attack at Carbon	117
6.04.5.4.1	Conjugated systems with exocyclic double bond and nucleophiles	117
6.04.5.4.2	Reactions of 1,4-oxa/thia-2-azolium salts and nucleophiles	117
6.04.5.4.3	Ring expansion reactions	118
6.04.5.5	Reactions with Electron-Deficient Species and at Surfaces	118
6.04.5.6	Reactions with Cyclic Transition States	119
6.04.6	Reactivity of Nonconjugated Rings	121
6.04.6.1	Unimolecular Thermal and Photochemical Reactions	121
6.04.6.1.1	Thermal decomposition of azolines	121
6.04.6.1.2	Thermal decomposition of azolidine derivatives	122
6.04.6.2	Electrophilic Attack at Ring Carbon, Nitrogen, and Sulfur	124
6.04.6.3	Nucleophilic Attack at Ring Carbon	124
6.04.6.4	Attack at Ring Hydrogen	125
6.04.6.5	Reactions at Surfaces	125
6.04.6.6	Reactions with Cyclic Transition States	125

6.04.7	Reactivity of Substituents Attached to Ring Carbon Atoms	126
6.04.8	Reactivity of Substituents Attached to Ring Heteroatom	127
6.04.9	Ring Synthesis Classified by Numbers in Each Component	127
6.04.9.1	Formation of One Bond Adjacent to a Heteroatom	127
6.04.9.2	Formation of Two Bonds: Four-Atom Fragment and Carbon	128
6.04.9.3	Formation of Two Bonds: [3+2] Atoms by Cycloaddition	130
6.04.9.4	Formation of Two Bonds: [3+2] Atoms by Other Processes	133
6.04.10	Ring Synthesis by Transformation of Another Ring	137
6.04.10.1	From Five-Membered Rings	137
6.04.10.2	From Three-Membered Rings	137
6.04.11	Best Synthetic Methods	138
6.04.12	Applications	140
6.04.12.1	Agrochemicals	140
6.04.12.2	Pharmaceuticals	141
6.04.12.3	Polymer Chemicals	141
6.04.12.4	Other Applications	142
6.04.13	Further Developments	142
	References	142

6.04.1 Introduction

The aim of this chapter is to update the literature on all possible structures of 1,4-(oxa/thia)-2-azole ring systems that have appeared since 1995. In CHEC(1984), all possible combinations of (oxa/thia)-azoles were covered in a single chapter <1984CHEC(6)897>. In CHEC-II(1996), coverage was divided into four separate chapters (Chapters 4.11–4.14) where 1,2-(oxa/thia)-3-azoles, 1,3-(oxa/thia)-2-azoles, 1,2-(oxa/thia)-4-azoles, and 1,4-(oxa/thia)-2-azoles were examined separately. 1,4-(Oxa/thia)-2-azoles were covered in 51 pages (Vol. 4, Chapter 14), and almost all their known chemistry was updated <1996CHEC-II(4)491>.

Historically, the first example of 1,4-(oxa/thia)-2-azole rings was described by Musante, in the late 1930s, who first correctly suggested the 5-imino-2-phenyl 1,4,2-oxathiazole structure **1** to the product obtained from the reaction of ammonium thiocyanate and benzhydroximoyl chloride <1938G331>. Also, the preparation and some properties of dioxazolones **2** described by Beck should be mentioned <1951CB688>, and also the synthesis of the first nonconjugated dioxazole derivative **3**, from hydroxamic acid and benzophenone diethylacetal, described by Exner <1956CLY779>.

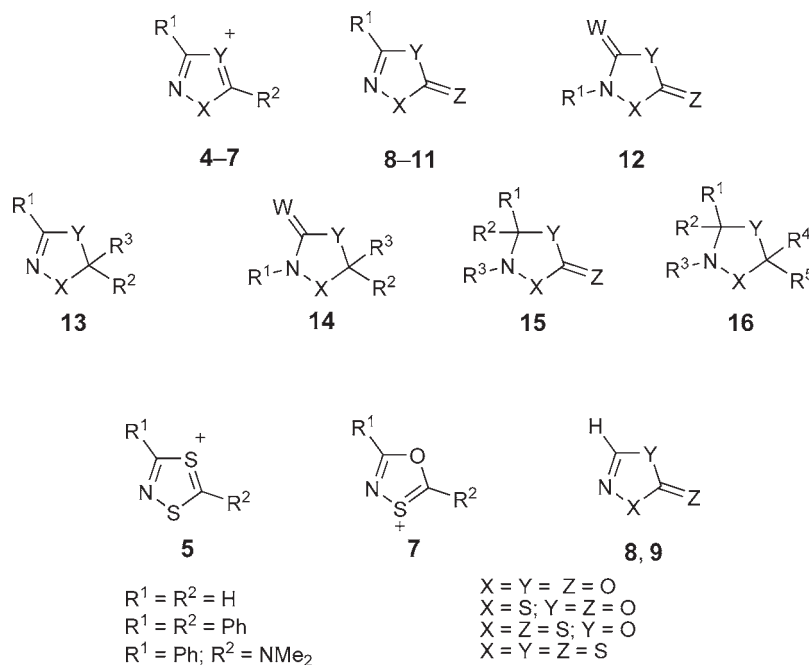


Generally, there is a lack of review articles concerning these ring systems. In addition to those cited in CHEC(1984) and CHEC-II(1996), recent accounts that should be mentioned are those in *Science of Synthesis* <2004HOU95, 2004HOU17, 2004HOU511>, mainly concerning preparative routes toward these ring systems.

6.04.1.1 Survey of Possible Structures

Structures **4–16** represent all possible combinations for the 1,4-(oxa/thia)-2-azole ring systems. Fully conjugated rings may exist either as unsaturated monocationics **4–7** or with exocyclic double bond(s) **8–12** having anionic(s) O, S, NR, or CR₂ group(s) attached to ring carbon atoms. Four possible structures may be proposed for the azolylium cations **4–7**: 1,4,2-dioxazolium **4** (X=Y=O); 1,4,2-dithiazolium **5** (X=Y=S); 1,4,2-oxathiazolium **6** (Y=S; X=O), and 1,3,4-oxathiazolium **7** (Y=O; X=S). For uniformity purposes, the positive charge will be always put on atom Y of the

ring regardless of its actual location. For (oxa/thia)-2-azoles with exocyclic conjugation, 16 possible structures may be written, involving azolinones **8** ($Z = O$; $X, Y = O$ and/or S ; four structures), azolinethiones **9** ($Z = S$; $X, Y = O$ and/or S ; four structures), azolinimines **10** ($Z = NR$; $X, Y = O$ and/or S ; four structures), and azolinylenes **11** ($Z = CR_2$; $X, Y = O$ and/or S ; four structures). For the (oxa/thia) azolidines **12** ($X, Y = O$ and/or S ; $Z, W = O, S, NR$, or CR_2) with two exocyclic double bonds, 64 structures are possible. Moreover, further structures for fully conjugated neutral rings may be written by incorporating $S(IV)$ and $S(VI)$ into the ring. Dihydro compounds **13–15** contain either one double bond in the ring (four possible structures) or an sp^2 carbon atom as part of an exocyclic double bond (eight possible structures). Finally, for tetrahydro derivatives **16**, four possible structures may be proposed.



The main body of known derivatives are 1,4,2-dithiazolium salts **5**, azolinones and related compounds **8–11**, as well as various combinations of dihydro and tetrahydro derivatives **13** and **16**, respectively. Benzo-fused systems cannot exist, but there are many examples of bicyclic or polycyclic compounds with a bridgehead nitrogen heteroatom: these are covered in Volume 10.

6.04.2 Theoretical Methods

In CHEC-II(1996), some semi-empirical calculations at the AM1 level of approximation for the typically conjugated 1,4-(oxa/thia)-2-azoles **5**, **7**, and the parent cross-conjugated azolinones **8** and the azolinethione **9** were reported. Comments about their stability and on the influence of substitution on their frontier molecular orbitals (FMOs) are given <1996CHEC-II(4)493>.

Semi-empirical calculations at the MP3 level have been reported for the parent 1,3,4-oxathiazolone **17** to study its complexation with $W(CO)_5$. FMO analysis of the Lewis acid–base interactions predicts that both sulfur and nitrogen do make a significant contribution to the highest occupied molecular orbital (HOMO), even though the calculated atomic charges (Figure 1) indicate their electron deficiencies <1996CJC107>. (A pictorial HOMO of the parent ring is given and also a copy of HyperChem PM3 logfile has been included with the supplementary material of the original paper.)

Sustmann and co-workers, in order to explain the unusual high reactivity of the $C=S$ group as a dipolarophile, performed a series of semi-empirical and *ab initio* calculations for the cycloaddition of the parent nitrone and thioformaldehyde to form 1,4,2-oxathiazoline. They examined various aspects of reaction pathways including the orientation complex, transition structures, regioselectivity, solvent effect, as well as the observed equilibrium between reactants and product in nitrone cycloadditions of thiones. Of interest to note are the calculated (Becke3LYP) negative activation energy relative to the reactants (e.g., ca. $-2.5 \text{ kcal mol}^{-1}$) and a small positive barrier ($+1.2 \text{ kcal mol}^{-1}$) relative to the orientation complex. In contrast, the corresponding values for

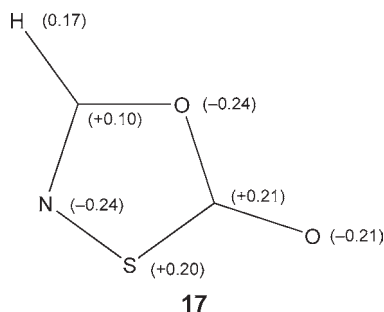


Figure 1 Semi-empirical calculations at the MP3 level for the parent 1,3,4-oxathiazolone.

ethylene as dipolarophile are $+13.7$ and $+15.5 \text{ kcal mol}^{-1}$, respectively. Perturbational analysis shows a strong $\text{HOMO}_{\text{nitron}}\text{--LUMO}_{\text{thioformaldehyde}}$ interaction as the principal reason for the high reactivity of thiones (LUMO = lowest unoccupied molecular orbital). *Ab initio* energies of ground states, orientation complexes, transition structures and adducts at different levels are given <1995JA9679>.

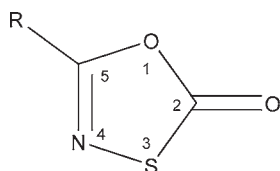
6.04.3 Experimental Structural Methods

6.04.3.1 X-Ray Diffraction

X-Ray crystal structure analysis is a valuable tool for elucidation of unknown structures, and many reports containing X-ray crystal data have appeared in CHEC-II(1996) <1996CHEC-II(4)495>. Additional data to those reported are given below.

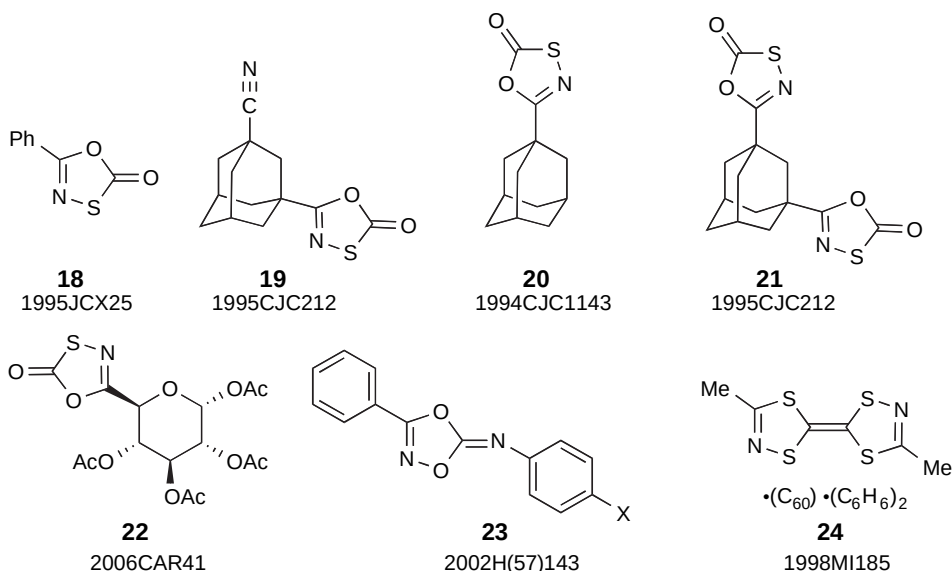
Generally, in all cases of conjugated 2,4-(oxa/thia)-2-azole ring systems, the heterocyclic ring is essentially planar. It is of interest to note that the oxathiazolone ring of all derivatives **19–22**, regardless of their structural differences, has almost the same structural details (Table 1). An extensive delocalization is claimed for the 1,3,4-oxathiazol-2-one ring of compound **18** <1995JCX25>, while a partial delocalization is reported for compounds **19–21**. Also, there are no significant differences in the adamantane frameworks between compounds **19–21** <1994CJC1143, 1995CJC212>. For compound **22**, the crystal structure shows an almost ideal cyclohexane chair conformation typical of pyranoid ring in the $^4C_1$ conformation <2006CAR41>. Typical bond distances and angles have been reported without comment for the 1,4,2-dioxazole-*N*-phenylimine derivative **23** <2002H(57)143>, while there are no available data for the charge-transfer complex **24** of the tetrathiadiazafulvalene derivative with fullerene <1998MI185>.

Table 1 Selected bond lengths and bond angles for oxathiazolones **19–22** <2006CAR41>

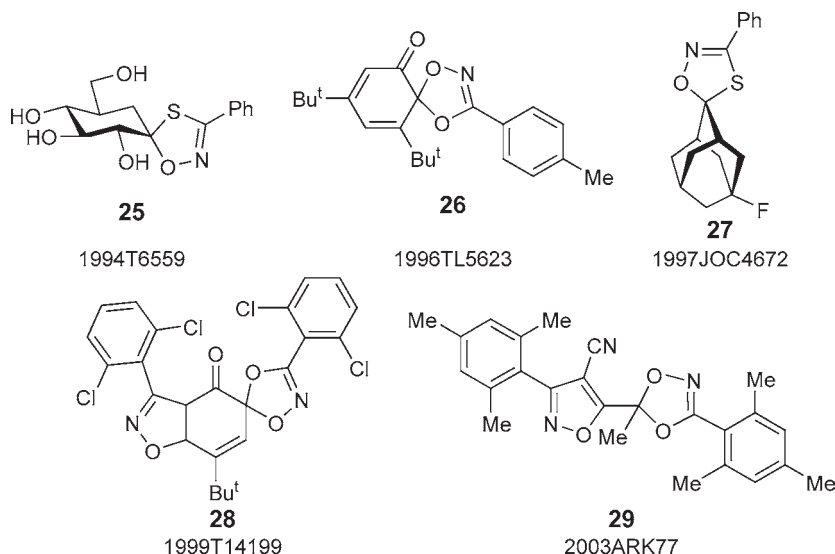


R = 5-(1,2,3,4-Tetra-O-acetyl- α -D-xylopyranos-5S-C-yl);
1-adamantanyl; Me, Ph, 4- $\text{CH}_3\text{C}_6\text{H}_4$

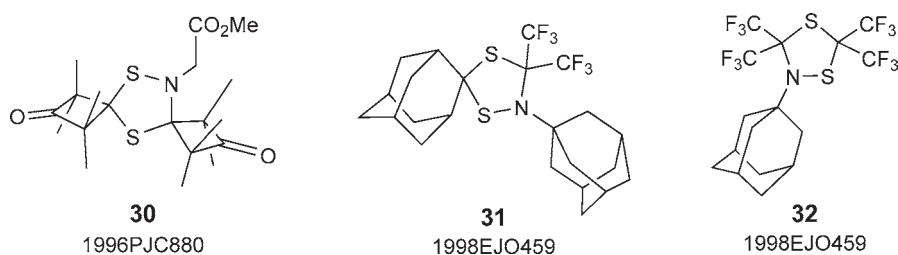
Bond	Length (Å)	Bond	Angle (deg)
O(1)–C(2)	1.380–1.392	C(5)–O(1)–C(2)	110.3–112.0
C(2)–S(3)	1.744–1.768	O(1)–C(2)–S(3)	106.4–107.2
S(3)–N(4)	1.677–1.689	C(2)–S(3)–N(4)	92.9–93.5
N(4)–C(5)	1.262–1.289	S(3)–N(4)–C(5)	108.5–110.5
C(5)–O(1)	1.365–1.380	N(4)–C(5)–O(1)	117.9–120.7
C(2)=O	1.184–1.198	O(1)–C(2)=O	121.7–123.6
C(5)–R	1.457–1.495	O(1)–C(5)–R	114.7–116.6

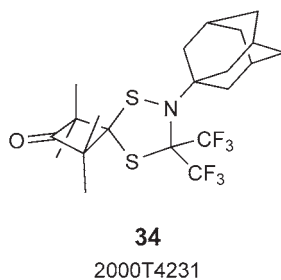
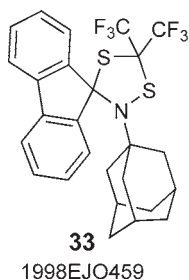


Several X-ray crystal structures of dioxazole or oxathiazole derivatives **25–29** have been reported mainly for clarification of relevant structures: **25** <1994T6559>; **26** <1996TL5623>; **27** <1997JOC4672>; **28** <1999T14199>; **29** <2003ARK77>.



Another group of X-ray crystal structures concerns several 1,4,2-dithiazolidines **30–34** <1996PJC880, 1998EJO459, 2000T4231>. The dithiazolidine ring of compound **30** shows an envelope conformation with the N atom as the flap position (torsion angles S(1)–C(5)–S(4)–C(3) = –1.8°, C(5)–S(4)–C(3)–N = 33.9°), and with the two carbon atoms and sulfur atom almost planar <1996PJC880>. Analogous conformations are found for compounds **31–33** <1998EJO459>.





6.04.3.2 Electron Diffraction and Microwave Spectra

The molecular structure of the parent 1,3,4-oxathiazol-2-one and its 5-methyl derivative **8** ($X=S$; $Y=Z=O$; $R^1=H$, Me) obtained by means of electron diffraction measurements in combination with microwave spectra was reported in CHEC-II(1996) <1996CHEC-II(4)496>. No other citations have been reported.

6.04.3.3 NMR Spectroscopy

Representative examples of ring proton and carbon chemical shifts of all known 1,4-(oxa/thia)-2-azoles were reported in CHEC-II(1996). A special notice should be given for ^1H and ^{13}C nuclear magnetic resonance (NMR) spectra of both dithiazolium **5** ($X=Y=S$) and oxathiazolium salts **6** ($X=O$; $Y=S$) and **7** ($X=S$; $Y=O$) <1996CHEC-II(4)489>. A δ downfield shift for both 3-H and 5-H as well as C-2 and C-5 is correlated with a potential π -electron delocalization and thus the aromaticity of these ring systems <1996CHEC-II(4)498>.

Regarding all other 1,4-(oxa/thia)-2 azoles, their ring hydrogen and carbon chemical shifts vary depending upon the substitution and the degree of unsaturation.

6.04.3.3.1 ^1H NMR spectra

Representative ring proton chemical shifts of 1,4,2-dioxazoline derivatives **13** ($X=Y=O$), 1,4,2-oxathiazolidine derivatives **16** ($X=O$; $Y=S$), and 1,4,2-dithiazolidine 2-oxide derivatives **16** ($X=SO$; $Y=S$) are given in **Tables 2–4**. Additional data for compounds previously described can be found in CHEC-II(1996) <1996CHEC-II(4)496>.

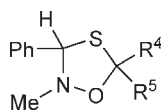
Table 2 Ring proton NMR data for 1,4,2-dioxazoline derivatives **13**

R^1	Ring hydrogen δ (ppm)	Reference
4-Cl-C ₆ H ₄	6.82	1996J(P1)747
CH ₂ COOMe	6.49 (t, $J = 5.2$ Hz)	2000TL7433
^a	6.32 (d, $J = 3.5$ Hz) ^b	2000T4299
^a	6.21 (d, $J = 5.8$ Hz) ^b	2000T4299
^c	6.04 (d, $J = 5.8$ Hz) ^b	2000T4299
^c	6.18 (d, $J = 3.0$ Hz) ^b	2000T4299

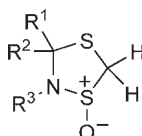
^a4-Isloxazoline residue.

^bDiastereomers.

^c5-Isloxazoline residue.

Table 3 Ring proton NMR data for 1,4,2-oxathiazoline derivatives **16**

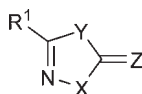
R^4	R^5	Ring hydrogen (δ , ppm)	Reference
Pr ⁿ	Pr ⁿ	4.79	1995JA9671
CMe ₂ (CH ₂) ₃ CMe ₂		4.65	1995JA9671
CMe ₂ C(=S)CMe ₂		5.01	1995JA9671

Table 4 Proton and carbon-13 NMR data of 1,4,2-dithiazolidine-1-oxide derivatives **16**

			Chemical shifts (δ , ppm)			Reference
			Ring carbon		Ring hydrogen	
R^1	R^2	R^3	C-3	C-5		
Ph	Ph	Ph	91.8	55.9	3.92, 4.00 (AB, close to A ₂ , ² J = 11.8 Hz)	1999HAC662
Ph	Ph	Ts	90.4	54.2	3.79 (AB, br s) 2.86, 2.99 (² J = 12.8 Hz) (in C ₆ D ₆)	1999HAC662
CMe ₂ C(=O)CMe ₂		Ph	96.5	58.9	4.21, 4.64 (AB, J = 12.0 Hz)	1999HAC662

6.04.3.3.2 ¹³C NMR spectra

Representative examples of the reported C-3 and C-5 chemical shifts of various 1,4-(oxa/thia)-2-azoles are given in **Tables 4–7**. Other relevant data can be found in CHEC-II(1996) for 1,4-(oxa/thia)-2-azoles described earlier <1996CHEC-II(4)498>.

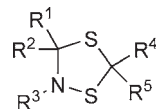
Table 5 Carbon-13 NMR data of azolinone and azolinethione derivatives **8**

Ring system				Chemical shifts (ppm) Ring carbon		Reference
X	Y	Z	R ¹	C-3	C-5	
S	O	O	a	155.4–156.1	170.0–172.2	2006CAR41
S	O	O	b	155.3–154.4	172.1–172.9	2001JME1560
S	S	O	Ar ^c	162.2–164.2	197.4–198.2	2002ARK121
S	S	S	Me	171.9	220.9	2002ARK121

^a5-(2,3,4,6-Tetra-O-acetyl- β -D-glucopyranosyl) or 5-(2,3,4-tri-O-acetyl- β -D-xylopyranosyl) residue.

^bPyridinyl or pyrazinyl residue.

^cX-C₆H₄ (X = 4-MeO, 4-Me, 4-F, 4-Cl, 3-Cl).

Table 6 Carbon-13 NMR data of 1,4,2-dithiazolidine derivatives **16**

R^1	R^2	R^3	R^4	R^5	Chemical shifts (ppm) Ring carbon		Other	Reference
					C-3	C-5		
$\text{CMe}_2\text{C}(=\text{O})\text{CMe}_2$			$\text{CMe}_2\text{C}(=\text{O})\text{CMe}_2$		103.1	80.3	C=O, 219.1, 217.4	1995HCA1067
$\text{CMe}_2\text{C}(=\text{O})\text{CMe}_2$		Ph	$\text{CMe}_2\text{C}(=\text{O})\text{CMe}_2$		99.7	81.2	C=O, 220.4, 218.8	1993HCA2147
$\text{CMe}_2\text{C}(=\text{O})\text{CMe}_2$		4-MeOPh	$\text{CMe}_2\text{C}(=\text{O})\text{CMe}_2$		100.3	81.0	C=O, 220.2, 218.9	1993HCA2147
$\text{CMe}_2\text{C}(=\text{O})\text{CMe}_2$		4-NO ₂ Ph	$\text{CMe}_2\text{C}(=\text{O})\text{CMe}_2$		98.8	81.8	C=O, 220.2, 217.2	1993HCA2147
$\text{CMe}_2\text{C}(=\text{O})\text{CMe}_2$		CH ₂ COOCH ₃	$\text{CMe}_2\text{C}(=\text{O})\text{CMe}_2$		103.0	80.0	C=O, 219.1, 217.5	1966PJC880
	^a	^b	CF ₃	CF ₃	88.9	66.2(sept, ² J _{C-F} = 29.5 Hz)		1998EJO459
Ph	Ph	^b	CF ₃	CF ₃	107.8	75.2(sept, ² J _{C-F} = 31.0 Hz)		1998EJO459
	^c	^b	CF ₃	CF ₃	81.9	66.3(sept, ² J _{C-F} = 31.0 Hz)		1998EJO459
	^d	^b	CF ₃	CF ₃	87.6	66.4(sept)		1998EJO459
CF ₃	CF ₃	^b	CF ₃	CF ₃	89.0	64.6(sept, ² J _{C-F} = 29.5 Hz)		1998EJO459
CF ₃	CF ₃	^b	^b		87.5(sept, ² J _{C-F} = 28.1 Hz)	64.0		1998EJO459
CF ₃	CF ₃	^b	$\text{CMe}_2\text{C}(=\text{O})\text{CMe}_2$		87.2(m, ² J _{C-F} = 27.8 Hz)	^e	C=O, 218.0	2000T4231
CF ₃	CF ₃	^b	$\text{CMe}_2\text{C}(=\text{S})\text{CMe}_2$		87.2(m, ² J _{C-F} = 27.8 Hz)	^e	C=S, 277.8	2000T4231

^aSpirofluorenyl residue.^b1-Adamantyl residue.^cSpiroxanthyl residue.^dSpirothioxanthyl residue.^eNot assigned.

Table 7 Carbon-13 NMR of 1,4,2-oxathiazolidine derivatives **16**

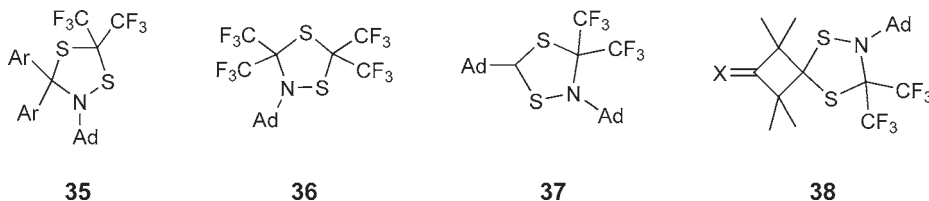
R^1	R^2	R^4	R^5	Chemical shifts (ppm)		Other	Reference
				C-3	C-5		
Ph	Ph	$\text{CMe}_2\text{C(=O)CMe}_2$		95.1, 104.1		C=O , 220.6	1995JA9671
Ph	Ph	$\text{CMe}_2\text{C(=S)CMe}_2$		95.0, 107.7		C=S , 285.4	1995JA9671
Ph	Ph	^a		93.1, 107.3			1995JA9671
$\text{CMe}_2\text{C(=O)CMe}_2$		$\text{CMe}_2\text{C(=O)CMe}_2$		95.4	104.9	C=O , 218.3, 220.3	1997LA1685
$\text{CMe}_2\text{C(=O)CMe}_2$		$\text{CMe}_2\text{C(=S)CMe}_2$		95.2	108.4	C=O , 218.0 C=S , 280.5	1997LA1685

^a1-Adamantyl residue.6.04.3.3.3 ^{14}N NMR

A resonance at δ ($\Delta\nu^{1/2}$ Hz) = -160(950) is reported for the nitrogen atom of 1,3,4-oxathiazol-2-one **20** <1994CJC1143>.

6.04.3.3.4 ^{19}F NMR

Chemical shifts of ^{19}F attached to a 1,3,4-dioxazolidine ring were reported in CHEC-II(1996), where other ^{19}F chemical shifts for fluorinated substituents are also included <1996CHEC-II(4)498>. Some new data for the chemical shifts of trifluoromethyl substituents of several 1,4,2-dithiazolidine derivatives are as expected with δ_{F} from -62.5 to -67.5 (CCl_3F as internal standard). Thus for the adamantyl dithiazolidines **35** δ_{F} appears at -65.2 to -67.5 depending on the aryl substituents, while the ^{19}F chemical shifts of dithiazolidines **36–38** are as follows: compound **36**: δ_{F} at -63.44 and -67.07; compound **37**: δ_{F} at -63.75 <1998EJO459>; compound **38**: δ_{F} at -62.5 for $\text{X}=\text{O}$ and -62.58 for $\text{X}=\text{S}$ <2000T4231>.



6.04.3.4 UV Spectroscopy

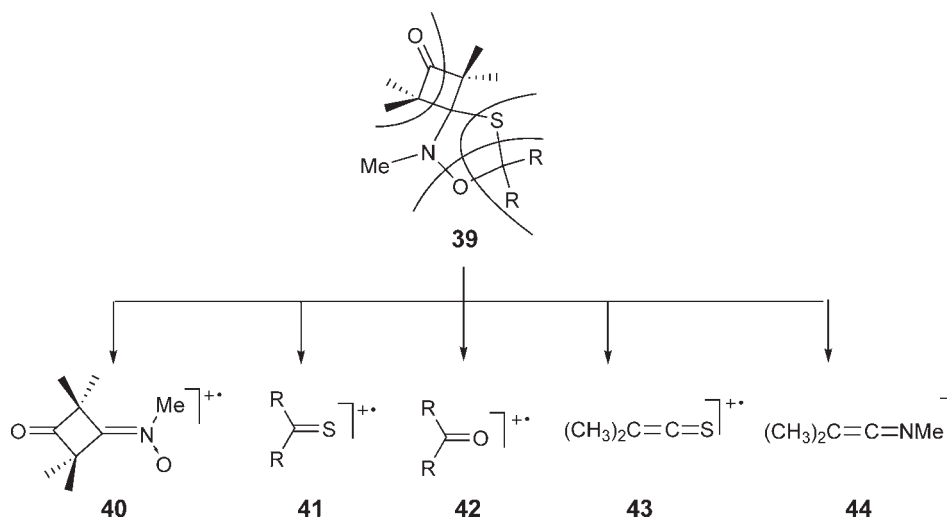
In CHEC-II(1996), some ultraviolet (UV) data of 1,4-(oxa/thia)-2-azole derivatives, mainly gathered from the experimental sections of published papers, have been reported <1996CHEC-II(4)501>. No new UV data have been reported since 1995.

6.04.3.5 Mass Spectrometry

In CHEC-II(1996), the fragmentation patterns of 1,4,2-dithiazolium salts, 1,4,2-dioxazoles, 1,3,4-oxathiazoles, 1,4,2-dithiazoles, 1,4,2-oxathiazole-5-imines, and 1,3,4-oxathiazole-5-ones were reported. Some other dithiazolidine and dioxazolidine derivatives have been also examined. The observed variations of fragmentation patterns depend on the differences in the arrangement of heteroatom, the degree of unsaturation, and also on the nature of substituents. In

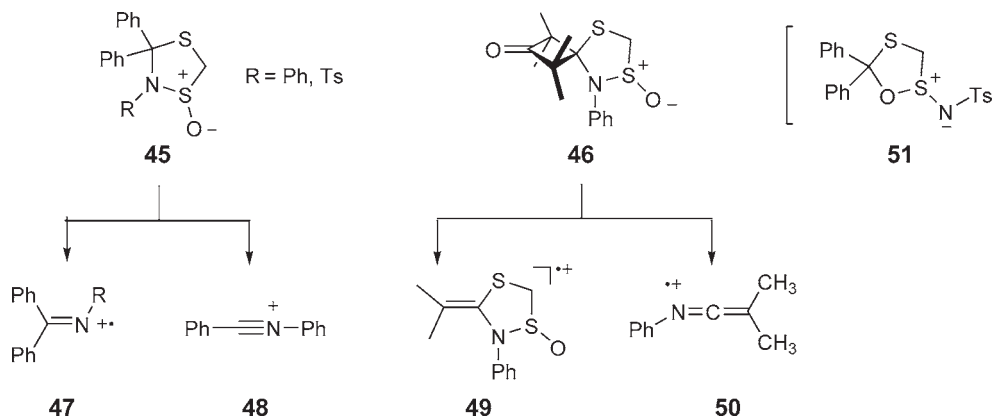
many cases, a retro-1,3-dipolar cycloaddition pathway predominates. A striking difference is observed in dithiazoles where the most abundant peak corresponds to the dithiazolium cation, obviously arising from its aromaticity <1996CHEC-II(4)501>.

Although many mass spectral details have been given in experimental sections for the sake of structure confirmation, only a few fragmentation patterns have been discussed. An example is the observed fragmentation of oxathiazolidine derivatives **39** (Scheme 1). The main fragments are those of nitron **40** and of thione **41**, arising from a [3+2] cycloreversion, a typical process for many other cycloadducts. A second [3+2] cycloreversion from an $M^{+} - R_2CO$ is also observed. Moreover, strong fragments corresponding to dimethylthioketene **43** and the ketenimine **44** are also observed <1997LA1685>.



Scheme 1

Other fragmentation patterns that have been discussed are those of 1,4,2-dithiazolidine 1-oxides **45** and **46**, which have been used to confirm their structures <1999HAC662>. Accordingly, the presence of peaks correspond to the fragments **47** and **48** as well as **49** and **50**, respectively; this allows the confirmation of connectivities in these adducts and excludes other possible isomeric structures, such as **51** (Scheme 2).



Scheme 2

6.04.3.6 IR Spectroscopy

Although there are no apparent common peaks assignable for a particular ring system and most peaks correspond to functional groups, in a few cases full assignments have been reported in CHEC-II(1996). Also, in a tabular form, several stretching vibrations of 1,4-(oxa/thia)-2-azole functionalities have been given <1996CHEC-II(4)503>. Generally, the presence of the characteristic C=N, C=O, and C=S group(s) may be assigned and these absorptions are currently given mainly in experimental sections. Summarizing these absorptions from those reported in CHEC-II(1996) and also from new data, C=N stretching vibrations are found at $\nu = 1560\text{--}1660\text{ cm}^{-1}$, C=O stretching vibrations at $\nu = 1745\text{--}1880\text{ cm}^{-1}$, and C=S stretching vibrations at $\nu = 1075\text{--}1315\text{ cm}^{-1}$.

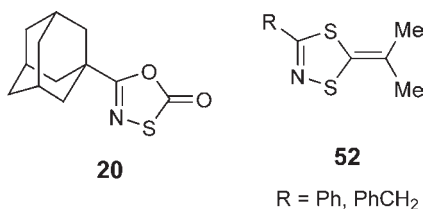
6.04.4 Thermodynamic Aspects

6.04.4.1 Intermolecular Forces

As pointed out in CHEC-II(1996), most of the parent 1,4-(oxa/thia)-2-azoles are unknown, except for 1,3,4-oxathiazol-2-one, 1,4,2-dithiazol-5-one, and 1,4,2-dithiazolium perchlorate <1996CHEC-II(4)505>. All other known compounds are generally heavily substituted, so generalizations about their inter- and intramolecular associations or chromatographic behavior are not available. However, details about their chromatographic separation and isolation are given in the experimental sections of the published articles without comments.

6.04.4.2 Stability and Aromaticity

All conjugated 1,4-(oxa/thia)-2-azoles may be formally considered as aromatic systems. The question of aromaticity of dithiazolium cations and their positive charge delocalization has been already discussed in CHEC-II(1996). It is worth noting the stability of adamantane oxathiazolone **20**, which sublimates at 50 °C without decomposition <1994CJC1143> and the high stability of azonylene derivatives **52** which are so stable that they survive distillation at 200 °C <1996PJC880>. However, it should be emphasized that there have been reported explosions occurring during the isolation of 1,4,2-oxathiazolium perchlorates and also in handling 5-trifluoromethyl-1,3,4-dioxazol-2-one <1996CHEC-II(4)505>.



6.04.4.3 Conformation

Rotational energy barrier measurements reported in CHEC-II(1996) for the NMe₂ group of 5-(*N,N*-dimethylamino)-1,4,2-dithiazolium salt and of 5-(*N,N*-dimethylamino)-1,3,4-oxathiazole-3,3-dioxide indicate a restricted rotation around the exocyclic C–N bond <1996CHEC-II(4)505>. The conformations of several 1,4,2-dithiazolidine derivatives, obtained from X-ray data, show that this particular ring adopts an envelope conformation with the nitrogen atom as the flap (see Section 6.04.3.1).

6.04.4.4 Tautomerism

Typically, the 1,4-(oxa/thia)-2-azole ring system does not exist in tautomeric forms. However, in some cases discussed in CHEC-II(1996), the 3-alkylamino-substituted 1,4,2-dithiazole-1-oxides may exist in tautomeric forms with the contribution of alkylamino substituents <1996CHEC-II(4)506>.

6.04.5 Reactivity of Fully Conjugated Rings

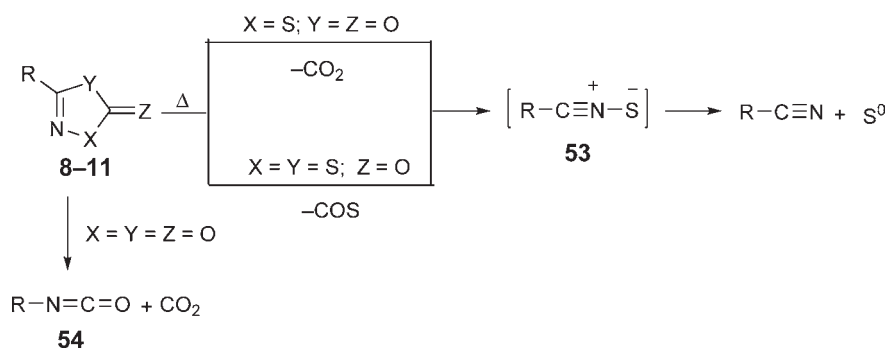
6.04.5.1 General Survey of Reactivity

Fully conjugated 1,4-(oxa/thia)-2-azoles are of electrophilic character. A large part of their chemistry concerns their reactions with nucleophiles. The site of nucleophilic attack is either the sp^2 ring carbon atom of the exocyclic double bond or the corresponding positively charged ring carbon atom of the azolylium cation. The other carbon atom of the ring seems to be unreactive. There are no reports of electrophilic attack at ring carbon or nitrogen.

6.04.5.2 Unimolecular Thermal and Photochemical Reactions

6.04.5.2.1 Thermal reactions

All azolones **8–11** are susceptible to thermolytic reactions. There are two major pathways of thermolysis both involving extrusion of YCZ or XCZ fragments via a thermally allowed $[\sigma 2_s + \sigma 2_s + \sigma 2_s]$ process (**Scheme 3**). A general overview of all reported cases is given in CHEC-II(1996) <1996CHEC-II(4)506>.



Scheme 3

The first pathway, followed by 1,3,4-oxathiazolones ($\text{X} = \text{S}; \text{Y} = \text{Z} = \text{O}$) and 1,4,2-dithiazolones ($\text{X} = \text{Y} = \text{S}; \text{Z} = \text{O}$), affords nitrile sulfides **53**, a class of transient 1,3-dipolar species, which in the absence of suitable dipolarophiles decompose further affording nitriles and sulfur. However, under flash vacuum pyrolysis (FVP) conditions, 5-methyl 1,3,4-oxathiazolone **8** ($\text{R} = \text{Me}; \text{X} = \text{S}; \text{Y} = \text{Z} = \text{O}$) does not produce acetonitrile sulfide but instead carbon dioxide, acetonitrile, and sulfur <2001PCA6258>.

The decarboxylation of 1,3,4-oxathiazolones is the method of choice for nitrile sulfide generation, and a great variety of substituted compounds have been tested as possible nitrile sulfide precursors <1996CHEC-II(4)506>. The rate of thermolysis depends on the substitution, being decreased by electron-withdrawing groups and increased by electron-donating groups in the order: $\text{Me} > \text{Pr} > \text{heptyl} > 4\text{-MeOC}_6\text{H}_4 > \text{Ph} >> 4\text{-ClC}_6\text{H}_4$ <2000ARK720>. An improved variation of nitrile sulfide generation by this route is the microwave-assisted thermolysis of 1,3,4-oxathiazolones (see Section 6.04.5.6) <2005SC807, 2006CAR41>.

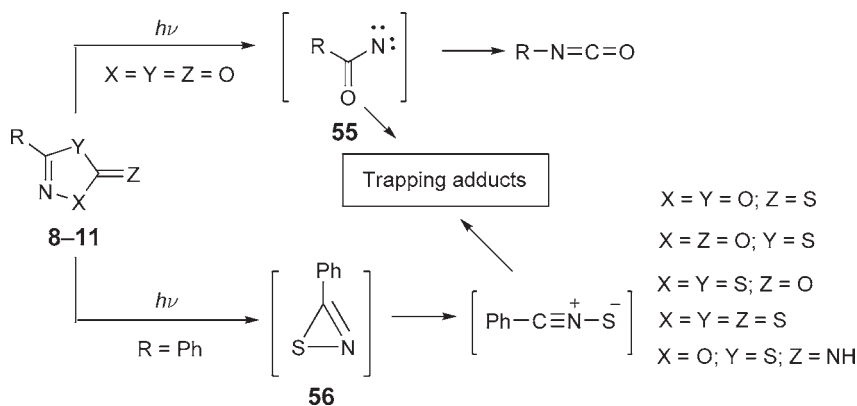
Although dithiazolones **8** ($\text{X} = \text{Y} = \text{S}; \text{Z} = \text{O}$) are more stable than oxathiazolones, under more drastic conditions they slowly decompose to give nitrile sulfides and carbon oxysulfide <1996CHEC-II(4)506>. In a reported example, more than 50 h in refluxing mesitylene (ca. 164°C) are required for decomposition (five to six half-lives) <2002ARK121>. Trapping reactions of these nitrile sulfides are discussed later (see Section 6.04.5.6). In the absence of a trapping dipolarophile, the thermolysis products are nitriles and sulfur.

The second pathway, followed by 1,4,2-dioxazolones, proceeds by extrusion of CO_2 and rearrangement to the corresponding isocyanates **54**. The question of a nitrene intermediate or a concerted CO_2 extrusion and relevant mechanistic aspects have been discussed in CHEC-II(1996). Also, various thermolytic reactions of other fully conjugated 1,4-(oxa/thia)-2-azole derivatives, in particular azonylenes **11** ($\text{X} = \text{S}; \text{Y} = \text{O}; \text{Z} = \text{CCl}_2$), azonylimines **10** ($\text{X} = \text{O}; \text{Y} = \text{S}; \text{Z} = \text{NR}$), and imino dioxazolidine derivatives **12** ($\text{X} = \text{Y} = \text{O}; \text{W} = \text{Z} = \text{NR}$) have been discussed in CHEC-II(1996) <1996CHEC-II(4)506>.

Dithiazole thiones **9** are thermally stable, at least under reflux in xylene, but in the presence of a dipolarophile their decomposition follows another route (see Section 6.04.5.6).

6.04.5.2.2 Photochemical reactions

Typically, analogous pathways to those reported for thermolysis of azolones are observed under photochemical conditions (Scheme 4). Thus 1,3,4-dioxazol-3-ones **8** ($X=Y=O$) extrude CO_2 and the resulting *N*-acylnitrene intermediate **55** may be either trapped or rearrange to an isocyanate. Various trapping reagents have been used to establish the nitrene formation. On the other hand, the photolysis of thiazolones and thiazolethiones **9** ($R=\text{Ph}$) having at least one sulfur atom in the ring affords the unstable nitrile sulfide, through an unstable antiaromatic thiazirine intermediate **56**. A detailed account of all reported cases is given in CHEC-II(1996) <1996CHEC-II(4)506>.



Scheme 4

6.04.5.3 Electrophilic Attack at Carbon, Nitrogen, and Sulfur

As previously noted, no electrophilic attack at ring carbon, nitrogen, and sulfur has been reported.

6.04.5.4 Nucleophilic Attack at Carbon

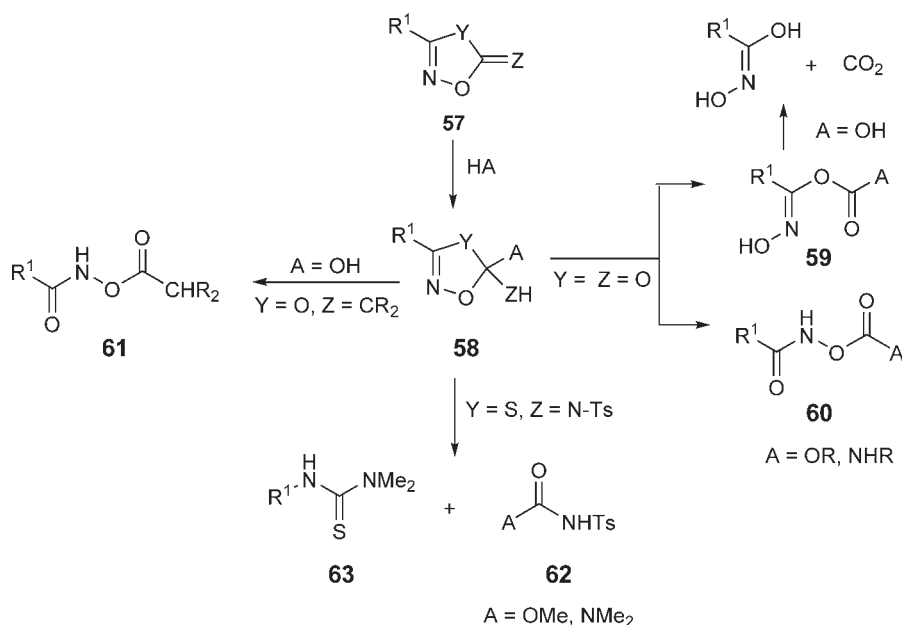
6.04.5.4.1 Conjugated systems with exocyclic double bond and nucleophiles

As previously noted, the most reactive site of neutral fully conjugated 1,4-(oxa/thia)-2-azoles is the sp^2 ring carbon atom of the exocyclic double bond. A detailed account of all reported data has been given in CHEC-II(1996) <1996CHEC-II(4)510>. An outline of all these reactions is given in Scheme 5.

Generally, nucleophilic attack results in ring opening followed by further transformations, depending on the nature of the ring system, the substituents, and the nucleophile. Thus, for the dioxazolones **57** ($Y=Z=\text{O}$), the ring opening of the initially formed adduct **58** may be performed by two ways: by scission of either the C–O bond or the N–O bond leading to the corresponding adducts **59** and **60**, respectively. The N–O bond scission is also followed by the azolinylene derivatives **57** ($Y=\text{O}; Z=\text{CR}_2$), affording compounds **61**. As regards the azolinimine derivative **57** ($R=\text{Ph}; Y=\text{S}; Z=\text{NTs}$), the ring opening of intermediate **58** is followed by a subsequent rearrangement of the phenyl group to give the urethane ($A=\text{OMe}$) or urea derivatives ($A=\text{NMe}_2$) **62** and **63**, depending upon the nucleophile.

6.04.5.4.2 Reactions of 1,4-oxa/thia-2-azolium salts and nucleophiles

All 1,4-(oxa/thia)-2-azolium salts are, in general, electrophilic species. In particular, both 1,3,4- and 1,4,2-oxathiazolium salts are extremely electrophilic, being attacked by solvents more nucleophilic than trifluoroacetic acids and nitromethane. On the other hand, 1,4,2-dithiazolium salts are more stable and in fact provide the main source of this

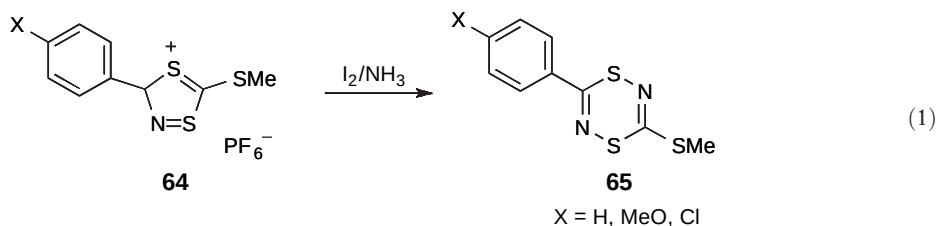


Scheme 5

class of azolium cation chemistry. Initially, all nucleophiles attack the more electrophilic C-5 position of 1,4,2-dithiazolium cations. In a few instances, isolable primary adducts are obtained, but in most cases these adducts are further transformed to various other ring systems or open-chain products. A full account of this chemistry is given in CHEC-II(1996) <1996CHEC-II(4)510>.

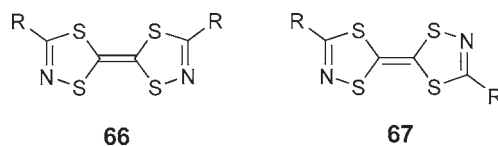
6.04.5.4.3 Ring expansion reactions

Ring expansion reactions of 1,4-(oxa/thia)-2-azole ring are in fact a part of dithiazolium salts chemistry. In some cases, the initial nucleophilic attack at C-5 of dithiazolium salts leads to incorporation of a nitrogen atom into the dithiazole ring. Depending on the reagent used, further transformations occur, affording either 1,4,2,5- or 1,4,2,6-dithiadiazines, which are heterocyclic rings with 8π -electrons. Several examples of these transformations, as well as all relative mechanistic aspects, have been reported in CHEC-II(1996) <1996CHEC-II(4)513>. An application of a ring expansion of dithiazolium salt **64** with an iodine–ammonia reagent has been proposed as an efficient synthesis of 1,4,2,5-dithiadiazine derivative **65** (Equation 1) <1997J(P1)1157>.



6.04.5.5 Reactions with Electron-Deficient Species and at Surfaces

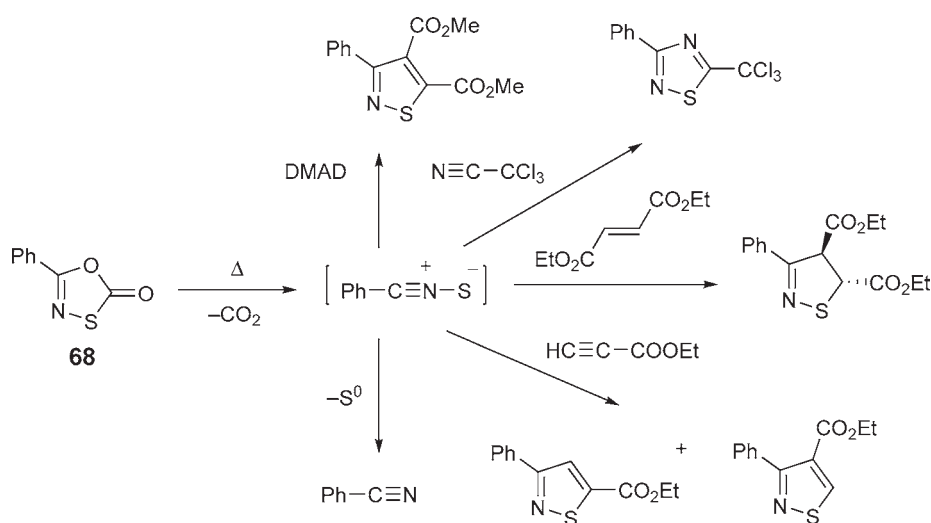
All known reactions of this category have been reported in CHEC-II(1996). Notable examples include: the carbene addition to 1,3,4-oxathiazol-2-ones to give 1,4,3-oxathiazines; the hydrogenation of 1,4,2-dioxazol-2-one over Raney nickel to give amides and CO₂; and the reductive dimerization of several 1,4,2-dithiazolium salts with Zn dust to give the tetrathiadiazafulvalenes **66** and **67** <1996CHEC-II(4)515>.



6.04.5.6 Reactions with Cyclic Transition States

It is well established that 1,3,4-oxathiazol-2-ones undergo ring fragmentation on heating to give nitrile sulfides, an unstable short-lived class of 1,3-dipole. In fact, the major part of oxathiazolone chemistry has been focused on nitrile sulfide-trapping reactions to form various sulfur-containing heterocycles. In general, electron-poor alkenes and alkynes are suitable dipolarophiles for nitrile sulfide trapping. Moreover many other π -bonds with low-lying LUMO energies, such as $\text{C}\equiv\text{N}$, $\text{C}=\text{N}-$, $\text{C}=\text{O}$, $\text{C}=\text{S}$, $\text{C}=\text{Se}$, and $\text{C}\equiv\text{P}$, have also been used, leading to various heterocyclic ring systems. A general survey of this chemistry has been summarized in CHEC-II(1996) <1996CHEC-II(4)515>.

From the new data, particularly significant is the reported remarkable improvement of nitrile sulfides generation by microwave-assisted thermolysis of 1,3,4-oxathiazolones <2005SC807>. The conventional thermolysis as a source of nitrile sulfides is restricted by the forcing conditions required to accomplish the decarboxylation of starting oxathiazolones. The microwave-assisted variation results in better yields, shortening of reaction time, and use of a small excess of dipolarophile. This variation has been tested to some well-known typical trapping reactions of benzonitrile sulfide generated from oxathiazolone **68** (Scheme 6) in comparison to the same reactions performed by conventional nitrile sulfide generation.



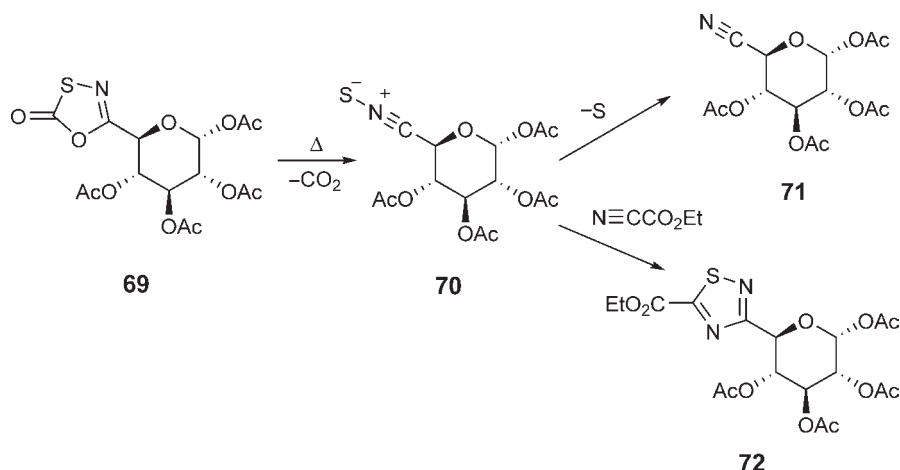
Scheme 6

Microwave-assisted thermolysis has also been applied to the unusually stable oxathiazolone **69**. In this case, appreciable amounts of the adduct **72** were obtained only by microwave irradiation of oxathiazolone **69** at 200 °C for 10 min (Scheme 7) <2006CAR41>.

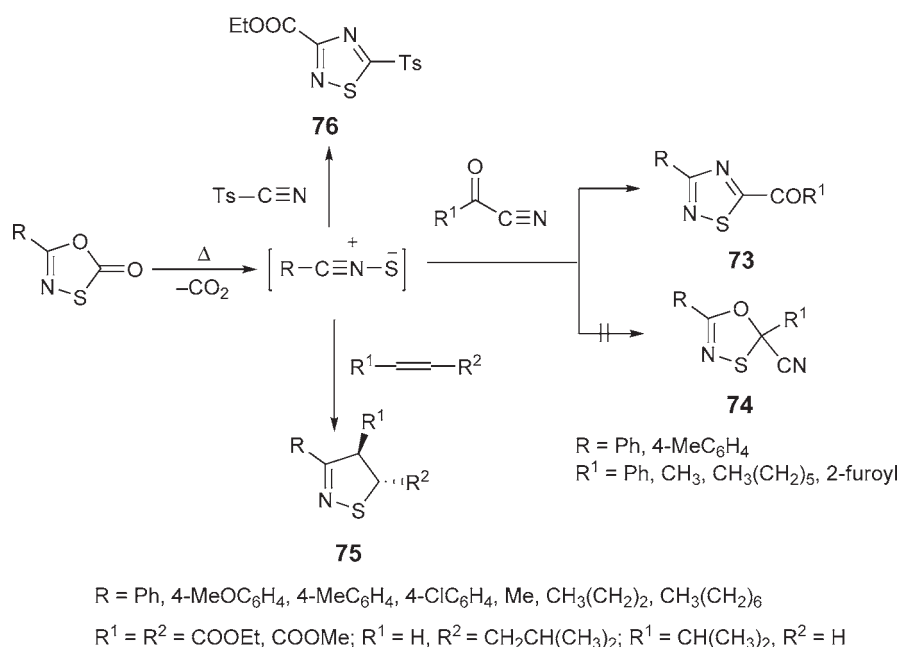
Other new reports dealing with nitrile sulfide cycloaddition chemistry are depicted in Scheme 8 <2000ARK720, 2002ARK15, 2003BMC5529>. There is a preference for the cyano group instead of the $\text{C}=\text{O}$ group to react with benzonitrile sulfide, affording the thiadiazole **73** instead of oxathiazole **74** <2002ARK15>, while *cis*- to *trans*-isomerizations are observed in cycloadditions of nitrile sulfides with dimethyl or diethyl maleate affording the isothiazolines **75** <2000ARK720>.

As previously noted (Section 6.04.5.2.1), more forcing conditions are required to generate nitrile sulfides from 1,4,2-dithiazol-5-ones than from 1,3,4-oxathiazol-2-ones. Thus these reactions are performed by a prolonged heating in

mesitylene using excess (1:10) dipolarophile to afford the isothiazole derivatives **78–80** (Scheme 9) <2002ARK121>. Donor substituents in the oxathiazolone ring facilitate the reaction course.

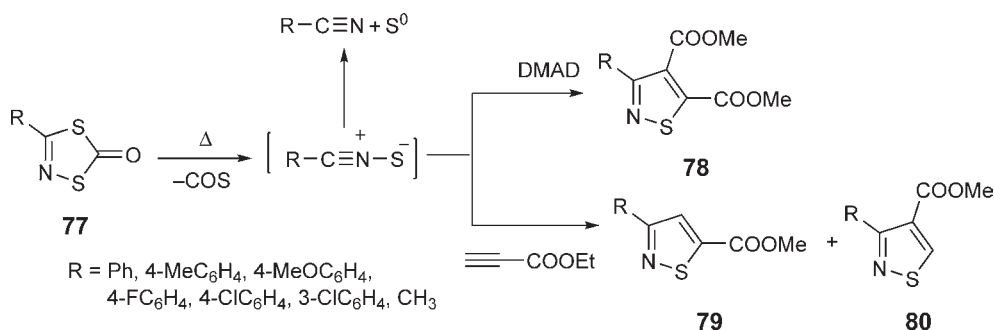


Scheme 7

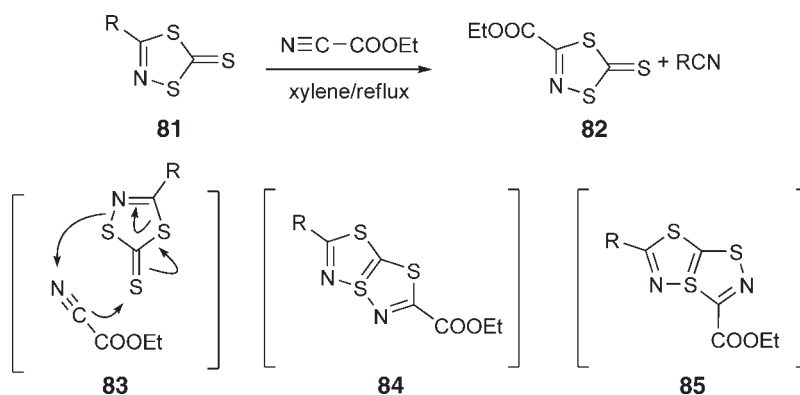


Scheme 8

As previously mentioned, 1,3,4-dithiazole-2-thiones are thermally stable (see Section 6.04.5.6). However, on heating in the presence of ethyl cyanofornate, a cycloaddition reaction occurs between the added reagent and the S–C–S fragment of the dithiazole ring, affording the dithiazolethione **82**. Two possible mechanisms have been proposed. A concerted mechanism, termed in this case as [2' + (1,2,3)] cyclodisubstitution, or cyclosubstitution, proceeding via the transition state (TS) **83** or a two-step mechanism proceeding via the hypervalent sulfur intermediates **84** and/or **85** (Scheme 10) <1996CHEC-II(4)516, 2002ARK121>.



Scheme 9



Scheme 10

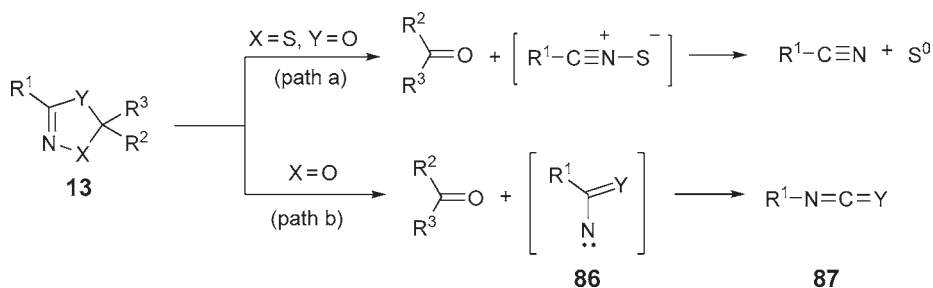
The thione groups of dithiazoethiones are very reactive heterodipolarophiles. Several cycloadditions with nitrile oxides, diphenylnitrimine, and ethyl azidoformate to give spiro derivatives have been reported <1996CHEC-II(4)517>.

6.04.6 Reactivity of Nonconjugated Rings

6.04.6.1 Unimolecular Thermal and Photochemical Reactions

6.04.6.1.1 Thermal decomposition of azolines

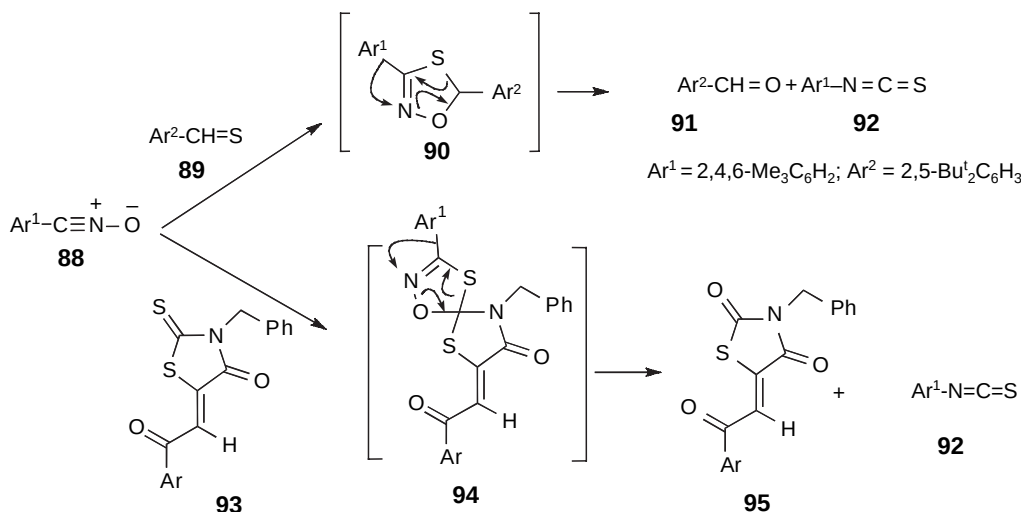
Thermal decomposition of azolines of type **13** follows an analogous pathway to that already discussed for azolones (see Section 6.04.5.2). As depicted in Scheme 11, those azolines having $X = S$ follow a typical retro-1,3-dipolar cycloaddition process (path a) affording carbonyl compounds and nitrile sulfide intermediates, which in the absence of a trapping



Scheme 11

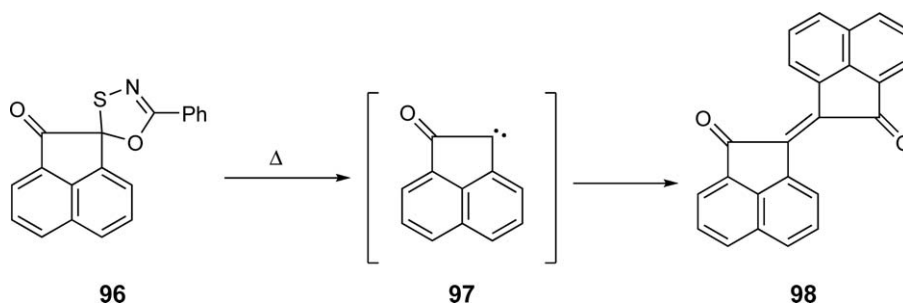
dipolarophile decompose further to nitriles and sulfur. On the other hand, the azolines with $X = O$ and $Y = O$ or S afford as final products iso(thio)cyanates **87**, possibly via an acyl ($Y = O$) or thioacyl ($Y = S$) nitrene intermediate **86** (path b). However, a concerted cycloreversion mechanism cannot be ruled out <1996CHEC-II(4)517>.

A cycloreversion mechanism is suggested for the transformation of the nonisolable cycloadduct **90** to the aldehyde **91** and isothiocyanate **92** <1996BCJ719> and for the spiro-1,4,2-oxathiazole intermediates **94** to the dioxathiazoline **95** and the aryl isothiocyanate **92** <2001MOL510>. Both cycloadducts are obtained by cycloaddition reactions of nitrile oxides **88** to thiocarbonyl compounds (Scheme 12).



Scheme 12

Thermolysis of spirooxathiazoline derivative **96** affords the bi(acenaphthylidene) dione derivative **98** (Scheme 13), obviously via another route. Carbene **97** is suggested as an intermediate – an assumption that is supported by cross-coupling experiments <1996JCR(S)8>.



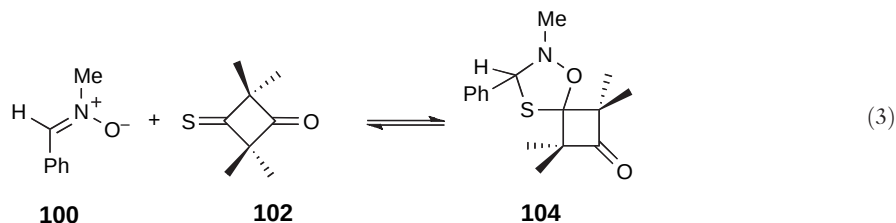
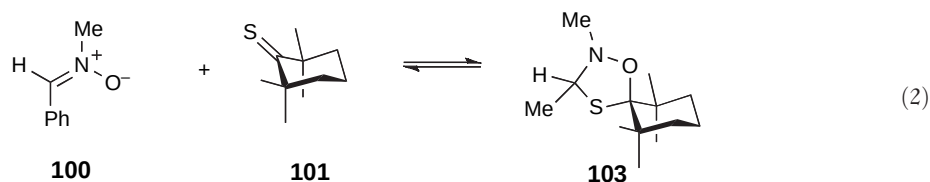
Scheme 13

6.04.6.1.2 Thermal decomposition of azolidine derivatives

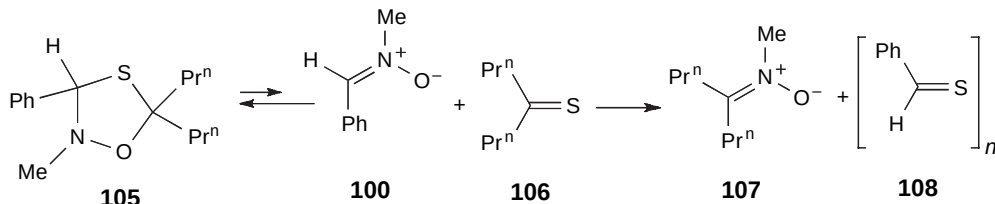
Generally the azolidine derivatives of structures **14–16** are less studied than other classes of (oxa/thia)-2-azoles, either because of their thermal instability or because of the difficulty in their preparation. Some of them are isolable compounds, others are nonisolable intermediates or reversibly dissociate to their starting precursors. Several examples dealing with thermal stability of certain 1,4,2-dioxazolidines, 3-imino-1,4,2-dioxazolidines, as well as 1,4,2-oxathiazolidine derivatives, have been reported <1996CHEC-II(4)519>. Some new data are given below.

Although the 1,4,2-oxathiazolidine derivatives **16** ($X = O$; $Y = S$) are usually nonisolable intermediates of reactions between nitrones and thiocarbonyl compounds, in some instances a cycloaddition/cycloreversion equilibrium is established with steric hindrance influencing its position. This is the case for the kinetically stable

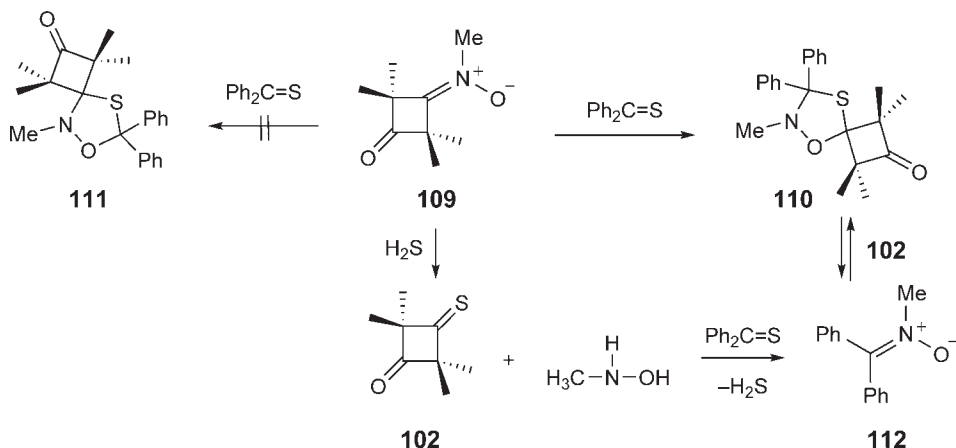
1,4,2-oxathiazolines **103** and **104**. From the linear temperature dependence of the free energy changes ΔG_{diss} for the reaction of *N*-methyl-*C*-phenylnitron **100** and 2,2,6,6-tetramethylhexanethione **101** (Equation 2), the thermodynamic state functions are found to be $\Delta H_{\text{diss}} = +10.8 \text{ kcal mol}^{-1}$ and $\Delta S_{\text{diss}} = +28 \text{ e.u.}$ Besides, K_{diss} of compound **104** (Equation 3) is found to be solvent dependent and rises with solvent polarity. This was attributed to the increasing solvation of nitron **100**, as the reactant with the highest dipole moment <1995JA9671>.



A surprising metathesis has been observed upon dissociation of oxathiazoline **105** to the corresponding nitron **100** and the thione **106**, which finally leads to the nitron **107** and the elusive thiobenzaldehyde **108** <1995JA9671>. The latter is presumably polymerized and the conversion goes to completion (Scheme 14). It has been suggested that this metathesis results in a 'sulfidrogenolysis' of nitron **100**, catalyzed by traces of hydrogen sulfide, present as hydrolysis by-product of thione **106**. This is supported by the closely related reaction of nitron **109** with thiobenzophenone, in which compound **110** is formed, via the nitron **112**, instead of the normal cycloadduct **111** (Scheme 15) <1995JA9671, 1997LA1685>.

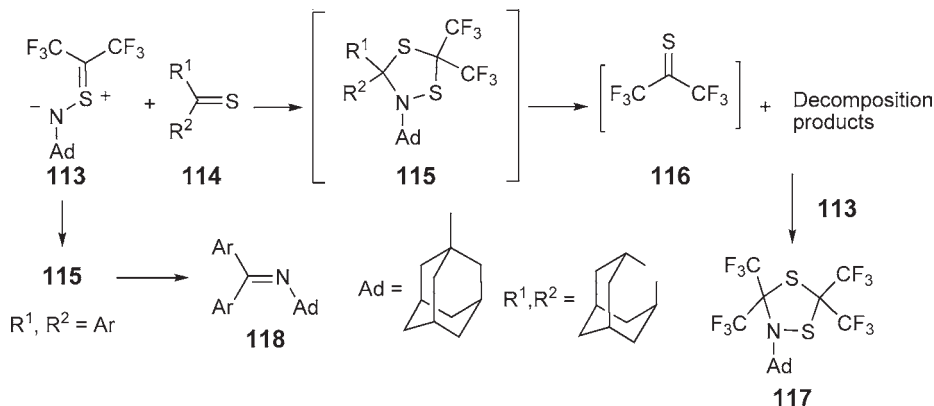


Scheme 14



Scheme 15

The dithiazolidine ring is of moderate stability, depending on its substitution. Some dithiazolidine derivatives, obtained by 1,3-dipolar cycloaddition of the thione-*S*-imide **113** and thiones **114**, are indefinitely stable at room temperature as compounds **115** ($R^1, R^2 = \text{Ar}$). Others decomposed during recrystallization affording the corresponding imines **118**, and some, such as the sterically crowded **115** ($R^1, R^2 = 2\text{-adamantyl}$), are so unstable that they spontaneously decompose, affording hexafluorothioacetone **116** and finally the more stable compound **117** (Scheme 16) <1998EJO459>.



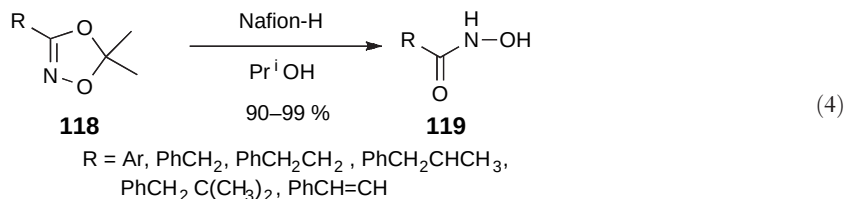
Scheme 16

6.04.6.2 Electrophilic Attack at Ring Carbon, Nitrogen, and Sulfur

The ring carbon atoms of all possible 1,4-(oxa/thia)-2-azoles are not expected to be attacked by electrophiles and such reactions have not been reported. A few known examples concerning alkylations or protonations at the ring nitrogen of certain types of dithiazoline derivatives, as well as oxidation of ring sulfur of certain 1,4,2-oxathiazolines to give sulfoxo compounds, have been discussed in CHEC-II(1996) <1996CHEC-II(4)519>.

6.04.6.3 Nucleophilic Attack at Ring Carbon

Several examples of hydrolysis of 1,3,4-dioxazolines, carried out under acidic, base-induced, or even neutral conditions, affording hydroxamic acids and carbonyl compounds have been reported in CHEC-II(1996) <1996CHEC-II(4)521>. Since the 1,3,4-dioxazoline ring may be formed from hydroxamic acids (see Section 6.04.9.2), this ring may serve as a protecting group for the starting hydroxamic acid. Accordingly, the hydrolysis of 1,3,4-dioxazolines **118** carried out in the presence of Nafion-H resin affording hydroxamic acids **119** has been proposed as an efficient deprotection reaction (Equation 4) <2002JOC4833>.

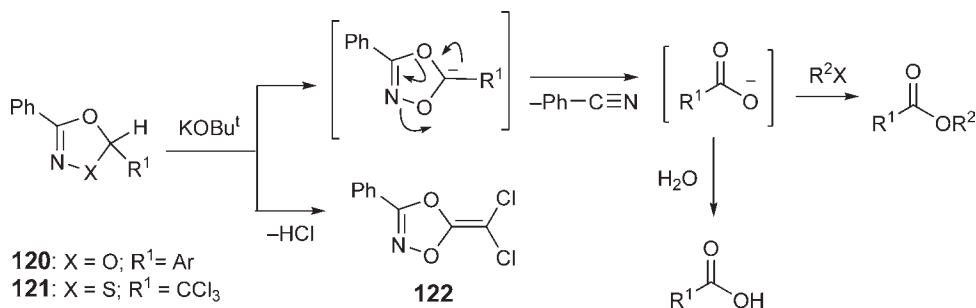


There have been also reported in CHEC-II(1996) several examples of acid hydrolysis or solvolysis reactions of certain 1,3,4- and 1,4,2-oxathiazolines. In almost all cases, open-chain or decomposition products are obtained <1996CHEC-II(4)521>.

Although in most cases studied the nucleophilic attack takes place at the tertiary carbon atom of dioxazolines and oxathiazolines, a few examples of attack at sp^2 carbon have also been reported <1996CHEC-II(4)522>.

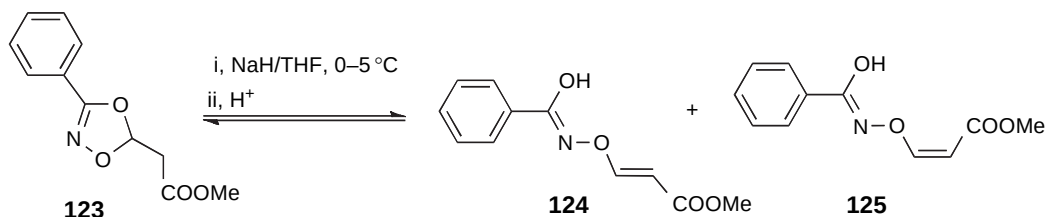
6.04.6.4 Attack at Ring Hydrogen

Deprotonation of 1,3,4-dioxazolines **120** with a strong base (**Scheme 17**) affords nitriles and carboxylate anions; the later are directly converted to acids or their esters. Since dioxazolines **120** are usually obtained from cycloadditions of aldehydes to nitrile oxides, this reaction pathway has been suggested as an alternative method for overall oxidation of aldehydes to acids or esters without using conventional oxidants <1996CHEC-II(4)523, 1996J(P1)747>. In the case of oxathiazoline **121**, dehydrohalogenation affords the azonylene **122** <1996CHEC-II(4)523>.



Scheme 17

Treatment of dioxazole derivative **123** with NaH and careful acidification of the resulting sodium salts afford compounds **124** and **125** in a ratio 5.5:1. These compounds either on standing or during silica gel chromatography revert to the starting dioxazole (**Scheme 18**) <2000TL7433>.



Scheme 18

6.04.6.5 Reactions at Surfaces

As previously mentioned, 1,4,2-dioxazoline rings may be used as a protected group for hydroxamic acids (see [Section 6.04.6.3](#)). In fact, this ring is susceptible to hydrogenolysis conditions (H₂/Pd) affording carbonyl compounds <1996CHEC-II(4)525, 2002JOC4833>.

6.04.6.6 Reactions with Cyclic Transition States

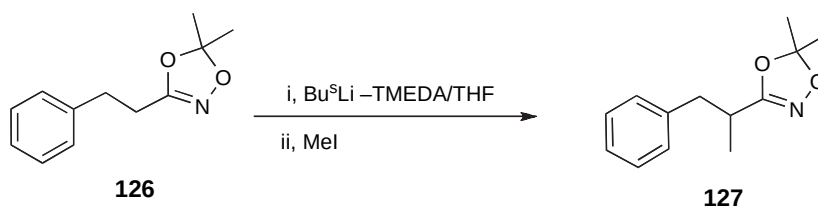
As reported before (see [Section 6.04.6.1.1](#)), thermolysis of 1,3,4-oxathiazolines proceeds via a retro-1,3-dipolar cycloaddition to give carbonyl compounds and nitrile sulfides. In CHEC-II(1996) several examples of trapping reactions using suitable dipolarophiles have been reported <1996CHEC-II(4)524>. It is also worth mentioning that the previously reported thermolysis reactions of dithiazolines **115**, which follow a typical retro-1,3-dipolar cycloaddition, afford thione-*S*-imides <1998EJO459>. The later compounds react further to give product **117** (see [Section 6.04.6.1](#), **Scheme 16**).

6.04.7 Reactivity of Substituents Attached to Ring Carbon Atoms

There have been numerous reports of transformations on substituents at both C-2 and C-5 of 1,3,4-dioxazoline ring in which the dioxazole ring remains intact <1996CHEC-II(4)524>. A group of these concern polyfluorinated substituents at the C-5 position, especially those having an α -hydrogen. These are strong C–H acids and readily undergo reactions with various electrophiles. Another group of reactions concerns substituents at the C-2 position. Thus, alkenyl substituents may act as Michael acceptors or acetyl groups may undergo haloform oxidations affording carboxylic acids.

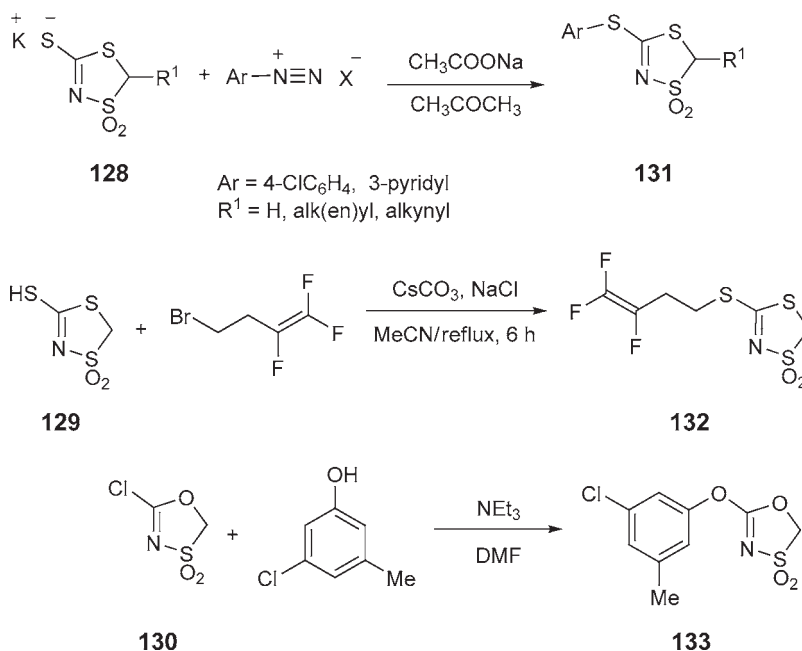
Other reactions carried out on 1,3,4-dioxazol-2-ones having an α - or β -hydroxyl group on the C-5 substituent result in ring cleavage accompanied with side reactions involving the hydroxyls. A more detailed account is given in CHEC-II(1996) <1996CHEC-II(4)524>.

α -Functionalization of dioxazoline **126** can be achieved using *sec*-butyllithium–TMEDA in tetrahydrofuran (THF; TMEDA = tetramethylethylenediamine [1,2-bis(dimethylamino)ethane]), and the resulting anion reacts with methyl iodide to give compound **127** (Scheme 19) <2002JOC4833>.



Scheme 19

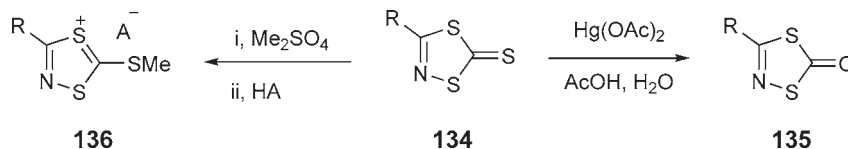
Some typical substitution reactions of 1,4,2-dithiazoline 1,1-dioxides **128–130** at the C-3 position afford compounds **131–133** of agrochemical interest (Scheme 20) (**131**: <1997DEP19545635, 1998GEP19721627>, **132**: <2000GEP10034133>, **133**: <2000DEP19918294>).



Scheme 20

Some reactions concerning the thione group of dithiazolethiones **134** have been discussed in CHEC-II(1996) <1996CHEC-II(4)517>. The thione group of thiones **134** may be oxidized to give the corresponding dithiazolone

135 on treatment with excess mercuric acetate in AcOH/CHCl₃/H₂O [<2002ARK121>](#). Also, it is methylated with Me₂SO₄, affording, after treatment with a strong acid (HClO₄ or HBF₄), the dithiazolium salts **136** ([Scheme 21](#)) [<1996CHEC-II\(4\)526>](#).



Scheme 21

1,4,2-Dithiazolium salts are also obtained by solvolysis in strongly acidic media ($\text{HClO}_4/\text{Ac}_2\text{O}$) of 1,4,2-dithiazolines having alkylamino, alkoxy, or methylthio groups at the C-5 position. Accordingly, analogous 1,4,2-oxathiazolines afford 1,4,2-oxathiazolium salts <1996CHEC-II(4)526>.

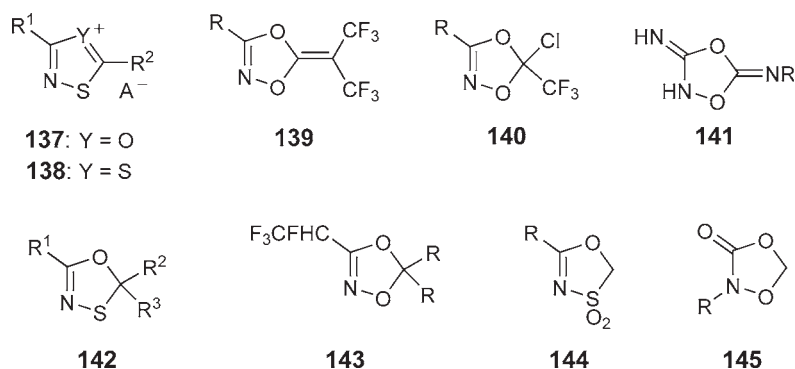
6.04.8 Reactivity of Substituents Attached to Ring Heteroatom

There are no reports concerning the reactivity of substituents attached to ring heteroatoms. In fact, known substituents attached to ring heteroatoms are limited to the *N*-alkyl substituents of various dithia or oxathiazolidine rings and the *S*-oxides and *S,S*-dioxides of dithiazolidine derivatives. The only available data concerning these compounds are limited to the preparation and to the reactivity of the ring system.

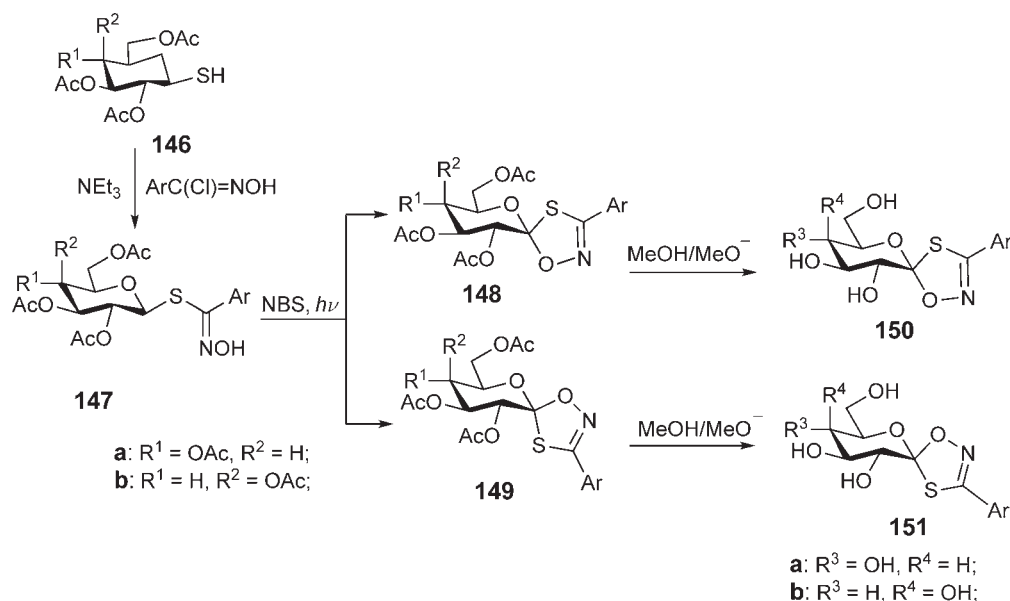
6.04.9 Ring Synthesis Classified by Numbers in Each Component

6.04.9.1 Formation of One Bond Adjacent to a Heteroatom

The most 1,4-(oxa/thia)-2-azole ring synthesis of this category deals with intramolecular cyclizations of various open-chain precursors. In CHEC-II(1996), many cases of such cyclizations leading to various 1,4-(oxa/thia)-2-azole ring systems [137–145](#) were reported <1996CHEC-II(4)527>. Of particular interest are cyclizations leading to 1,4,2-dithiazolium salts [138](#). All of them have as common starting materials various sodium salts of dithiocarboxylic acids. These salts are transformed to suitable open-chain precursors, which in turn give the final products, either by dehydration or by oxidative cyclization or by elimination reactions. More details are given in CHEC-II(1996) <1996CHEC-II(4)527>.



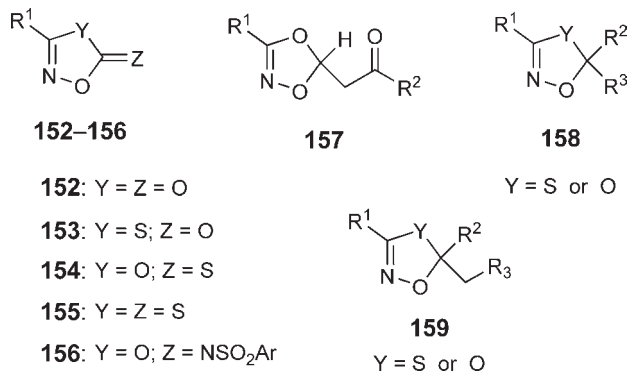
Oxidative intramolecular cyclizations of sugar-derived hydroximates **147**, having either the D-*gluco*-configuration (**147a**) <1994T6559> or the D-*galacto* configuration (**147b**) <2005CAR1397>, afford the corresponding diastereomeric spiro-oxathiazoline derivatives **148** and **149**. Compounds **148** with the (1*S*)-configuration are predominantly formed (*S/R* ratio ~ 5:1) (**Scheme 22**).



Scheme 22

6.04.9.2 Formation of Two Bonds: Four-Atom Fragment and Carbon

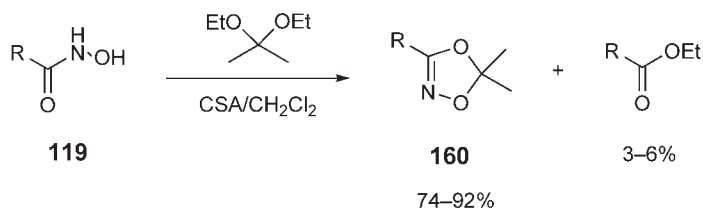
The cyclizations of hydroxamic or thiohydroxamic acids with various electrophilic reagents are important routes for the synthesis of many oxa/thiazoles of the general structures **152–159**. In CHEC-II many examples of this kind of reactions were reported <1996CHEC-II(4)528>. Summarizing these data, the following combinations have been reported: (1) reactions carried out between hydroxamic or thiohydroxamic acids with phosgene, thiophosgene, carbonyl, thiocarbonyl compounds and imino-transfer reagents (compounds **152–156**); (2) reactions carried out between hydroxamic acids or alkali hydroxamates or thiohydroxamic acids with ketals, 1,1-dichlorides, alkynyl compounds, and chloroenones (compounds **157–159**).



An improved synthesis of 1,4-dioxazolines from hydroxamic acids **119** and 2,2-diethoxypropane in the presence of camphorsulfonic acid as an acidic catalyst via a transketalization reaction has been reported (Scheme 23) <2002JOC4833>.

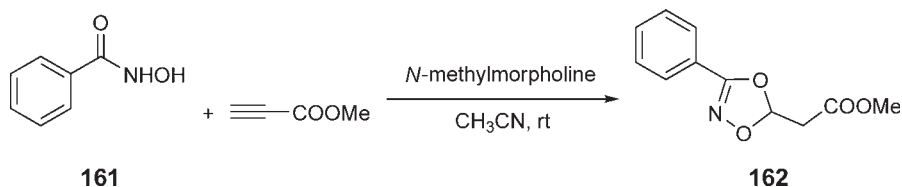
Another approach for the synthesis of dioxazoline derivative **162** is achieved by Michael addition of benzohydroxamic acid **161** to methyl propiolate, catalyzed by *N*-methylmorpholine (Scheme 24) <2000TL7433>.

A silver ion-mediated desulfurization of thiocarbonyl compounds **163** or **164** followed by condensation with benzohydroxamic acid in the presence of excess triethylamine affords, respectively, dioxazole derivatives **165** or **166** (Scheme 25) <2002H(57)143>. Other reports concern the synthesis of 1,4-(oxa/thia)-2-azoles **170–173** from unusual four-atom components such as the sulfur diimides **167**, the thietan sulfimide **168**, and the carbimidoyl chloride **169** <1996CHEC-II(4)530>.

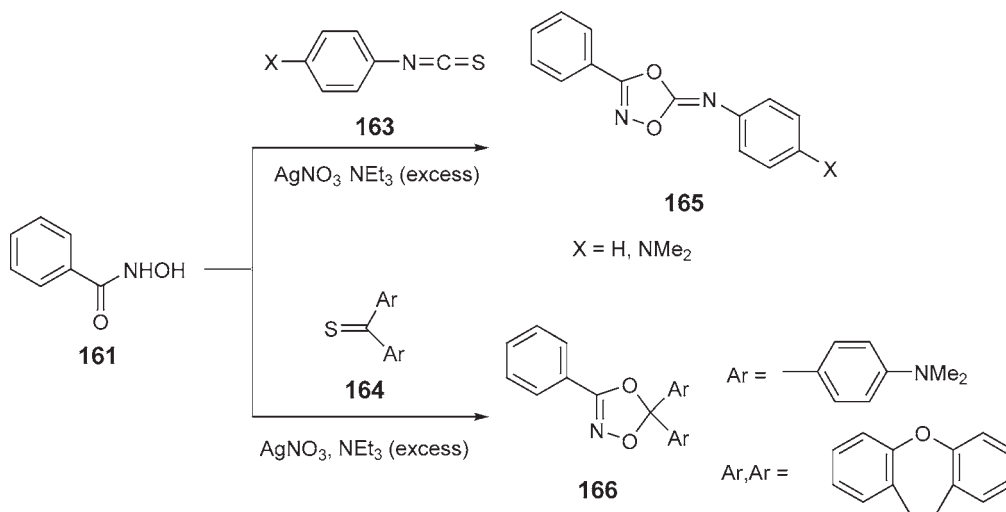


R = Ph, 4-MeOC₆H₄, 4-NO₂C₆H₄, 4-PhC₆H₄, PhCH₂CH(CH₃), PhCH₂C(CH₃)₂, PhCH=CH

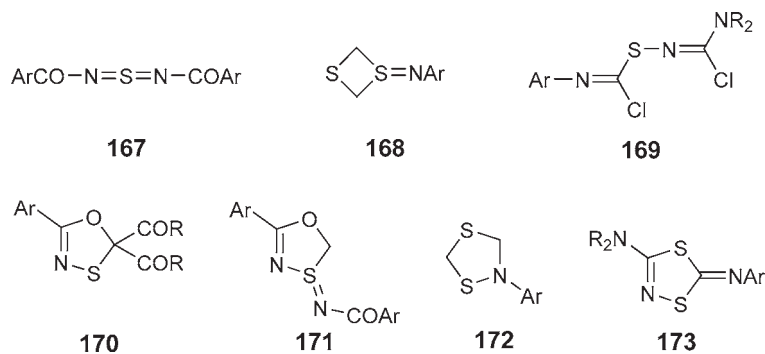
Scheme 23



Scheme 24

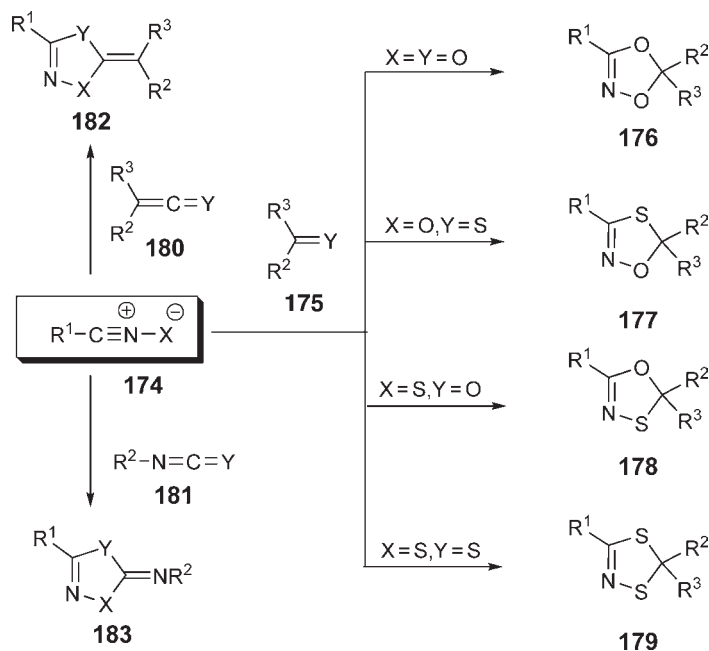


Scheme 25



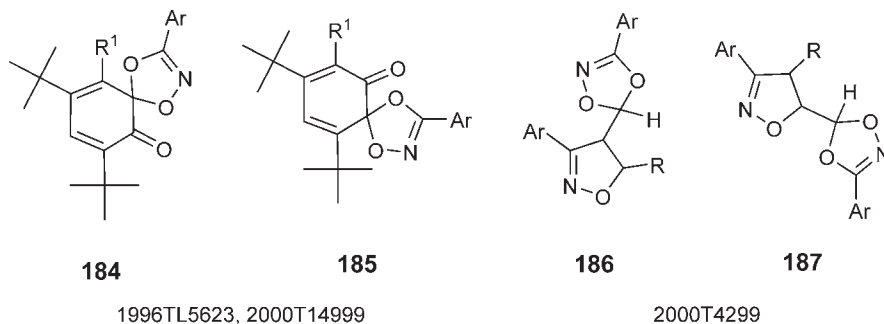
6.04.9.3 Formation of Two Bonds: [3+2] Atoms by Cycloaddition

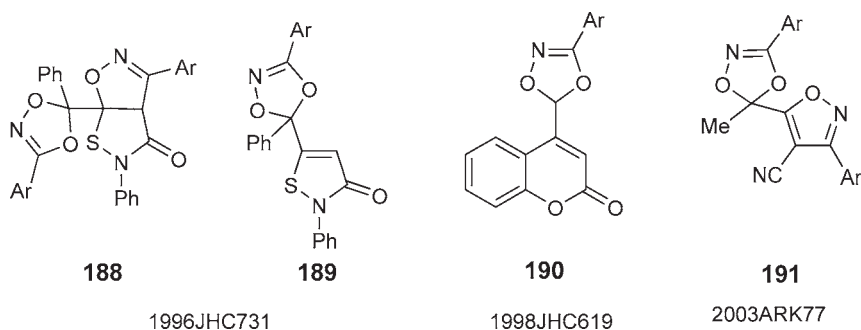
It is well established that 1,3-dipolar cycloadditions are an important method for the synthesis of five-membered ring heterocycles. In particular, for the 1,4-oxa/thia-2-azole system, nitrile oxides or nitrile sulfides are usually employed as the 1,3-dipoles and C=O and/or C=S groups as the dipolarophiles. There are many examples of all possible dipole–dipolarophile combinations leading to azoline derivatives **176–179** and also to compounds of the general structures **182** and **183** (X, Y = O, and/or S) (Scheme 26) <1996CHEC-II(4)530>.



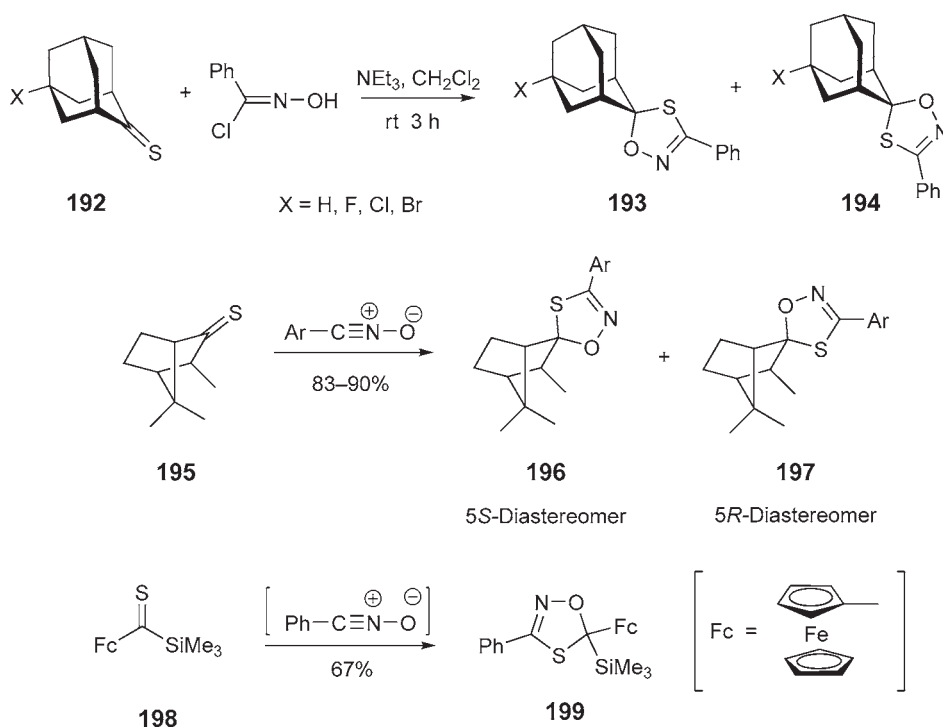
Scheme 26

Generally, carbonyl compounds are of low dipolarophilic activity toward nitrile oxides; only aldehydes and ketones activated by an adjacent electron-withdrawing group show sufficient activity leading to 5*H*-1,4,2-dioxazole derivatives **176**. In most cases, simple aldehydes and ketones react with nitrile oxides only in the presence of a Lewis acid catalyst such as BF_3 . Other reactive carbonyl groups are part of cumulative unsaturated systems like ketenes **180** or isocyanates **181** (Y = O), which yield fully conjugated dioxazole derivatives **182** or **183** (X = Y = O), respectively <CHEC-II(4)530, 1998RJO106>. In some cases, reactive carbonyl groups are part of cyclic systems such as quinones, which upon cycloaddition with nitrile oxides give compounds **184–187** <1996CHEC-II(4)530, 1996TL5623, 2000T14199>, and other heterocyclic rings or substituents to other heterocyclic rings, which give compounds **188–191** <1996CHEC-II(4)530, 1996JHC731, 1998JHC619, 2003ARK77>.





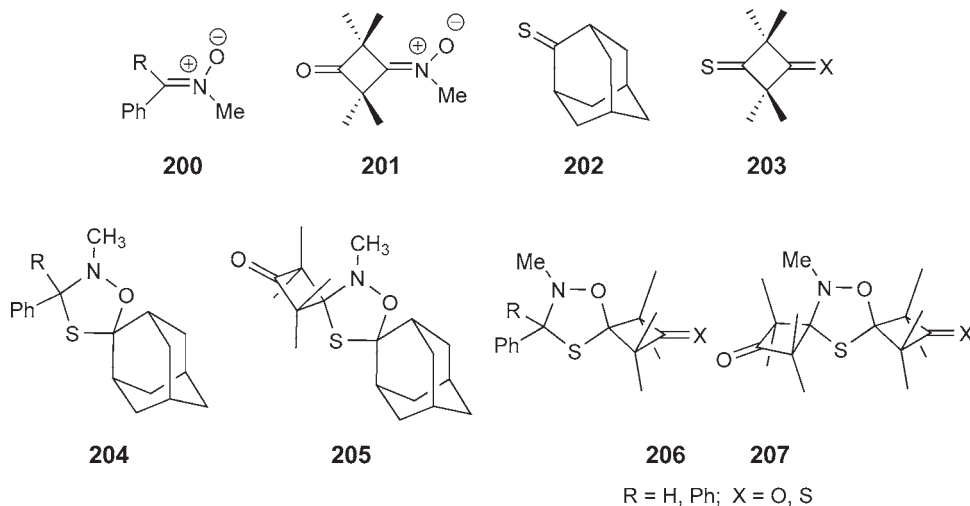
Thiocarbonyl compounds are more reactive toward nitrile oxides than the corresponding carbonyl dipolarophiles. Thus, 1,4,2-oxathiazoles **177** are easily obtained by cycloaddition of nitrile oxides with many classes of thiocarbonyl compounds, such as thioketones, dithiocarboxylic esters, thionocarboxylic esters, thioamides, and trithiocarbonates. Also, fully conjugated 1,4,2-oxathiazoles **182** and **183** ($X=O$; $Y=S$) are obtained from the $C=S$ bond of several cumulated unsaturated systems such as thioketenes, sulfonyl isothiocyanates, sulfines, CS_2 , etc. <1996CHEC-II(4)530>. Cycloadditions of various adamantane thione derivatives **192** with benzonitrile oxide result in the formation of geometrically isomeric spiro 5*H*-1,4,2-oxathiazoles **193** and **194** <1997JOC4672>. The preferred formation of the (*E*)-isomer **193**, obtained from the *syn*-face addition of nitrile oxide, is explained on the basis of a transition state hyperconjugation model where the nitrile oxide approaches the sp^2 carbon from an antiparallel direction to the most electron-rich vicinal bonds. Analogous diastereomeric cycloadducts **196** and **197** although inseparable, are obtained from reactions with the (1*R*)-thiocamphor **195** <2004JHC731>. Thioaldehydes are generally difficult to handle and unstable compounds. However, some of them can be trapped by cycloaddition with nitrile oxides <1996CHEC-II(4)530>. An interesting version is that of ferrocenyl thioacyl silane **198**, which acts as a thioaldehyde equivalent affording with benzonitrile oxide the corresponding 5*H*-1,4,2-oxathiazole derivative **199** (Scheme 27) <1999TL6473>.



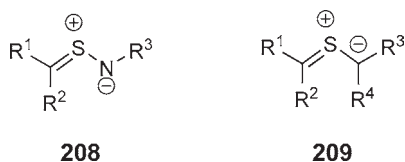
Scheme 27

The 1,3,4-oxathiazole **178** and 1,4,2-dithiazole derivatives **179** are obtained by cycloadditions of nitrile sulfides with C=O or C=S bonds, respectively. Typical electrophilic carbonyl compounds are required for the synthesis of 5*H*-1,3,4-oxathiazoles **178**. For the 5*H*-1,4,2-dithiazoles **179**, the high dipolarophilic activity of C=S groups makes this way a potentially general synthetic route for this class of compound <1996CHEC-II(4)530>.

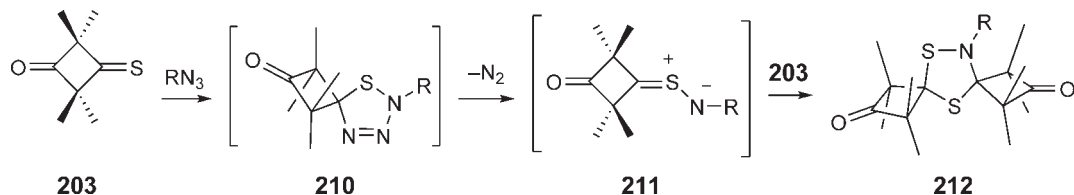
Nitrones and nitronate esters are potentially suitable classes of 1,3-dipoles that could give tetrahydro 1,4-oxa/thia-2-azoles by cycloaddition across C=O or C=S dipolarophiles. While cycloadditions of nitrones with C=O groups are scarce, the C=S group is a very reactive one <1996CHEC-II(4)530>. Although the C=S group has been characterized as a 'superdipolarophile' by Huisgen, in fact in most cases of reactions with nitrones the resulting oxathiazolidine cyclodducts are reversibly dissociated and a rapid cycloaddition/cycloreversion equilibrium is established (see Section 6.04.6.1.2) However, in some cases of sterically hindered nitrones and/or thiones, such as compounds **200–203** the isolable 1,4,2-oxathiazolidine derivatives **204–207** are obtained <1995JA9671, 1997LA1685>.



Thiocarbonyl-*S*-imides **208** and thiocarbonyl-*S*-ylides **209** are two unusual classes of sulfur-centered 1,3-dipoles that may be possible candidates as 4π-components for the synthesis of tetrahydro-1,4-(oxa/thia)-2-azoles. Both are unstable transient species that can be trapped by suitable dipolarophiles.



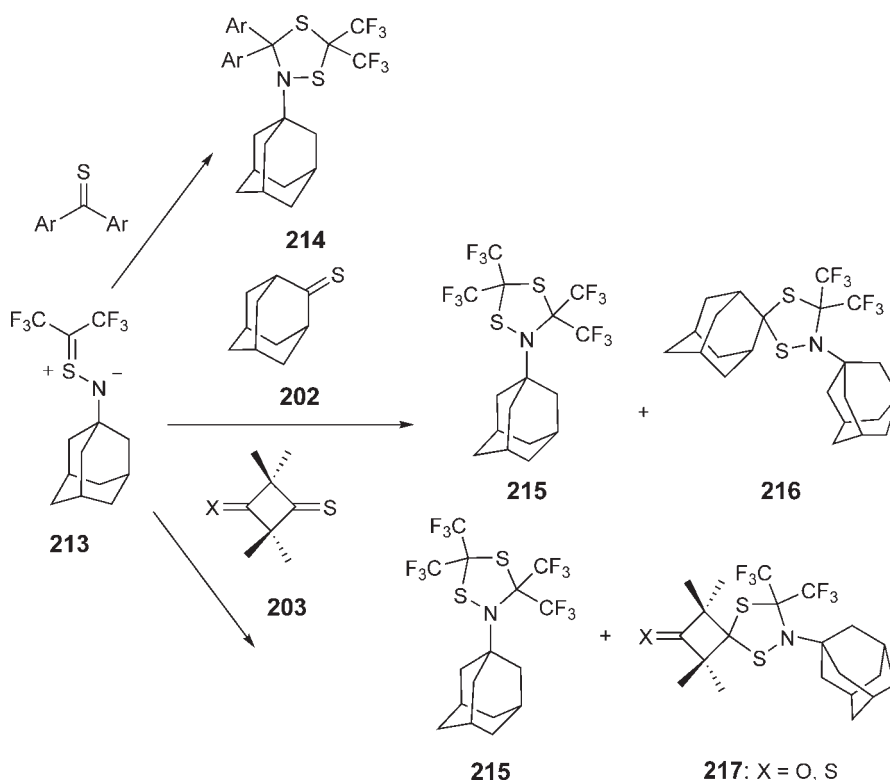
In CHEC-II(1996), the formation of 1,4,2-dithiazolidine derivatives **212** (R=Ar) from the sterically crowded thione **203** and arylazides (R=Ar) was reported. Nitrogen is evolved from the initially formed thiatiazoline cycloadduct **210** and the *in situ*-formed thiocarbonyl-*S*-imide **211** is trapped by the superdipolarophilic thione **203** (Scheme 28) <1996CHEC-II(4)532, 1993HCA2147>. Some new examples of this reaction have appeared. Thus, methyl azidoacetate and the thione **203** afford the corresponding dithiazolidine **212** (R=CH₂COOMe)



Scheme 28

<1996PJC880>. Even in cases of three-component reactions, that is, the thione, arylazides, and, as third component, a reactive C=C dipolarophile, the dithiazolidine derivatives **212** are also formed (although in moderate yields) <1995HCA1067, 1995HCA1298>.

Although thione-*S*-imides **208** are transient species, the presence of electron-withdrawing substituents at the carbon atom and a bulky substituent at the nitrogen results in their stabilization. A rare example of a stable thione-*S*-imide is compound **213**, bearing two CF₃ groups at one end and a bulky 1-adamantyl group at the other end <1990CB1475>. A different behavior is observed using this 1,3-dipole and aromatic or cycloaliphatic thiones. While cycloaddition reaction with aromatic thiones affords the typical [3+2] dithiazolidine derivatives **214**, reaction with adamantanethione **202**, a stable compound of moderate dipolarophilic activity, affords the dithiazolidine derivatives **215** and **216** <1998EJO459>. In the same way, cycloadditions of compound **213** and the stable thione **203** (X=O) afford the dithiazolidines **215** and **217** (X=O), while with dithione **203** (X=S) the dithiazolidine **217** (X=S) is obtained (Scheme 29) <2000T4231>. The different behavior of cycloaliphatic thiones is attributed to their lower dipolarophilic activity and to the low stability of the initially formed primary cycloadducts which cannot be isolated under the applied reaction conditions. Multistep processes are invoked, involving cycloreversions of the primary adducts leading to a thionitrone intermediate and/or hexafluorothioacetone, to explain the formation of compounds **215–217** (Scheme 29) <1998EJO459, 2000T4231>.



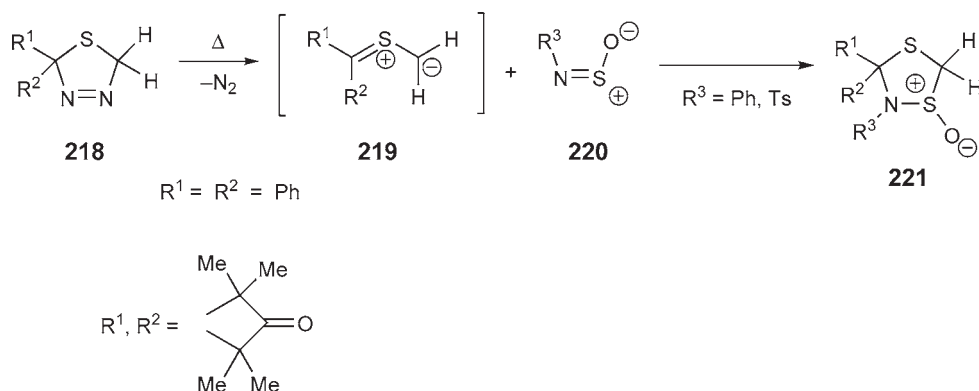
Scheme 29

Thione-*S*-ylides **219** are unstable compounds which are formed *in situ* from the thermally labile 1,3,4-thiadiazolines **218**, via a 1,3-dipolar cycloreversion process liberating nitrogen. They react with the N=S bond of *N*-sulfinylamines **220**, affording the 1,4,2-dithiazolidine-*S*-oxide derivatives **221** (Scheme 30) <1999HAC662>.

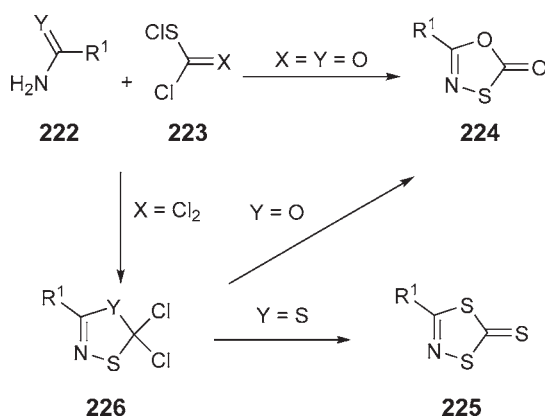
6.04.9.4 Formation of Two Bonds: [3+2] Atoms by Other Processes

A general method for the preparation of oxathiazoles and dithiazoles with exocyclic conjugation is the cyclization reaction of carboxamides and appropriately substituted sulfonyl chlorides. Most of the known reactions of this

category were reported in CHEC-II(1996) <1996CHEC-II(4)523>. Briefly, carboxamides **222** (Y=O) or thiocarboxamides (Y=S) react with various sulfonyl chlorides **223**, such as chlorocarbonylsulfonyl chloride (X=O), or perchloromethanethiol (X=Cl₂) to give the products **224** and **225** (Scheme 31).

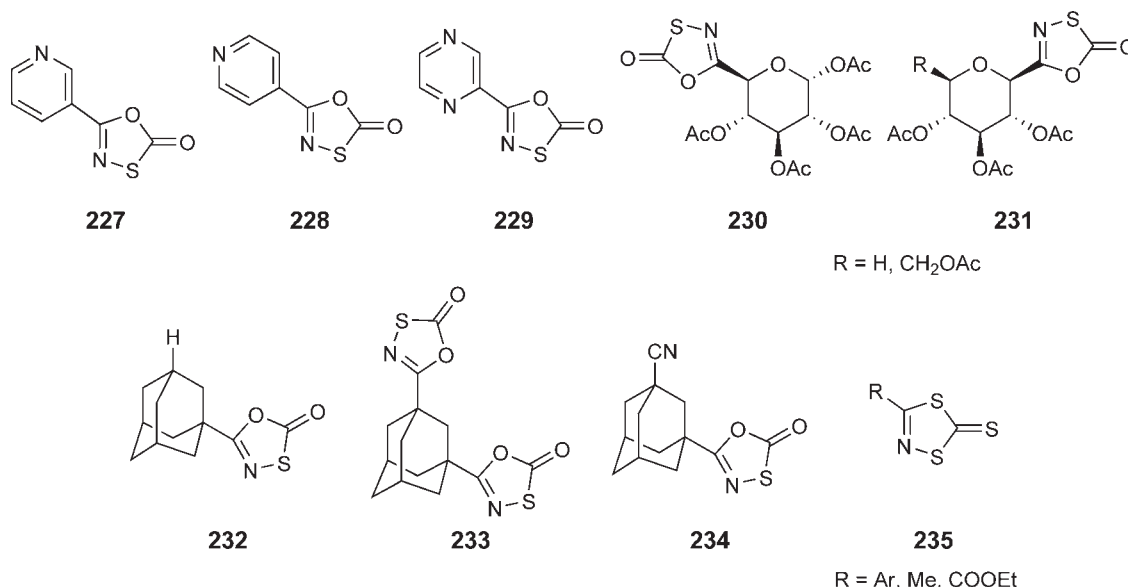


Scheme 30

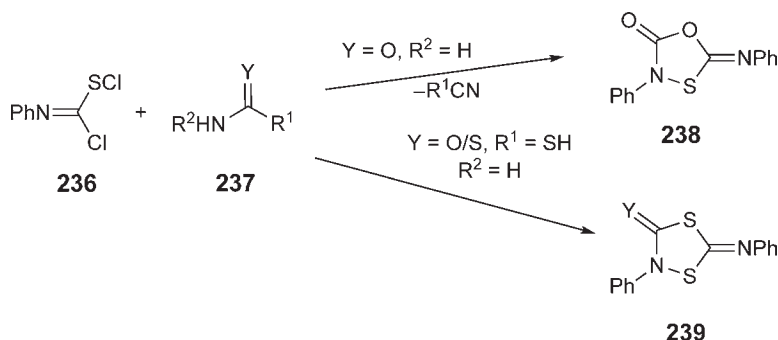


Scheme 31

Some new reports following this general scheme have appeared. Thus, starting from suitable carboxamides and chlorocarbonylsulfonyl chloride (ClCOSCl), the corresponding 1,3,4-oxathiazol-2-ones **227–234** were obtained <2001JME1560, 2006CAR41, 1994CJC1143, 1995CJC212>. In particular, compounds **227–229** were obtained from the corresponding nicotinamide, 4-pyridinecarboxamide, and pyrazinecarboxamide, respectively <2001JME1560>. In the same way, compound **230**, with a pyranosyl substituent at the 5-position, was prepared from glucuronamide, while compounds **231** (R=H, CH₂OAc), having the oxathiazolone ring at the anomeric center, were obtained from carboxamide precursors and readily available D-xylose (**231**: R=H) or D-glucose (**231**: R=CH₂OAc) <2006CAR41>. The oxathiazolones **232** were prepared from 1-adamantane carboxamide <1994CJC1143>, while the corresponding dicarboxamide affords both the expected bis(oxathiazolone) **233** and the oxathiazolone **234**. The latter is obviously formed as the result of a partial decomposition of one oxathiazolone ring of compound **233**, a well-known thermal process of this ring (see Section 6.04.5.6) <1995CJC212>. The dithiazoethiones **235** were obtained from thiocarboxamides and perchloromethanethiol (CCl₃SCl) <2002ARK121>.



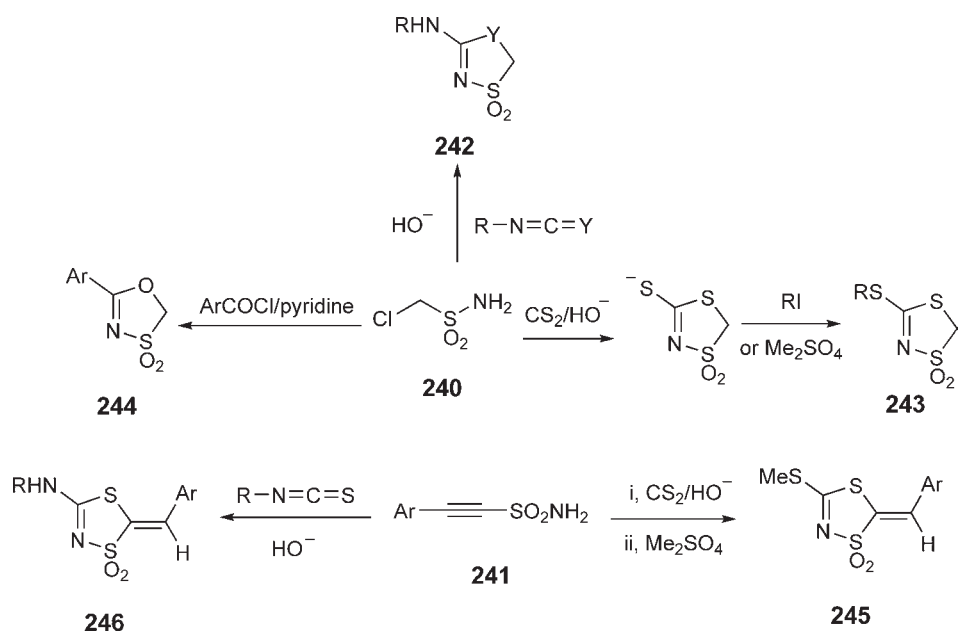
Closely related to the above reactions are those of phenyliminomethanesulfenyl chloride **236** (mustard oil chloride) with benzamide and with triethylamine salts of thiono- or dithiocarbamic acids **237**. In the first case, the iminooxathiazoline thione **238** is obtained and with the carbamic salts the corresponding phenylimino dithiazolinone (Y = O) or dithiazoline thione derivatives (Y = S) **239** are formed (Scheme 32) <1996CHEC-II(4)534>.



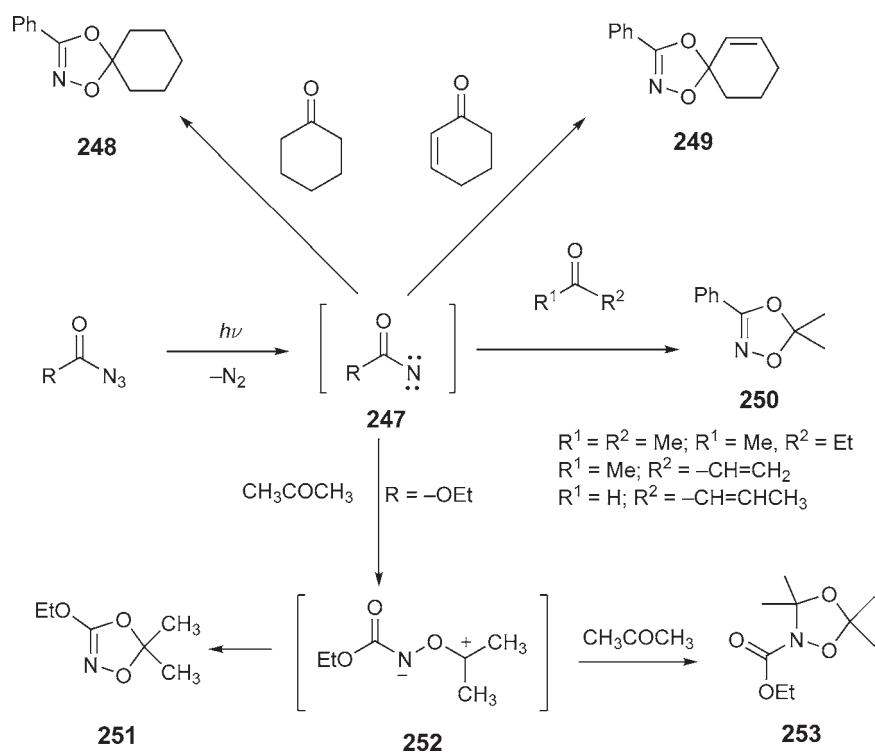
Scheme 32

Another type of cyclization reported in CHEC-II(1996) involves sulfonamides **240** and **241** as three-atom components and electrophilic C=O or C=S double bonds, mainly those of heterocumulenes, affording 1,4,2-oxa/thia)2-azoline-1,1-dioxide derivatives **242–246** (Scheme 33) <1996CHEC-II(4)534>.

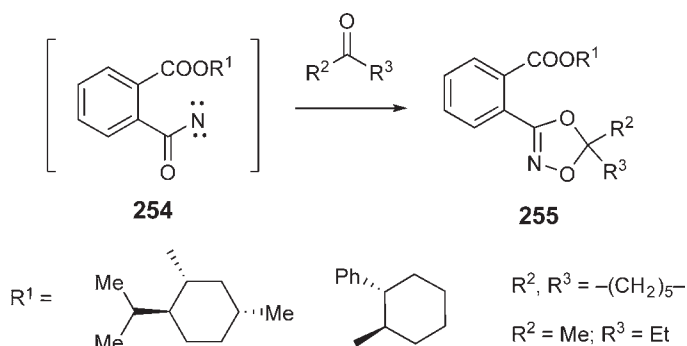
Benzoyl nitrene **247** (R = Ph) generated by photolysis of benzoyl azide in the presence of carbonyl compounds affords 1,4,2-dioxazolines **248–251** (Scheme 34). Moderate yields are obtained upon irradiation at 254 nm, while better yields are obtained upon irradiation at 365 nm in the presence of a sensitizer, such as Michler's ketone, which diminishes the photo-Curtius side reaction of acylnitrene to isocyanate. With ethoxycarbonylnitrene **247** (R = -OEt) and acetone, compounds **251** and **252** are obtained; the latter is possibly formed from acetone and the dipolar intermediate **252** <1995T7181>. In another report on reactions of chiral aroylnitrene **254**, the obtained dioxazolines **255** do not show any diastereoselectivity, although the presence of a chiral auxiliary in the *ortho*-position ensures its vicinity to the reaction center (Scheme 35) <2001S1125>.



Scheme 33



Scheme 34



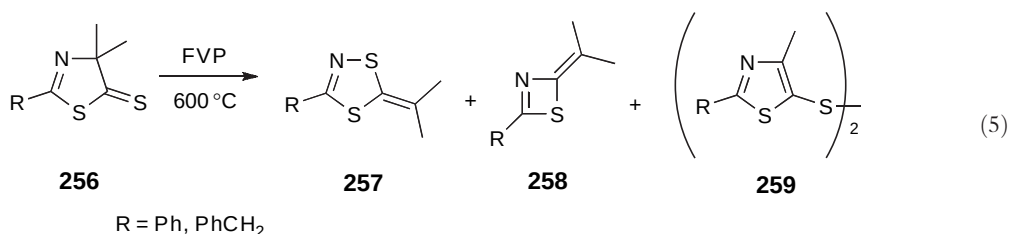
Scheme 35

6.04.10 Ring Synthesis by Transformation of Another Ring

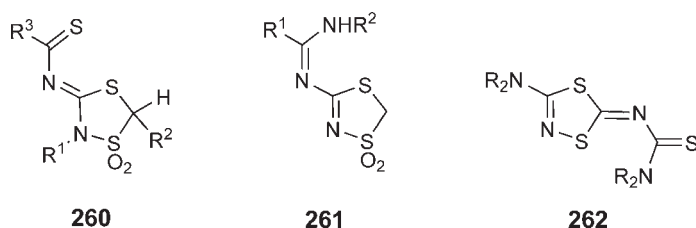
Several reports concerning the synthesis of oxa/thia-2-azole rings by transformations of other heterocyclic rings appeared in CHEC-II(1996) <1996CHEC-II(4)535>. All new reports are classified in accordance with the size of the ring to be transformed.

6.04.10.1 From Five-Membered Rings

FVP at 600 °C of 1,3-thiazole-5-(4*H*)-thiones **256** yields as main products the dithiazole derivatives **257** and as minor by-products the thiazete **258** and the disulfide derivatives **259** (Equation 5). A biradical intermediate has been suggested for the formation of azonylene **257** as well as for the other by-products <1998PJC1915>.

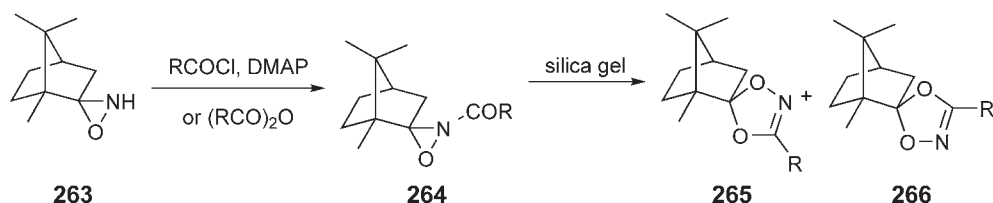


The synthesis of several complex 1,4-(oxa/thia)-2-azole derivatives **260–262** from other five-membered heterocycles has been reported in CHEC-II(1996) <1996CHEC-II(4)535>.



6.04.10.2 From Three-Membered Rings

In CHEC-II(1996), several synthetic routes to 1,3,4-dioxazolines and dioxazolidines starting from *N*-aryloxaziridines or azirines were reported <1996CHEC-II(4)536>. In a new report, the enantiomerically pure *N*-acyl oxaziridines **264** obtained from the corresponding camphor derivative **263**, rearranged after treatment with silica to give inseparable mixtures of the isomeric adducts **265** and **266** in almost equal amounts and in good yields (63–90%) (Scheme 36) <2000JOC4204>.



Scheme 36

6.04.11 Best Synthetic Methods

There are many ways to assemble the 1,4-(oxa/thia)-2-azole ring system. Most of them are performed by inter- or intramolecular cyclizations of suitable acyclic precursors. In some instances, ring transformations of other heterocycles may be used, although the scope of these reactions has not been widely studied. The most important cyclizations are:

- cyclizations of sulfonyl amides and related compounds;
- cyclizations of hydroxamic acids with various electrophiles;
- 1,3-dipolar cycloaddition reactions;
- cyclizations of chlorosulfonyl chlorides; and
- cyclizations of chloromethane sulfonamides.

All available data on the cyclizations of various sulfonyl amides affording (oxa/thia)azolium salts have been reported in CHEC-II(1996) <1996CHEC-II(4)527>. A considerable part of the literature on cyclizations of hydroxamic acid and derivatives with electrophiles was also reported in CHEC-II(1996) <1996CHEC-II(4)528>. This general way has the advantage of flexibility of using various types of electrophiles, affording either conjugated or nonconjugated (oxa/thia)azole derivatives. The 1,3-dipolar cycloaddition methodology is probably the most efficient and convenient way to obtain almost all (oxa/thia)azole ring systems. The proper choice of 1,3-dipoles and/or dipolarophiles allows the convenient formation of various types of these ring systems. A large amount of data on this methodology have been reported in this chapter and also in CHEC-II(1996) <1996CHEC-II(4)530>. The cyclization of various chlorosulfonyl chlorides with carboxamides is a method for the synthesis of (oxa/thia)azole derivatives with exocyclic conjugation. There are no new results on cyclization of chloromethane sulfonamides except those given in CHEC-II(1996) <1996CHEC-II(4)534>.

Following the format used in CHEC(1984) and CHEC-II(1996), all new data have been tabulated in **Tables 8–10**.

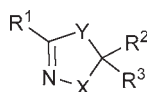
Table 8 Best synthetic methods for azolinones **8**, azolinethiones **9**, azolinimines **10**, and azonylene **11**

Structure type	Ring systems			Substituents		Yield (%)	Method	Reference
	X	Y	Z	R ¹				
8	S	O	O	a		59	5.14.9.4	1994CJC1143
8	S	O	O	CH ₃ (CH ₂) ₆		61	5.14.9.4	2000ARK720
8	S	O	O	b		74–79	5.14.9.4	2006CAR41
8	S	O	O	3-pyridinyl		43	5.14.9.4	2001JME1560
8	S	O	O	4-pyridinyl		43	5.14.9.4	2001JME1560
8	S	O	O	3-pyrazinyl		33	5.14.9.4	2001JME1560
8	S	S	O	Ar ^c		43–97	5.14.7	2002ARK121
8	S	S	O	Me		38	5.14.7	2002ARK121
8	S	S	O	CO ₂ Et		76	5.14.7	2002ARK121
9	S	S	S	Ar ^d		19–22	5.14.9.4	2002ARK121

(Continued)

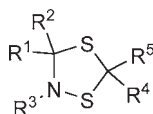
Table 8 (Continued)

Structure type	Ring systems			Substituents		Yield (%)	Method	Reference
	X	Y	Z	R ¹				
9	S	S	S	Me		9	5.14.9.4	2002ARK121
10	O	O	NAr	Ph		73–76	5.14.10.2	2002H(57)143
11	S	S	C(CH ₃) ₂	Ph		50	5.14.10.1	1998PJC1915
11	S	S	C(CH ₃) ₂	PhCH ₂		60	5.14.10.1	1998PJC1915

^a1-Adamantyl residue.^b α -D-xylo or gluco-pyranosyl residue.^cPh, 4-MeOC₆H₄, 4-MeC₆H₄, 4-FC₆H₄, 4-ClC₆H₄, 3-ClC₆H₄.^d4-FC₆H₄, 3-ClC₆H₄.**Table 9** Best synthetic methods for dioxazoles, oxathiazoles, and dithiazoles **13**

Ring system		Substituents			Yield (%)	Method	Reference
X	Y	R ¹	R ²	R ³			
O	O	Ph	Ar	H	26–63	5.14.9.3	1996J(P1)747
O	O	Ar		a	80–100	5.14.9.3	1999T14199
O	O	4-MeOC ₆ H ₄	H	b	83	5.14.9.3	1998JHC619
O	S	Ph		c	75–82	5.14.9.3	1997JOC4672
O	S	Ar		c	78–94	5.14.9.3	1999JOC1099
O	S	Ar		d	44–78 ^f	5.14.9.1	2005CAR1397
O	S	Ar		e	46–70 ^f	5.14.9.1	1994T6559
O	O	3-OTBDMS, 4-MeOC ₆ H ₃	3,4,5-(MeO) ₃ C ₆ H ₂	H	10	5.14.8.3	2004TL3359
O	O	Ar, Aralkyl	Me	Me	74–92	5.14.8.2	2002JOC4833
O	O	Ar	-C(=O)-C(R)=C H-C(R)=CH-		80–100	5.14.9.3	1999T14199
O	O	Ph	H, Me	Alkyl	45–82	5.14.9.4	1995T7181
O	O	Ar	Me	Et	21–30	5.14.9.4	2001S1125
O	O	Ar	-(CH ₂) ₅ -		41	5.14.9.4	2001S1125
O	O	Ph	H	Alkyl	90	5.14.9.2	2000TL7433
O	O	Ph	Ar	Ar	42–45	5.14.9.2	2002H(57)143
O	O	Me, Ar		g	63–90	5.14.10.2	2000JOC4204
O	O	Ar		h	72	5.14.9.3	2000T4299
O	O	Ar		i	34	5.14.9.3	2003ARK77
O	S	Ph		j	86	5.14.9.3	1996JCR(S)8
O	S	Ph	Fc	SiMe ₃	67	5.14.9.3	1999TL6473

^aSpirocyclohexadienone residue.^b4-Benzopyranone residue.^c5-(R)-Spiroadamantyl residue (R = F, Cl, Br).^dSpiro-D-galactopyranosylidene residue.^eSpiro-D-glucopyranosylidene residue.^fCombined yield of both 1(S)- and 1(R)-stereoisomers.^gSpirocamphoryl residue.^hIsoxazoline residue.ⁱSpiroacenaphthylenone residue.

Table 10 Best synthetic methods for various azolidine derivatives **16**

<i>X</i>	<i>Y</i>	<i>R</i> ¹	<i>R</i> ²	<i>R</i> ³	<i>R</i> ⁴	<i>R</i> ⁵	Yield (%)	Method	Reference
S	S	CMe ₂ C(=O)CMe ₂		4-MeOPh	CMe ₂ C(=O)CMe ₂		45	5.14.9.3	1993HCA2147
S	S	CMe ₂ C(=O)CMe ₂		4-NO ₂ Ph	CMe ₂ C(=O)CMe ₂		49	5.14.9.3	1993HCA2147
S	S	CMe ₂ C(=O)CMe ₂		4-NO ₂ Ph	CMe ₂ C(=O)CMe ₂		38	5.14.9.3	1995HCA2147
S	S	CMe ₂ C(=O)CMe ₂		Ph	CMe ₂ C(=O)CMe ₂		54	5.14.9.3	1993HCA2147
S	S	CMe ₂ C(=O)CMe ₂		Ph	CMe ₂ C(=O)CMe ₂		47	5.14.9.3	1995HCA1298
S	S	CMe ₂ C(=O)CMe ₂		CH ₂ CO ₂ Me	CMe ₂ C(=O)CMe ₂		38	5.14.9.3	1996PJC880
O	S	CMe ₂ C(=O)CMe ₂		Me	^a		74	5.14.9.3	1997LA1685
O	S	CMe ₂ C(=O)CMe ₂		Me	CMe ₂ C(=O)CMe ₂		80	5.14.9.3	1997LA1685
O	S	CMe ₂ C(=O)CMe ₂		Me	CMe ₂ C(=S)CMe ₂		74	5.14.9.3	1997LA1685
O	S	Ph	Ph	Me	^a		79	5.14.9.3	1995JA9671
O	S	Ph	Ph	Me	CMe ₂ C(=O)CMe ₂		90	5.14.9.3	1995JA9671
O	S	Ph	Ph	Me	CMe ₂ C(=S)CMe ₂		86	5.14.9.3	1995JA9671
O	S	H	Ph	Me	CMe ₂ C(=S)CMe ₂		84	5.14.9.3	1995JA9671
O	S	H	Ph	Me	Pr ⁿ	Pr ⁿ	78	5.14.9.3	1995JA9671
S	S	Ph	Ph	^b	CF ₃	CF ₃	76	5.14.9.3	1998EJO459
S	S		^c	^b	CF ₃	CF ₃	65–78	5.14.9.3	1998EJO459
S	S	CF ₃	CF ₃	^b		^a	53	5.14.9.3	1998EJO459
S	S	CF ₃	CF ₃	^b	CF ₃	CF ₃	8	5.14.9.3	1998EJO459
S	S	CF ₃	CF ₃	^b	CF ₃	CF ₃	70	5.14.9.3	2000T4231
S	S	CF ₃	CF ₃	^b	CMe ₂ C(=O)CMe ₂		27	5.14.9.3	2000T4231
S	S	CF ₃	CF ₃	^b	CMe ₂ C(=S)CMe ₂		29	5.14.9.3	2000T4231
SO	S	Ph	Ph	Ph	H	H	69	5.14.9.3	1999HAC662
SO	S	Ph	Ph	Ts	H	H	66	5.14.9.3	1999HAC662
SO	S	CMe ₂ C(=O)CMe ₂		Ph	H	H	49	5.14.9.3	1999HAC662

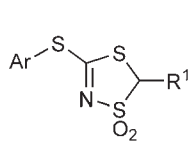
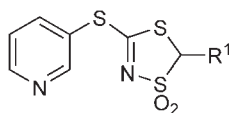
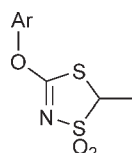
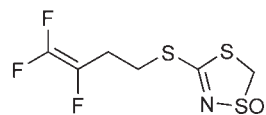
^aR⁴, R⁵ = spiroadamantyl residue.^b1-Adamantyl residue.^cR¹, R² = spirofluorenyl, spiroxanthyl, or spirothioxanthyl residue.

6.04.12 Applications

A considerable amount of data, appearing mainly in the patent literature, concerns possible or suggested applications of various types of 1,4-(oxa/thia)-2-azole derivatives. This covers many areas such as agrochemicals, pharmaceuticals, polymers, etc. Some derivatives are commercially important. A brief account of all new reports is given.

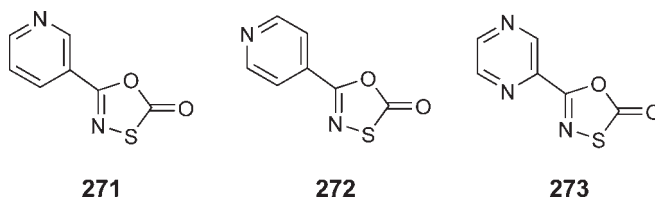
6.04.12.1 Agrochemicals

In CHEC-II(1996), there have been reported many types of 1,4-(oxa/thia)-2-azole derivatives as agrochemical fungicides, herbicides, and insecticides <1996CHEC-II(4)541>. Several biologically active 1,4,2-dithiazole-1,1-dioxide derivatives have potential use as agrochemicals. Thus the arylthio-1,4,2-dithiazole-1,1-dioxides **267** show microbicidal activity as microbicides <1997DEP19545635>, while the closely related compounds **268** inhibited growth of *Aspergillus niger* (MIC 20 ppm) <1998DEP19721627>. Fungicide activities are shown by the 3-aryloxy-1,4,2-dithiazole-1,1-dioxides **269** against *Plasmopara viticola* on vines (90% control at 250 g ha⁻¹) <2000DEP19918294>. Also, compound **270** shows activity against nematoids *Meloidogyne incognita* (100% kill at 20 ppm) <2000DEP10034133>.

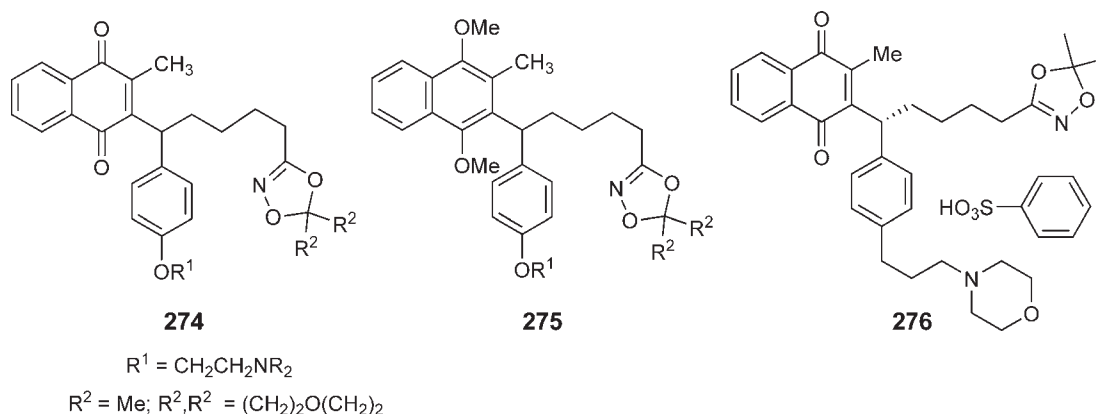
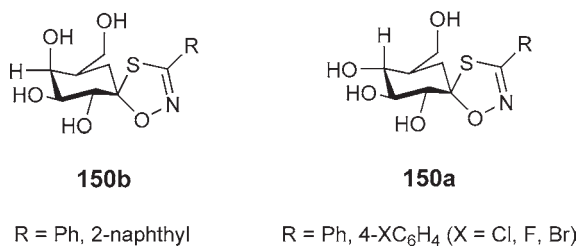
**267****268****269****270**

6.04.12.2 Pharmaceuticals

Many 1,4-(oxa/thia)-2-azoles show a broad spectrum of interesting biological activities potentially useful as pharmaceuticals. Several suggested applications of these derivatives as antibiotics, analgesic agents, tranquilizers, low-toxicity ataraxics, and central nervous system (CNS) depressant agents were reported in CHEC-II(1996) <1996CHEC-II(4)541>. Some new data have also appeared. Thus the pyridinyl- and pyrazinyloxathiazolones **271**–**273** are found to be active against *Mycobacterium tuberculosis* *H*₃₇*R*_v (ATCC 27294), with minimum inhibitory concentration (MIC) values ranking from 25 to 50 μ M. The activity of these compounds ranges from 8 to 16 times the activity of pyrazinamide <2001JME1560>.



D-Galactopyranosylidene-spiro-oxathiazoles **150a**, with the (*S*)-configuration of the anomeric carbon atom, are competitive inhibitors of *E. coli*, β -D-galactosidase in the millimolar range <2005CAR1397>. Also the D-*gluco*-counterparts of **150b** (R = Ph, 4-BrC₆H₄) and two other halogenated analogues are found to be weak competitive inhibitors of sweet almond β -D-glucosidase <1994T6559>. Compounds **275** and **276** are claimed to be useful for neurodegeneration inhibition in prevention and treatment of nerve disease <1999JP11199570, 2003TA3525>.



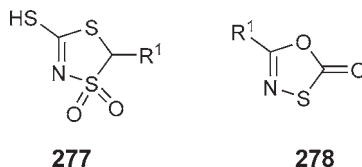
6.04.12.3 Polymer Chemicals

There are no new reports concerning possible applications of 1,4-(oxa/thia)-2-azoles as polymer chemicals. However, it should be mentioned that CHEC-II(1996) extensively covers the 1,3,4-dioxazol-2-ones based polymer chemicals,

which are mainly found in the patent literature. These compounds, also referred to as nitrile carbonates and especially the so-called dinitrile carbonates, are important and widely used monomers for polyurethane industry.

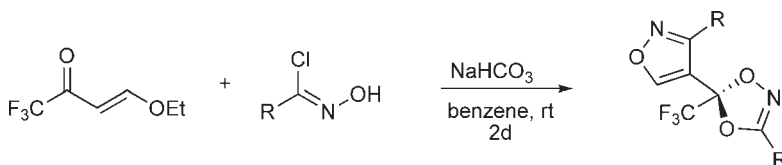
6.04.12.4 Other Applications

Several applications, which also appeared in patent literature, can be found in CHEC-II(1996). In brief, it is worthy to mention the potential use of several 3-alkylamino-1,4,2-dithiazolium salts as cationic dyes, electroconducting materials, and antifogging agents. A ripening method for photographic silver halide emulsions has been claimed for compounds of type **277** ($R^1 = \text{H}$, alkyl), which result in improved sensitivity without increasing fog <2000DEP19838299>. The oxathiazolones **278** ($R^1 = \text{alkyl}$, alkenyl, cycloalkyl, aryl, etc.) exhibit a marked effect against pathogenic Gram-positive and Gram-negative bacteria, as well as against yeasts and fungi, and could possibly be used as disinfectants and microbicides for cosmetics, paper, fabrics, etc. <2000EP98810749>.



6.04.13 Further Developments

During the editing process of this chapter, two new reports have appeared concerning 1,4,2-dioxazoles <2006BMC4067, 2007T2315>. In particular 3,5-diaryl-1,4,2-dioxazoles, which were obtained from nitrile oxides and aromatic aldehydes according to the cycloaddition route (see Section 6.04.9.3), were evaluated biologically for antitubulin activity as combretastatin analogues A-4 <2006BMC4067>. The other report concerns the synthesis of *bis* cycloadducts from nitrile oxides and 4-ethoxy-1,1,1-trifluoro-3-buten-2-one (Scheme 37) <2007T2315>.



Scheme 37

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Biographical Sketch



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6.05

Five-membered Rings with Three Oxygen or Sulfur Atoms in 1,2,3-Positions

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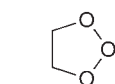
6.05.1	Introduction	146
6.05.2	Theoretical Methods	146
6.05.3	Experimental Structural Methods	148
6.05.3.1	X-Ray and Electron Diffraction	148
6.05.3.2	Microwave Spectroscopy	149
6.05.3.3	NMR Spectroscopy	149
6.05.3.4	Mass Spectrometry	149
6.05.3.5	IR and Raman Spectroscopy	149
6.05.3.6	UV Spectroscopy	149
6.05.3.7	PE Spectroscopy	149
6.05.3.8	Dipole Moments	149
6.05.4	Thermodynamic Aspects	149
6.05.4.1	Stability	149
6.05.4.2	Conformational Analysis	150
6.05.4.3	Thermodynamic Properties	151
6.05.5	Reactivity of Rings	151
6.05.5.1	Thermal and Photochemical Reactions Formally Involving No Other Species	151
6.05.5.1.1	Thermolysis	151
6.05.5.1.2	Photolysis	152
6.05.5.1.3	Polymerization	152
6.05.5.2	Reactions with Electrophiles	152
6.05.5.2.1	Reactions involving protons or Lewis acids	152
6.05.5.2.2	Reactions at double bonds	152
6.05.5.2.3	Oxidation without ring cleavage	152
6.05.5.2.4	Oxidation with ring cleavage	152
6.05.5.3	Reactions with Nucleophiles and Bases	153
6.05.5.3.1	O-Nucleophiles	153
6.05.5.3.2	N-, P-, and As-nucleophiles	160
6.05.5.3.3	S- and Se-nucleophiles	169
6.05.5.3.4	C-Nucleophiles	172
6.05.5.3.5	Halide ions	177
6.05.5.3.6	Strong bases	178
6.05.5.4	Reduction	180
6.05.5.5	Reactions with Radicals and Carbenes	181
6.05.6	Reactivity of Substituents Attached to Ring Carbon Atoms	181
6.05.7	Reactivity of Substituents Attached to Ring Heteroatoms	182
6.05.8	Ring Synthesis	182
6.05.9	Synthesis by Transformations of Another Ring	182
6.05.10	Syntheses of Particular Classes of Compounds	183

6.05.10.1	Parent Systems	183
6.05.10.2	Benzo Derivatives	183
6.05.10.3	C-Linked Substituents	183
6.05.10.4	N-Linked Substituents	185
6.05.10.5	O-Linked Substituents Including Keto Derivatives	185
6.05.10.6	Halogens Attached to Ring	185
6.05.10.7	S- and Si-Linked Substituents	185
6.05.11	Important Compounds and Applications	185
6.05.11.1	Applications in Research and Industry	185
6.05.11.2	Biological Activity	185
	References	185

6.05.1 Introduction

The compounds with five-membered rings containing three sequential oxygen or sulfur atoms in the 1,2,3-positions were covered, together with the isomeric 1,2,4-heterocycles, in CHEC(1984) <1984CHEC(6)851> and separately from isomeric structures in CHEC-II(1996) <1996CHEC-II(4)545>. This chapter is intended to continue this coverage focusing on new advances published since 1995.

There are six possible five-membered monocycles **1–6** containing three oxygen or sulfur atoms in the 1,2,3-positions <1996CHEC-II(4)545>. 1,2,3-Trioxolane **1** is the parent compound of the so-called primary ozonides, the primary reaction products in the reaction of alkenes with ozone. They are extremely unstable and rearrange to the more stable ozonides (1,2,4-trioxolanes). This rearrangement represents a key step in the reaction of ozonolysis. However, the parent compound **1** and a few derivatives have been characterized at low temperatures (see Section 6.05.10.1). 1,2,3-Trithiolanes have been synthesized (Section 6.05.10.3); some of them undergo slow decomposition at room temperature. Derivatives of 1,2,3-dioxathiolane **3** are unknown, and the other heterocycles of the mixed types **4–6** are known only in the oxidized forms, mostly as *S*-oxides and *S,S*-dioxides, and also *S*-imino and *S*-thiono derivatives <1996CHEC-II(4)545>. The *S*-oxides and *S,S*-dioxides of 1,3,2-dioxathiolane, that is, the cyclic sulfites and sulfates of 1,2-diols, are by far the largest and synthetically the most useful group among these heterocycles. The chemistry of the cyclic sulfites and sulfates, and especially their applications in organic synthesis, has been summarized in comprehensive review articles <1997AHC89, 2000T7051>.



1
1,2,3-Trioxolane



2
1,2,3-Trithiolane



3
1,2,3-Dioxathiolane



4
1,3,2-Dioxathiolane



5
1,2,3-Oxadithiolane



6
1,2,5-Oxadithiolane

6.05.2 Theoretical Methods

1,2,3-Trioxolane **1** remains an unchallenged champion of computational studies, as it was described previously <1996CHEC-II(4)545>. However, the focus has changed from conformational analysis to evaluation of the mechanism pathways for the reaction of ozone with alkenes, primarily with ethene, using high-level *ab initio* and density functional theory (DFT) approaches <1996JA3687, 1997JA7330, 1997PCA9421, 1998MI161, 1999CEJ1809, 2000MI608, 2000MI194, 2001CCA251, 2002JA2692, 2002PCA4745, 2003JCP1688, 2003PCA7574, 2003MI3, 2004IJQ309, 2005PCA9284, 2005PJP77, 2005ZP85>, and semi-empirical AM1 calculations <1997JOC2757>. Mechanistic studies

of gas-phase alkene ozonolysis were the subject of a review <1998ACR387>. The theoretical and some experimental efforts in this area were also elegantly summarized by Haas and co-workers <1997JOC2757>.

A comparison of various calculations revealed <1997PCA9421> that an accurate description of the ozonolysis of ethene is obtained at the CCSD(T) level with a TZ+2P basis set, while other methods, which cover less correlation effects, fail to provide a consistent description of all reaction steps. It was shown that the primary ozonides (1,2,3-trioxolanes) are not collisionally stabilized under atmosphere conditions <1997PCA9421>.

A systematic study of the gas-phase mechanism of the reaction of ozone with ethene has been performed using high-level *ab initio* quantum-chemical calculations <1999CEJ1809>. The formation of trioxolane **1** (primary ozonide) is calculated to be exothermic by 49.2 kcal mol⁻¹ with an activation energy relative to the reactants of 5.0 kcal mol⁻¹ at 0 K, in agreement with experimental estimates. Due to the large exothermicity involved, the formation of 1,2,3-trioxolane is a rate-determining step for the whole ozonolysis <1999CEJ1809, 2003PCA7574>. Interestingly, the corresponding activation energies for ozone addition to fluoro- and chloroethene were lower than in the case of ethene itself <2004IJQ309>. According to DFT calculations <2003PCA7574>, the ozone-*cis*-1,2-difluoroethene reaction is slower and the ozone-*trans*-1,2-difluoroethene reaction is faster than the ozone-ethene reaction. Thus, some derivatives of ethene have a higher ability to react with ozone and to deplete the ozone layer.

The activation energies of ozone cycloaddition to the two double bonds of isoprene were found to be comparable (3.3–3.4 kcal mol⁻¹) by DFT and *ab initio* calculations <2002JA2692>. The reaction energies are between -47 and -48 kcal mol⁻¹.

The reaction of ozone with benzene and phenol was studied for the first time by *ab initio* methods <2003PCA7574>. The addition to benzene had the largest calculated activation energy (15.8 kcal mol⁻¹; the experimental value is 14.6 kcal mol⁻¹) and is the least exothermic (18.9 kcal mol⁻¹). Obviously, the reason is the loss of aromaticity, which destabilizes the primary ozonide by more than 30 kcal mol⁻¹. The presence of a hydroxyl group unambiguously assists the addition, decreasing the activation energy to 9.5 kcal mol⁻¹ and increasing exothermicity to 29.0 kcal mol⁻¹. The addition of ozone in the immediate vicinity of the hydroxyl group is found to be the most favorable approach for phenol, which agrees with the empirical fact that catechol is an initial product for this oxidation <2003PCA7574>.

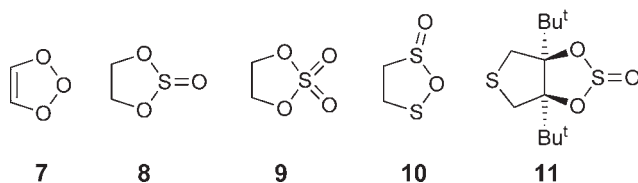
The geometrical parameters and conformations of 1,2,3-trioxolane **1** have been estimated by *ab initio* calculations using various basis sets <1998MI161, 1999CEJ1809, 2002PCA4745, 2003PCA7574, 2003MI3, 2004IJQ309>. They generally agree with the previously published experimental and computational results <1996CHEC-II(4)545>.

The dipole moment for 1,2,3-trioxolane **1** was calculated to be 3.54 D, which is close to the experimentally determined value of 3.43 D <2002PCA4745>.

Along with geometric and thermodynamic parameters, vibrational frequencies and infrared (IR) intensities have been calculated for 1,2,3-trioxolanes, and are in good agreement with available experimental data <1996JA3687, 1996SAA1479, 1997PCA2471, 1998MI161, 2002PCA4745, 2003MI3>. The calculated data were used for the assignment of experimental IR spectra of ozonides obtained in a cryogenic matrix of argon or carbon dioxide <1996JA3687>.

The addition of ozone to ethyne leads initially to formation of 1,2,3-trioxolene **7** with an estimated activation enthalpy of 9.6 kcal mol⁻¹ at 298 K (cf. experiment, 10.2 kcal mol⁻¹) and a reaction enthalpy of -55.5 kcal mol⁻¹ <2001CPL268, 2001JA6127>. The vibrational frequencies were calculated for structure **7** by the PM3 method <1997PCA2471>. The intermediate **7** rapidly decomposes into a number of other intermediate products (see Section 6.05.4.1).

Other heterocycles of types **2–6** have had much poorer investigation by computational studies. The strain energies in the five-membered rings of 1,3,2-dioxathiolane **4**, 1,3,2-dioxathiolane *S*-oxide **8**, and 1,3,2-dioxathiolane *S,S*-dioxide **9** have been evaluated using DFT and MP2 methods <1999ACS1003>. With cyclohexane as a reference, the strain energies are 10.1, -1.3, and 5.8 kcal mol⁻¹ for dioxathiolanes **4**, **8**, and **9**, respectively. The negative value for structure **8** is interpreted in terms of absence of destabilizing interactions present in structures **4** and **9** <1999ACS1003>. The geometry and the relative energy have been estimated by DFT calculations for two diastereomers of the sterically strained 1,3,2-dioxathiolane *S*-oxide **11**. The predicted molecular structures are in good agreement with X-ray data <2003HAC587>. A detailed *ab initio* investigation of the hydrolysis and of the intramolecular sulfonyl group transfer for the dioxide **9** has been performed <1996J(P2)767, 1996JOC5986>. 1,2,5-Oxadithiolane *S*-oxide **10** has been calculated by DFT to be a key intermediate in dimerization of sulfine <1999JOC8880>.

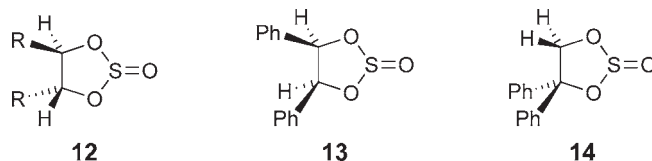


6.05.3 Experimental Structural Methods

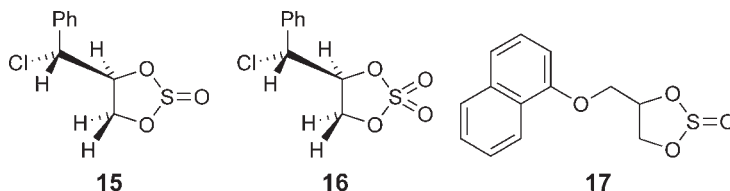
Very little new data have been obtained in this area since the previous reviews [<1996CHEC-II\(4\)545, 1997AHC89>](#). The use of spectroscopic methods for routine structural assignments is not covered in this section.

6.05.3.1 X-Ray and Electron Diffraction

Single crystal X-ray diffraction data for disubstituted 1,3,2-dioxathiolane *S*-oxides **12** ($R = n\text{-C}_6\text{H}_{11}$) [<1995AXC129>](#), **12** ($R = \text{Ph}$), **13**, and **14** [<1996AXC739>](#) revealed half-chair (envelope) conformations of the five-membered cycles with the $\text{S}=\text{O}$ group in a pseudoaxial position and other substituents in pseudoequatorial positions.

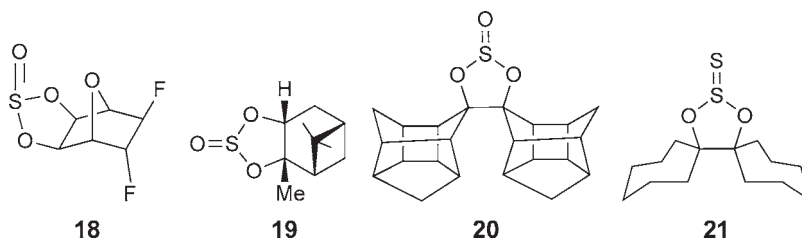


Similar geometries have been found for 1,3,2-dioxathiolane *S*-oxide **15**, the corresponding *S,S*-dioxide **16** [<2000IZV1586, 2000RCB1575>](#), and *cis*- and *trans*-isomers of the naphthyloxymethyl derivative **17**, a precursor in the synthesis of propranolol [<2006IZV1095>](#).

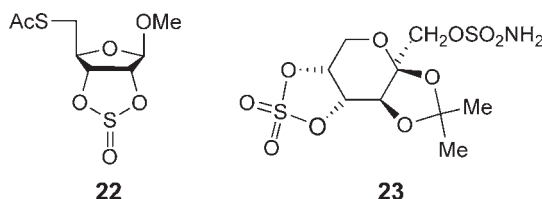


Due to small energy differences and low barriers, the conformers of 1,3,2-dioxathiolane ring are not well defined, and the routinely used term 'half-chair (envelope) conformation' may give an incorrect description. Bredikhin *et al.* [<2006IZV1095>](#) emphasize that the ring of 1,3,2-dioxathiolane *S*-oxide appears to be very flexible: it adopts various conformations corresponding to all phases of pseudorotation depending on the substitution pattern and the nature of substituents. They found that in the crystal state a relatively more frequent conformation for such compounds is an O-1-envelope [<2006IZV1095>](#).

In the rigid structure **18**, the 1,3,2-dioxathiolane *S*-oxide ring is an almost flat S-envelope with a dihedral angle between the planes $\text{O}(1)\text{--}\text{S}(2)\text{--}\text{O}(3)$ and $\text{O}(1)\text{--}\text{C}(1)\text{--}\text{C}(2)\text{--}\text{O}(2)$ of 8.2° [<2002JFC13>](#). The relatively small torsional angle $\text{O}(1)\text{--}\text{C}(1)\text{--}\text{C}(2)\text{--}\text{O}(2)$ of 5.1° in structure **18** is comparable to the value of 3.4° in the fused cyclic sulfite **19** with a bicyclo[3.1.1]heptane moiety and *cis*-orientation of the $\text{S}=\text{O}$ and methyl group [<1995AXC116>](#). In contrast, the corresponding torsional angle is 21.1° in the isomer of sulfite **19** with *trans* $\text{S}=\text{O}$ and methyl groups, comparable with a typical value of 35° for structure **8** [<1995AXC116>](#). It is even larger in the strained sulfites **11** (two diastereomers: 38.7° , 41.5° [<2003HAC587>](#)) and **20** (43.5° [<1995JCX215>](#)), and thionosulfite **21** (45° [<2003JOC7059>](#)). The *cis*- and *trans*-isomers of sulfite **19** demonstrate distinct differences in $\text{S}=\text{O}$ and $\text{S}\text{--}\text{O}$ bond lengths [<1995AXC116>](#). The pseudoaxial $\text{S}=\text{O}$ and $\text{S}\text{--}\text{S}$ bonds in structures **20** and **21** are very short (1.362 and $1.910 \text{ \AA}$, respectively) compared to standard bonds [<1995JCX215, 2003JOC7059>](#).



Single crystal X-ray diffraction data have been reported for the sugar derivatives **22** [<2001S229>](#) and (potential anticonvulsant) **23** [<1998JME1315>](#).



6.05.3.2 Microwave Spectroscopy

No significant developments have been reported since the publication of <1996CHEC-II(4)545>.

6.05.3.3 NMR Spectroscopy

No significant developments have been reported since the publication of <1996CHEC-II(4)545>.

6.05.3.4 Mass Spectrometry

No significant developments have been reported since the publication of <1996CHEC-II(4)545>.

6.05.3.5 IR and Raman Spectroscopy

The formation of 1,2,3-trioxolane **1** (the primary ozonide) and of 1,2,4-trioxolane (the secondary ozonide) in the reaction of ozone with ethene in a cryogenic matrix was observed by IR spectroscopy at much lower temperatures than previously reported: as low as 25 K in the amorphous CO₂ matrix <1996JA3687>. There was no indication of Criegee intermediates—carbonyl oxide and formaldehyde. No reaction was found in an argon matrix at temperatures up to 35 K. The identification of the ozonides was supported by *ab initio* calculation of the IR spectrum <1996JA3687, 1996SAA1479>.

6.05.3.6 UV Spectroscopy

No significant developments have been reported since the publication of <1996CHEC-II(4)545>.

6.05.3.7 PE Spectroscopy

No significant developments have been reported since the publication of <1996CHEC-II(4)545>.

6.05.3.8 Dipole Moments

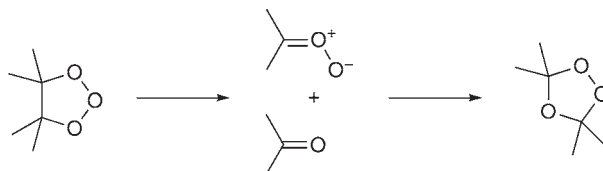
No significant developments have been reported since the publication of <1996CHEC-II(4)545>.

6.05.4 Thermodynamic Aspects

6.05.4.1 Stability

1,2,3-Trioxolanes are generally highly unstable and fragment rapidly at low temperatures to give a zwitterionic carbonyl oxide and a carbonyl compound (Criegee intermediates), which then recombine to form the more stable 1,2,4-trioxolanes (secondary ozonides) (Scheme 1) <1996CHEC-II(4)545>.

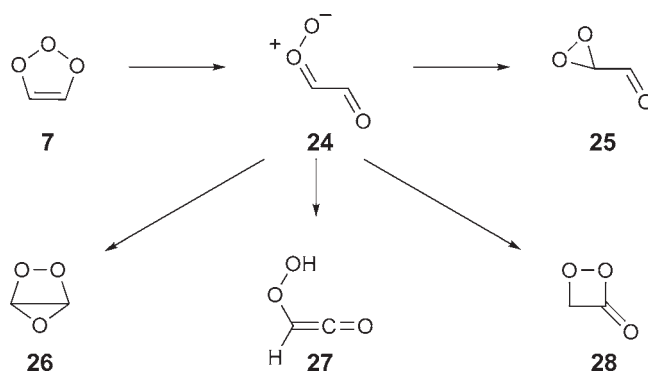
Two different paths have been found theoretically for the cleavage of 1,2,3-trioxolane **1**: a concerted and a stepwise mechanism <1999CEJ1809>. The concerted path leads to the formation of a carbonyl oxide–formaldehyde pair with an activation energy of 18.7 kcal mol^{−1} at 0 K. The nonconcerted mechanism involves three different routes for the decomposition of trioxolane **1**, leading to Criegee intermediates with activation energy of 21.6 kcal mol^{−1} at 0 K, to hydroperoxyacetaldehyde (22.8 kcal mol^{−1} at 0 K), and to oxirane and excited molecular oxygen with a higher activation energy <1999CEJ1809>. Other possibilities have also been suggested <1997PCA9421, 2004IJQ309, 2003PCA7574>.



Scheme 1

Cleavage of the isoprene primary ozonides occurs with a barrier of 11–16 kcal mol⁻¹ above their ground state, and the decomposition energies range from -5 to -13 kcal mol⁻¹ according to DFT and *ab initio* estimations <2002JA2692>.

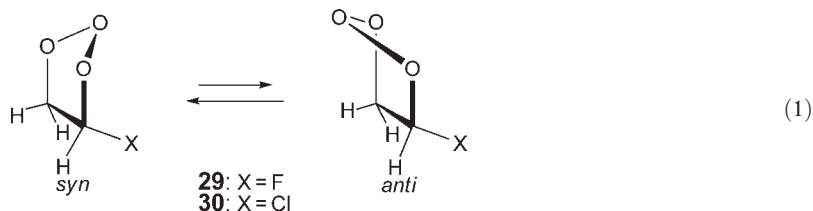
The ozonolysis of ethyne has a very complicated mechanism, which was studied in detail by DFT and *ab initio* methods <2001CPL268, 2001JA6127>. The cycloaddition between ozone and ethyne yields 1,2,3-trioxolene **7**, which rapidly opens to α -ketocarbonyl oxide **24** (Scheme 2). This key intermediate is the starting point for (1) the isomerization to the corresponding dioxirane **25** with an activation enthalpy of 16.9 kcal mol⁻¹ at 298 K, (2) the cyclization to trioxabicyclo[2.1.0]pentane **26** (19.5 kcal mol⁻¹), (3) the formation of hydroperoxyketene **27** (20.6 kcal mol⁻¹), and (4) the rearrangement to dioxetanone **28** (23.6 kcal mol⁻¹). The intermediates **25–28** rearrange or decompose further, with barriers between 13 and 16 kcal mol⁻¹, to yield formic anhydride, glyoxal, formaldehyde, formic acid, and glyoxylic acid as major products <2001JA6127>.



Scheme 2

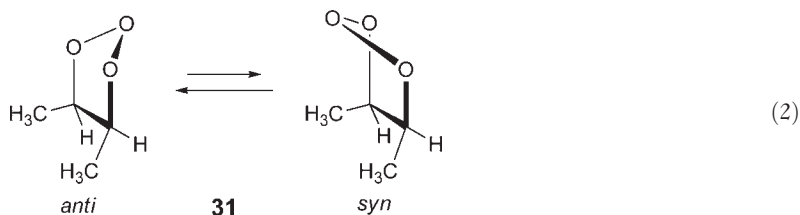
6.05.4.2 Conformational Analysis

The geometrical parameters of 1,2,3-trioxolane **1** have been estimated by *ab initio* calculations with various basis sets <1998MI161, 1999CEJ1809, 2002PCA4745, 2003PCA7574, 2003MI3, 2004IJQ309>. They generally agree with the previously published experimental and computational results <1996CHEC-II(4)545>. The ring undergoes an inversion through low barriers without ever becoming planar, and the envelope conformation of **1** with the out-of-plane central oxygen atom (the oxygen envelope, or the O-envelope) is the most stable <1997JOC2757, 1999CEJ1809, 2002PCA4745, 2003PCA7574>. In the case of halo-1,2,3-trioxolanes, the *syn*-conformation is estimated to be more stable than the *anti*-conformation by 2.3 kcal mol⁻¹ for the fluoride **29**, and by 1.7 kcal mol⁻¹ for the chloride **30** (Equation 1), due mainly to the electrostatic repulsion and the anomeric effect <2002PCA4745>.



An *ab initio* study of the ozonolysis of (*E*)- and (*Z*)-butene-2 <1999PCP3981> revealed slightly twisted O-envelope conformations for the primary ozonides. The (*E*)-butene-2 ozonide has a distorted geometry, with its two O–O bonds

having significantly different bond lengths. The (*Z*)-butene-2 ozonide **31** exists as two different conformers (*syn* and *anti*), of which the one with the central oxygen atom *anti* to methyl groups is more stable by 0.60 kcal mol⁻¹ (Equation 2).



A detailed structural and conformational study by DFT and *ab initio* methods has been reported for the ozonolysis of isoprene <2002JA2692>. The O-envelope conformers of the primary ozonides have the lowest energy.

According to the results of *ab initio* calculations <2003PCA7574>, the two O-envelope conformers of the bicyclic primary ozonide of benzene are nearly equally stable. The product of ozone addition in the immediate vicinity of the hydroxyl group of phenol prefers an *exo*-O-conformation. The carbon rings in the primary ozonides of benzene and phenol are found to retain their planarity.

The structure of unsaturated 1,2,3-trioxolene **7** was calculated by DFT and *ab initio* methods <2001CPL268, 2001JA6127>. It has the O-envelope conformation with the folding angle 151°. A planar geometry for trioxolene **7** is not favorable because of antiaromatic 8 π -interactions.

Single crystal X-ray data have shown that the ring of 1,3,2-dioxathiolane *S*-oxides (cyclic sulfites) appears to be very flexible (Section 6.05.3.1). Depending on the substitution pattern and the nature of substituents, it adopts in the crystal state various conformations corresponding to all phases of pseudorotation <2006IZV1095>. The relatively more frequent conformation found in the crystal state is an O-1-envelope <2006IZV1095>. Thus, the term 'half-chair (envelope)', often applied to 1,3,2-dioxathiolane *S*-oxides, may be rather misleading. The S atom in the cycle is highly pyramidal, with the bond angle O–S–O close to 94° <1995JCX215, 2000IZV1586, 2000RCB1575, 2003HAC587, 2006IZV1095>. It is well known that S=O group in 1,3,2-dioxathiolane *S*-oxides usually occupies a (pseudo)axial position <1984CHEC(6)851, 1996CHEC-II(4)545>. Additional support to this already firm regularity was obtained from X-ray studies <1995AXC116, 1995AXC129, 1995JCX215, 1996AXC739, 2000IZV1586, 2000RCB1575, 2003HAC587, 2006IZV1095> and from calculations for the gas phase by DFT and MP2 <1999ACS1003, 2003HAC587>. The torsional angle O(1)–C(1)–C(2)–O(2) in the 1,3,2-dioxathiolane *S*-oxide ring strongly depends on the substituents. It can be as small as 5.1° and 3.4° in the rigid structures **18** <2002JFC13> and **19** <1995AXC116>, respectively, or it can be as large as 41.5° and 43.5° in the sterically crowded compounds **11** <2003HAC587> and **20** <1995JCX215>, respectively, which is comparable to 45° in the strained 1,3,2-dioxathiolane 2-sulfide **21** and similar structures <2003JOC7059>.

6.05.4.3 Thermodynamic Properties

Semi-empirical AM1 calculations for alkyl-substituted 1,2,3-trioxolanes show that the products derived from *trans*-alkenes are systematically more stable than those arising from *cis*-alkenes. The absolute values of the heat of formation increase as the substituents become more bulky <1997JOC2757>.

6.05.5 Reactivity of Rings

With the exception of nucleophilic ring cleavage in 1,3,2-dioxathiolane *S*-oxides and *S,S*-dioxides (Section 6.05.5.3), little new development has been reported on transformations of the heterocycles under consideration since the last review <1996CHEC-II(4)545>.

6.05.5.1 Thermal and Photochemical Reactions Formally Involving No Other Species

6.05.5.1.1 Thermolysis

Fragmentation, even at low temperatures, of highly unstable 1,2,3-trioxolanes (the primary ozonides) to carbonyl oxides and carbonyl compound (Criegee intermediates) with a subsequent recombination to more stable 1,2,4-trioxolanes

(the secondary ozonides), and the even more complicated decomposition of 1,2,3-trioxolene **7**, have been discussed in Section 6.05.4.1.

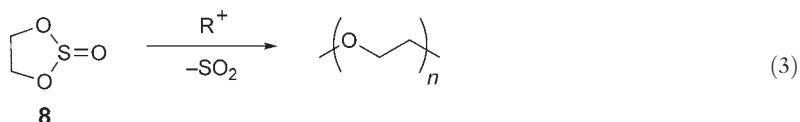
Attempted thermal epimerization of the diastereomeric 1,3,2-dioxathiolane *S*-oxides **11** failed even when these compounds were refluxed in *o*-dichlorobenzene, which indicated a kinetic control of the diastereomeric ratio in the course of their synthesis <2003HAC587>.

6.05.5.1.2 Photolysis

No significant developments have been reported since the publication of <1996CHEC-II(4)545>.

6.05.5.1.3 Polymerization

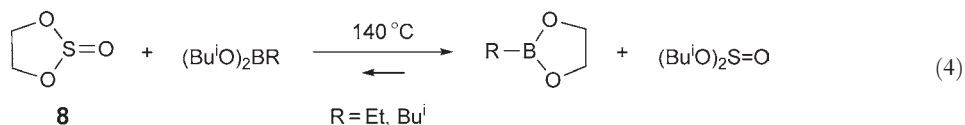
1,3,2-Dioxathiolane *S*-oxide **8** polymerizes in the presence of cationic initiators such as TfOMe, TsOMe, and $\text{BF}_3 \cdot \text{Et}_2\text{O}$ in bulk to afford a polyether, accompanied by quantitative desulfoxylation (Equation 3) <1998MI1785>.



6.05.5.2 Reactions with Electrophiles

6.05.5.2.1 Reactions involving protons or Lewis acids

1,3,2-Dioxathiolane *S*-oxide **8** reacts with diisobutyl alkylborates at 140 °C to give the corresponding cyclic alkylborate ester. The reaction is reversible, although the equilibrium favors the products (90–95%) (Equation 4) <1995ZOR146>.



6.05.5.2.2 Reactions at double bonds

No significant developments have been reported since the publication of CHEC-2 <1996CHEC-II(4)545>.

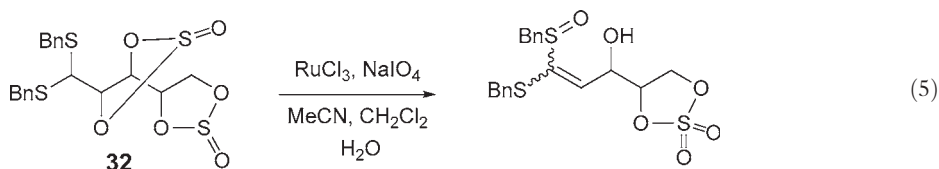
6.05.5.2.3 Oxidation without ring cleavage

In synthetic procedures, the 1,3,2-dioxathiolane *S*-oxides (cyclic sulfites) are often converted into the corresponding *S,S*-oxides (sulfates), which are more reactive toward nucleophiles (Section 6.05.5.3). The most widely used method is ruthenium tetroxide oxidation, which is commonly performed using a catalytic amount of ruthenium trichloride and sodium periodate as a stoichiometric oxidant. This method is favored due to the variety of functional groups tolerated under the mild reaction conditions. Other oxidants may also be used <1996CHEC-II(4)545, 1997AHC89, 1999MC236, 2000IZV1586, 2000RCB1575, 2000T7051, 2003JPP2003238556>. The recent data on 1,3,2-dioxathiolane *S,S*-oxides obtained by oxidation of the corresponding *S*-oxides are summarized in Tables 1–7.

A catalytic enantioselective oxidation of cyclic sulfites to sulfates has been performed using cyclohexanone monooxygenase <1998CC415>.

6.05.5.2.4 Oxidation with ring cleavage

In an attempt to oxidize the bis-sulfite **32** to the corresponding bis-sulfate, one of the rings was cleaved producing isomeric α,β -unsaturated sulfoxides (Equation 5) <2004TL4365>.



6.05.5.3 Reactions with Nucleophiles and Bases

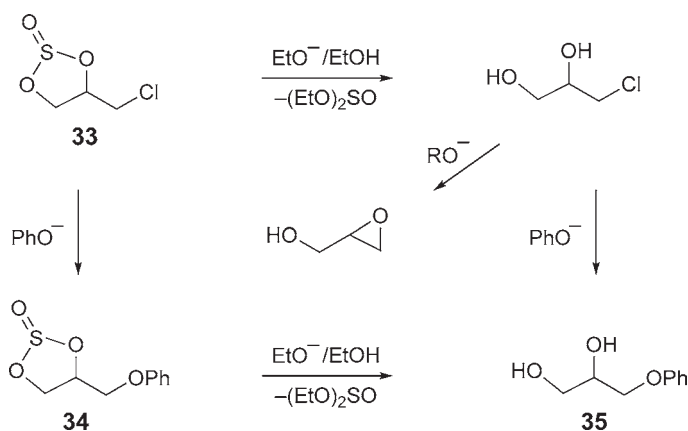
During the last decade, 1,3,2-dioxathiolane *S*-oxides (cyclic sulfites) and 1,3,2-dioxathiolane *S,S*-dioxides (cyclic sulfates) have become extremely important reagents in organic synthesis <1996CHEC-II(4)545, 1997AHC89, 2000T7051>. The development of catalytic asymmetric dihydroxylation allows transformation of a variety of alkenes into chiral 1,2-diols, which can be easily converted into the chiral cyclic sulfites and sulfates (Section 6.05.10). These heterocycles are synthetic analogs of epoxides: cyclic sulfates are more reactive than epoxides toward various nucleophiles, whereas cyclic sulfites are less reactive. In case of chiral heterocycles, their nucleophilic cleavage affords a wide variety of chiral products. Under certain conditions, the cyclic sulfates can perform two sequential substitution reactions at vicinal carbons. Moreover, the intermediate product of nucleophilic substitution is usually easy to separate, since it is a salt of a monosulfate ester <1996CHEC-II(4)545, 1997AHC89, 2000T7051>.

The regioselectivity of the cleavage of cyclic sulfites depends on the nature of the nucleophile, and this dependence can be interpreted in terms of the hard and soft acid and base principle <2000T7051>. For instance, in reactions with PhONa, PhSNa, NaN₃, NaCN, BnNH₂, and PrⁱNH₂, the S_N2 attack occurs exclusively at the less sterically hindered carbon atom. In contrast, the harder, less polarizable nucleophiles BnNHNa, PhNHNa, BnONa, and BnSNa attack at both the carbon and the sulfur atoms, sometimes with a predominance at the latter <2000T7051>.

6.05.5.3.1 O-Nucleophiles

1,3,2-Dioxathiolane *S,S*-dioxides (cyclic sulfates) are more reactive toward nucleophilic reagents than 1,3,2-dioxathiolane *S*-oxides (cyclic sulfites) due to the difference in the ring strain and in the degree of the partial double bond character between the ring oxygen atoms and the sulfur atom <2000T7051>. Since cyclic sulfites are less reactive, the attack at the sulfur atom competes with substitution at carbon <1996CHEC-II(4)545, 1997AHC89, 2000T7051>. Thus, the hydrolysis of cyclic sulfites usually occurs via nucleophilic attack at sulfur followed by S–O bond cleavage, producing 1,2-diols with retention of configuration <1996CHEC-II(4)545>. The cleavage of cyclic sulfites by alkoxides occurs exclusively via nucleophilic attack at sulfur, while phenolates react predominantly at carbon <1996CHEC-II(4)545, 2000T7051>.

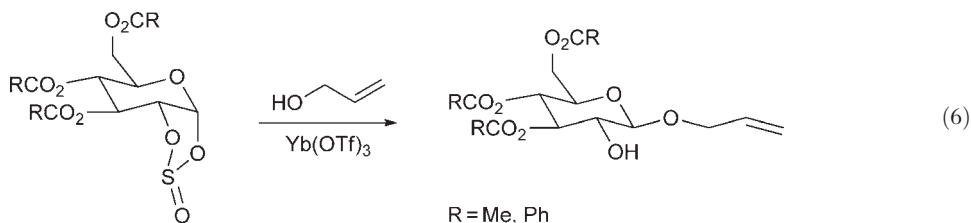
This mixed reactivity is illustrated by the results of a recent reinvestigation of the reaction between 4-chloromethyl-1,3,2-dioxathiolane *S*-oxide **33** and sodium phenoxide in ethanol (Scheme 3) <2000IZV1774, 2000RCB1753>. 3-Phenoxypropane-1,2-diol **35** has been obtained as the major product (45%), while only traces of



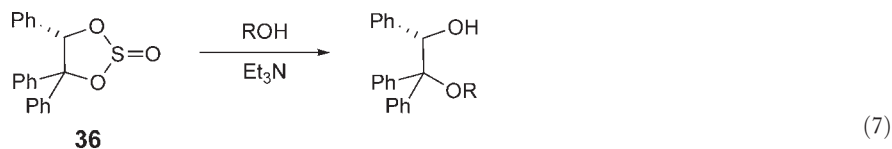
Scheme 3

compound **34** have been detected. Diethyl sulfite (20%), glycidol, phenol, and the starting compound **33** have also been identified. This outcome suggests that phenoxide attacks predominantly the chloromethyl group, whereas the harder nucleophile ethoxide anion, which is present in the mixture, attacks preferably the sulfur atom in compounds **33** and **34**. Only product **34** was obtained (>80%) when compound **33** reacted with PhONa in toluene <2000IZV1774, 2000RCB1753>.

Cyclic sulfites have been used for selective β -glycosylation of alcohols catalyzed by Yb(OTf)₃ or Ho(OTf)₃ (Equation 6) <1995JOC6254, 1997T16391>. The stereochemistry at sulfur does not affect the β -selectivity of the reaction (β : α = 8–13:1). Similar reactions of other carbohydrate-based cyclic sulfites with alcohols have been reported previously <1994TL7335>.

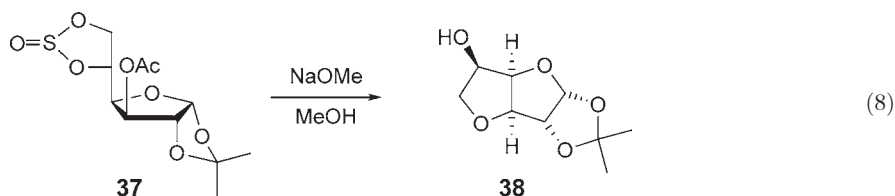


The paradigm of S_N2 attack at either C or S atoms in cyclic sulfites has been violated by the alcoholysis of (*S*)-4,4,5-triphenyl-1,3,2-dioxathiolane *S*-oxide **36** (*trans:ci* = 9:1) (Equation 7) <1997LA1189>. In a completely regioselective S_N1 fashion, the tertiary C–O bond has been cleaved to yield the enantiomerically pure (*S*)-products.



R = Me (71%), Et (42%), Pr (21%), Bn (62%), Prⁱ (17%), Bu^t (0%),
CH₂CH₂OH (25%), (CH₂)₃OH (42%), (CH₂)₄OH (52%)

3,6-Anhydro sugar **38**, an intermediate in the synthesis of bicyclonucleosides, has been prepared by an intramolecular nucleophilic attack in the cyclic sulfite **37**, when it was treated with NaOMe in methanol (Equation 8) <1999T14649>.



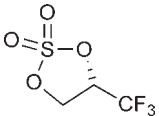
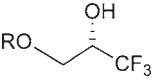
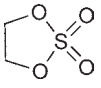
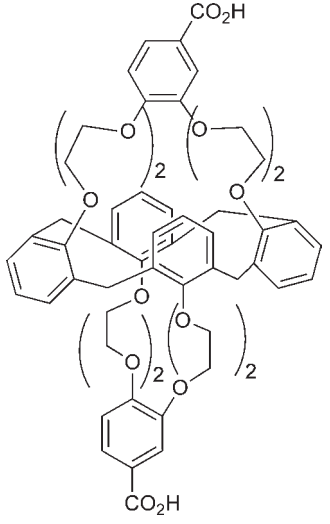
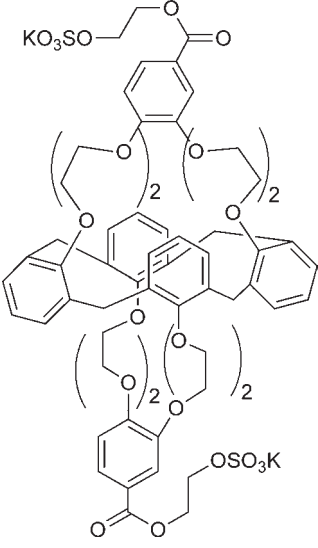
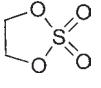
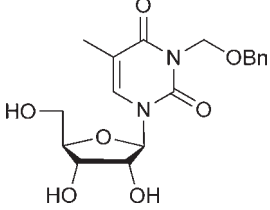
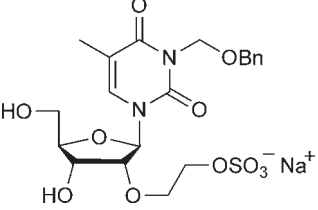
Higher reactivity of 1,3,2-dioxathiolane *S,S*-dioxides (cyclic sulfates) toward nucleophiles, and practically guaranteed S_N2 stereochemistry of C–O bond cleavage, make them extremely useful synthetic intermediates <1996CHEC-II(4)545, 1997AHC89, 2000T7051>. The starting cyclic sulfates and the products of their reactions with O-nucleophiles are summarized in Table 1.

Regioselective ring opening of 5,6-cyclic sulfates of protected manno- and glucofuranose with carbohydrate alkoxides gave ether linked pseudo-di- or trisaccharides <1996MI143, 1997MI1089>.

Reaction of cyclic sulfates with intramolecular O-nucleophiles leads to cyclic ethers and other heterocycles (Table 1). For example, a hydrolysis of compound **39** has produced predominantly the cyclic alcohols **41** (Scheme 4) <1995JA12873>. When the reaction was buffered with pyridine, the sulfate ester **40** was isolated rather than the free alcohol. An alcohol function in an intermediate product may give a route to a polysulfate cascade cyclization, which has been successfully realized in the synthesis of poly(tetrahydrofurans) (Table 1) <1995JA12873>.

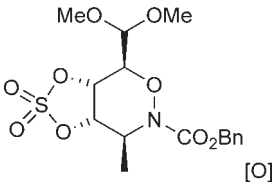
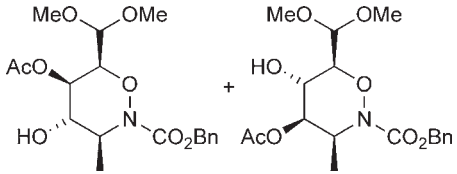
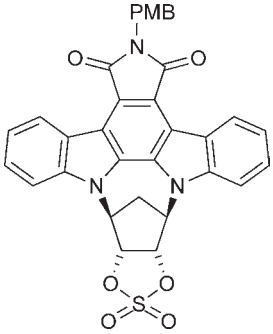
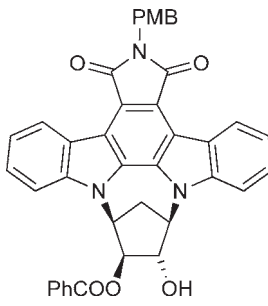
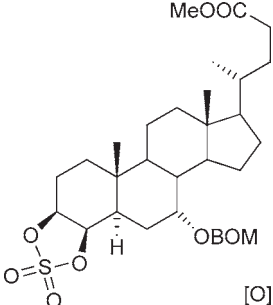
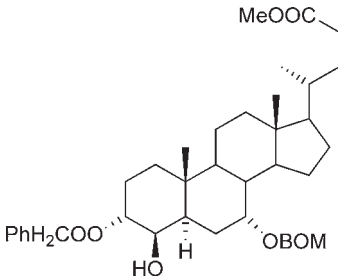
A new hydrogenation–cyclization procedure has been developed, involving the generation of an *N*-carboxylate anion from an *N*-Cbz derivative under basic hydrogenation conditions and an intramolecular nucleophilic attack (Table 1) <1996JOC7162>. In particular, the treatment of compound **42** gives a protected form of natural C₁₈-phytosphingosine **43** as the only detectable isomer in 71% yield (Equation 9) <1996JOC7162>.

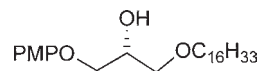
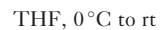
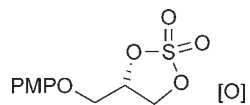
Table 1 Reactions of 1,3,2-dioxathiolane S,S-dioxides (cyclic sulfates) with O-nucleophiles

Substrate ^a	Nucleophile	Conditions	Product(s)	Yield (%)	References
	4-MeOC ₆ H ₄ OH or 1-naphthol	THF, Bu ^t OK, rt	 R = 4-MeOC ₆ H ₄ R = 1-naphthyl	68 65	1997CEJ517
		K ₂ CO ₃ , CH ₂ Cl ₂ , Δ, 36 h		71	2003T10313
		DMF, NaH, −45 °C to rt			2000TL1523 2002B11642

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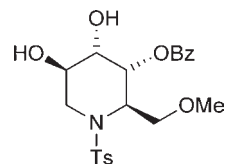
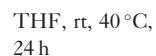
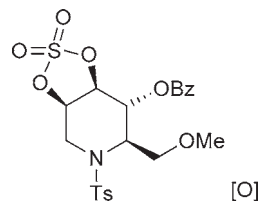
Table 1 (Continued)

<i>Substrate^a</i>	<i>Nucleophile</i>	<i>Conditions</i>	<i>Product(s)</i>	<i>Yield (%)</i>	<i>References</i>
 [O]	AcONH ₄	DMF, 70 °C			2006BML1172
	PhCO ₂ NH ₄	DMF, 70 °C		88	2004TL7469
 [O]	PhCO ₂ H, Cs ₂ CO ₃	DMF, rt, 6 h		75	2004T6971



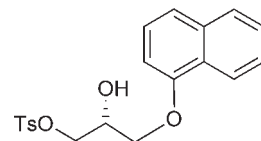
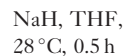
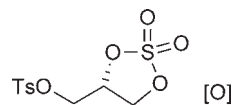
90

1998JOC5696



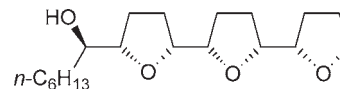
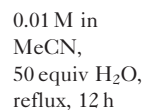
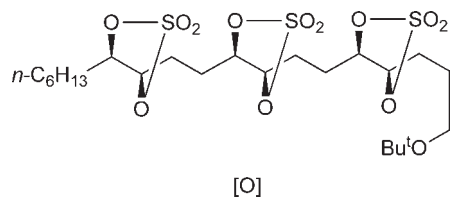
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1997J(P1)741



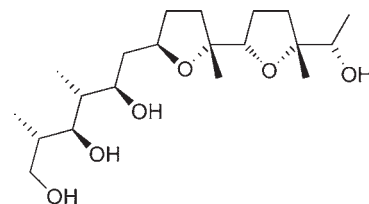
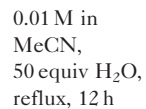
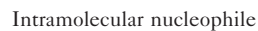
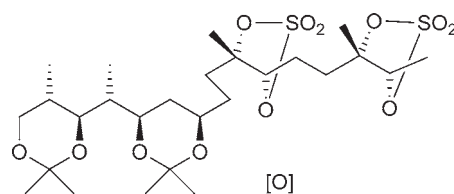
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2002IJB586



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1995JA12873

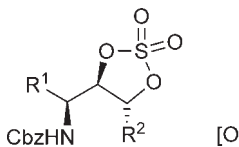
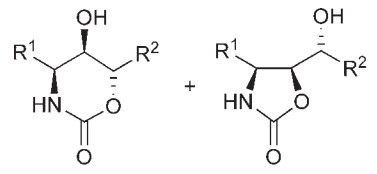
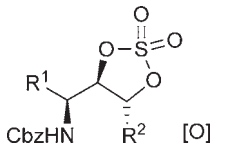
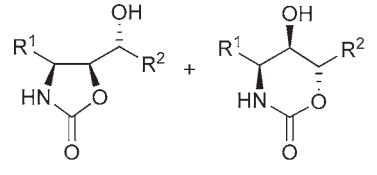
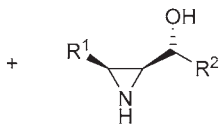
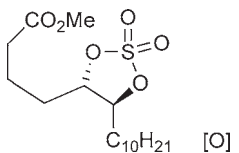
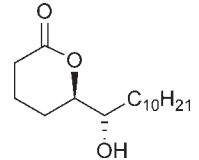


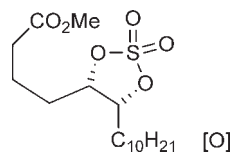
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1995JA12873

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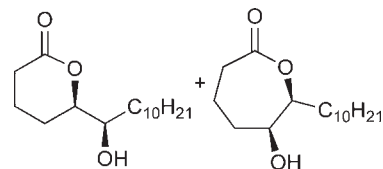
Table 1 (Continued)

<i>Substrate^a</i>	<i>Nucleophile</i>	<i>Conditions</i>	<i>Product(s)</i>	<i>Yield (%)</i>	<i>References</i>
 [O]	Intramolecular nucleophile	i, MeCN, heat; ii, THF, H ₂ SO ₄	 6:1–19:1 R ¹ = Bn, Pr ⁱ ; R ² = Bu ⁱ , Pr ⁱ , PhCH ₂ CH ₂	45–89 and 0–15	1996JOC7162
 [O]	Intramolecular nucleophile	H ₂ , 5% Pd/C Et ₃ N (4 equiv) THF	 3:1–20:1 +  R ¹ = Bn, Pr ⁱ ; R ² = Bu ⁱ , Pr ⁱ , PhCH ₂ CH ₂	48–77 and 2–23 0–57	1996JOC7162
 [O]	Intramolecular nucleophile	i, LiOH, THF–H ₂ O, 65–70 °C, 2 h; ii, H ₂ SO ₄		54	1997TA633

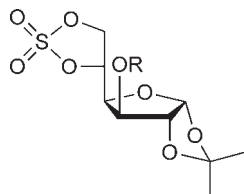


Intramolecular nucleophile

i, LiOH,
THF-H₂O,
65–70 °C, 2 h;
ii, H₂SO₄



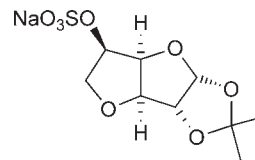
38
and
34
[1998IJB209](#)



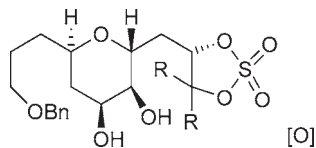
R = Ac, Me, Bn [O]

Intramolecular nucleophile

Na₂SO₃,
Me₂CO-H₂O,
rt, 16 h, reflux,
4 h; or NaHCO₃,
THF-H₂O,
reflux, 4 h

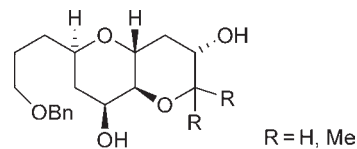


75–80
[1999T14649](#)

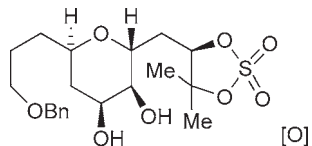


Intramolecular nucleophile

cat. *p*-TsOH
1% H₂O in
MeCN, reflux,
6 h

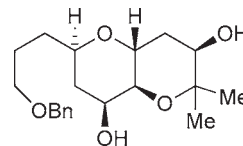


15–21
[1999TL2235](#)



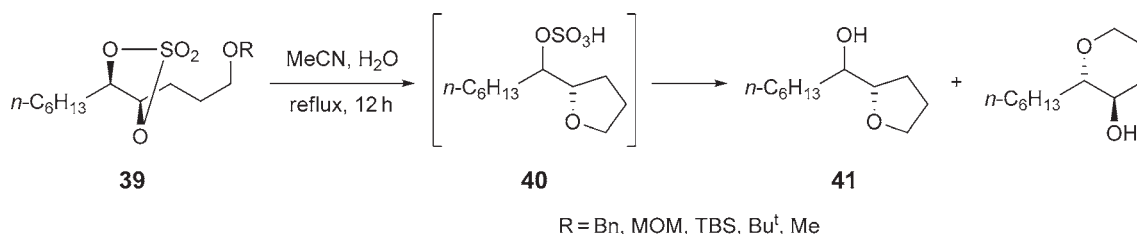
Intramolecular nucleophile

cat. *p*-TsOH
1% H₂O in
MeCN, reflux,
6 h

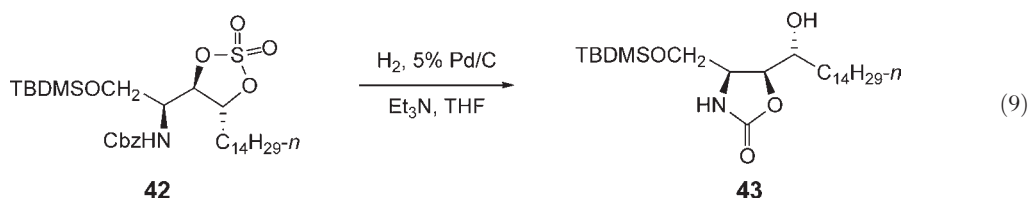


15–21
[1999TL2235](#)

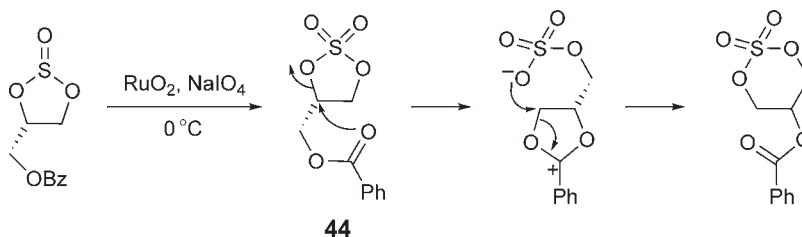
^aThe sulfates labeled [O] were obtained by oxidation of the corresponding cyclic sulfites.



Scheme 4



Increased reactivity toward nucleophiles may render the five-membered cyclic sulfates unstable, for instance, because of an intramolecular nucleophilic attack [\[1997J\(P1\)3173\]](#). Thus, when the sulfate **44** is prepared by oxidation of the corresponding sulfite with ruthenium tetroxide, it undergoes a clean rearrangement at room temperature to the isomeric six-membered cyclic sulfate of 2-benzoyloxypropane-1,3-diol ([Scheme 5](#)) [\[1997J\(P1\)3173\]](#).



Scheme 5

6.05.5.3.2 N-, P-, and As-nucleophiles

The data available at the time of previous reviews [\[1996CHEC-II\(4\)545, 1997AHC89\]](#) indicated that 1,3,2-dioxathiolane *S*-oxides (cyclic sulfites) and 1,3,2-dioxathiolane *S,S*-dioxides (cyclic sulfates) react with N-nucleophiles exclusively at carbon. More recently, it has become clear that the regioselectivity of the cleavage of cyclic sulfites depends on the nature of nucleophile, and this dependence can be interpreted in terms of the hard and soft acid and base principle [\[2000T7051\]](#). For instance, in the reactions with PhONa , PhSNa , NaN_3 , NaCN , BnNH_2 , and Pr^iNH_2 , the $\text{S}_{\text{N}}2$ attack occurs exclusively at the less sterically hindered carbon atom. On contrary, the harder, less polarizable nucleophiles BnNHNa , PhNHNa , BnONa , and BnSNa attack at both the carbon and the sulfur atoms, sometimes with a predominance of the latter direction [\[2000T7051\]](#).

The reactions of cyclic sulfates proceed with high regioselectivity and with better yields than with corresponding epoxides [\[1997AHC89, 2002IJB586\]](#). However, an excessive reactivity of cyclic sulfates may become a disadvantage that makes a use of the corresponding sulfites preferable [\[1996TL2353\]](#).

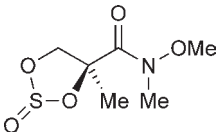
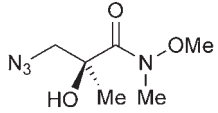
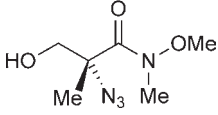
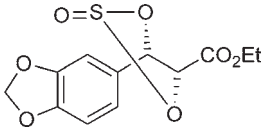
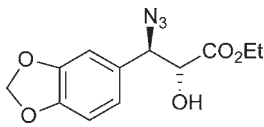
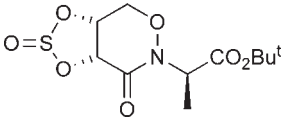
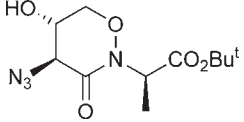
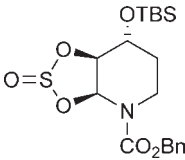
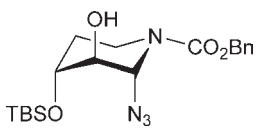
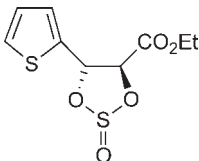
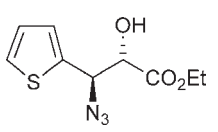
The cleavage of cyclic sulfites and cyclic sulfates with N-nucleophiles has become a popular synthetic tool for preparation of ubiquitous aminoalcohols and their derivatives. Recent examples of such reactions are summarized in [Tables 2 and 3](#). Azide ion appears to be the most convenient and most often used among all N-nucleophiles [\[1997AHC89, 2000T7051\]](#). Its reactivity is sufficient to ensure attack at carbon even in cyclic sulfites, and their oxidation to more reactive sulfates is often unnecessary. Also, the azide group may be reduced to an amino group (e.g., by LiAlH_4), which in the case of one-pot reactions can perform an intramolecular substitution of the hydrosulfate group that was formed in the cycle cleavage, thus giving an aziridine – a product of a double displacement in cyclic sulfate [\[1995J\(P1\)693\]](#). However, even such a strong and small nucleophile as azide ion may be unable to react even with cyclic sulfates in cases of severe steric hindrance, as happened for a paclitaxel derivative [\[2000T6407\]](#).

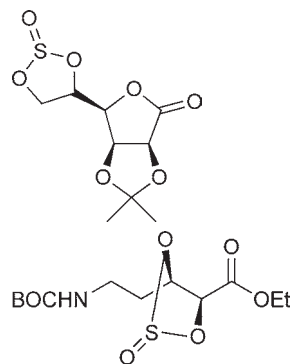
Table 2 Reactions of 1,3,2-dioxathiolane S-oxides (cyclic sulfites) with N-nucleophiles

Substrate	Nucleophile	Conditions	Product(s)	Yield (%)	References
	NaN ₃	DMF, 105 °C, 6 h		81	1996TL2353 1997NN1059 1999JOC4733
	LiN ₃	DMF, 80 °C		97	1999JOC1941
	LiN ₃	i, DMF, reflux, 12 h; ii, MeONa, MeOH, rt, 1 h		58	1999TA4755
	LiN ₃	DMF, 70 °C		24 74	1999TL4203
	NaN ₃	DMF, 55 °C		92	2001TL7513
	NaN ₃	DMF, 60 °C, 2 h		93	2004BMC2749

(Continued)

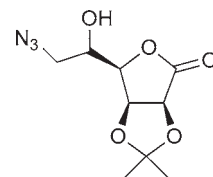
Table 2 (Continued)

<i>Substrate</i>	<i>Nucleophile</i>	<i>Conditions</i>	<i>Product(s)</i>	<i>Yield (%)</i>	<i>References</i>
	NaN ₃	DMF, 70 °C, 48 h	 + 4:1 	69 (major)	2004TA131 2001TA949
	NaN ₃	DMF, 80 °C, 6 h		82	2004TA3111
	NaN ₃	DMF, rt, 24 h		16	2005CJC93
	LiN ₃	DMF, −30 °C to 0 °C, 2 h		96	2005JOC7715
	NaN ₃	DMF, MeCN, 15 °C, 16 h		70	2005T6580



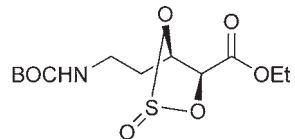
NaN₃

DMF, 80 °C, 24 h



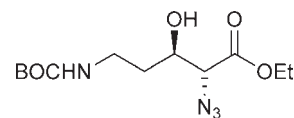
93

[2006T7455](#)



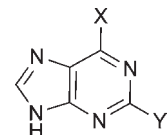
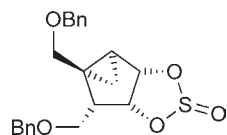
NaN₃

DMF, 60 °C, 20 h

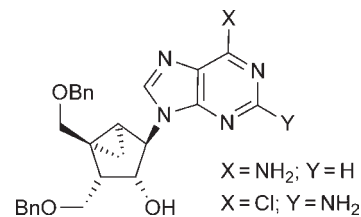


93

[2006TL4167](#)
[1999TA4797](#)

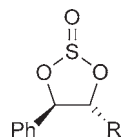


NaH, DMF,
18-crown-6,
120 °C, 72 h



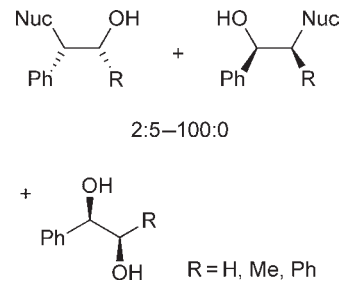
50

[1996TL2353](#)
[1997NN1059](#)
[1999JOC4733](#)



NucH = succinimide,
phthalimide,
O₂NC₆H₄SO₂NH₂,
TsNH₂

NaH, DMF,
70–80 °C



37–100
0–32

[1998ACS1060](#)

(Continued)

Table 2 (Continued)

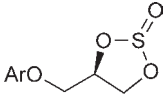
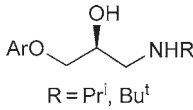
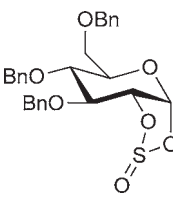
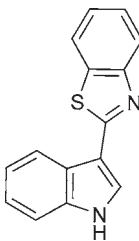
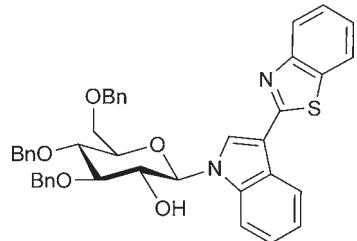
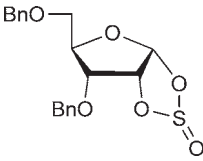
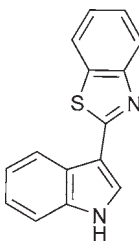
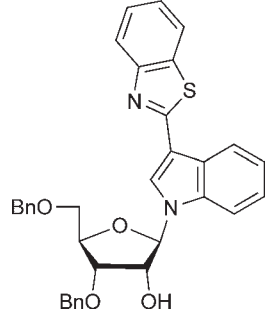
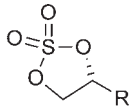
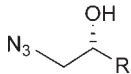
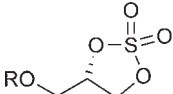
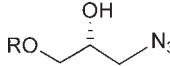
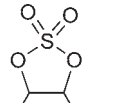
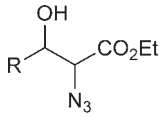
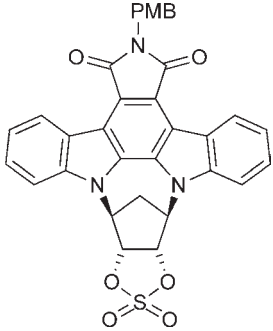
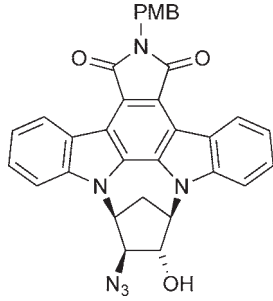
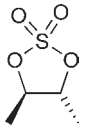
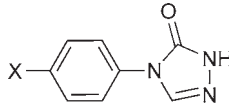
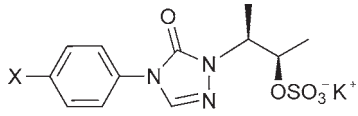
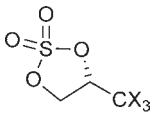
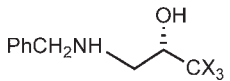
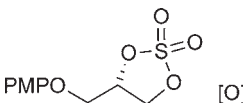
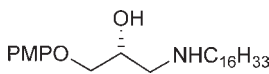
<i>Substrate</i>	<i>Nucleophile</i>	<i>Conditions</i>	<i>Product(s)</i>	<i>Yield (%)</i>	<i>References</i>
	Pr^iNH_2 , or Bu^tNH_2	DMF, 60–80 °C, 30–45 h	 $\text{R} = \text{Pr}^i, \text{Bu}^t$	30–91	1999MC236 2001RCB436 2002RJO213 2004IZV203 2004RCB213
		KOH (8 equiv), DMF, Na_2SO_4 , rt, 0.5 h		44	2005CCC487
		KOH (8 equiv), DMF, Na_2SO_4 , rt, 0.5 h		29	2005CCC487

Table 3 Reactions of 1,3,2-dioxathiolane S,S-dioxides (cyclic sulfates) with N-nucleophiles

<i>Substrate</i> ^a	<i>Nucleophile</i>	<i>Conditions</i>	<i>Product(s)</i>	<i>Yield (%)</i>	<i>References</i>
 R = CF ₃ , CCl ₃	NaN ₃	Me ₂ CO/H ₂ O, rt, 4 h (CF ₃); DMF, 90 °C, 4 h (CCl ₃)	 R = CF ₃ CCl ₃	85 93	1997CEJ517
 R = PMP, Ts [O]	NaN ₃	Me ₂ CO/H ₂ O, 28 °C, 2 h	 R = PMP Ts	94 88	1998JOC5696 2002IJB586
 R = alkyl, R ¹ O-alkyl, CO ₂ R ¹	NaN ₃ , or LiN ₃	Me ₂ CO/H ₂ O, or Me ₂ CO, or DMF	 R = alkyl, R ¹ O-alkyl, CO ₂ R ¹	68–95	2000JOC7618 2003TA3301 2004TL8461 2004TL9641 2005TA3268 2005TA3908

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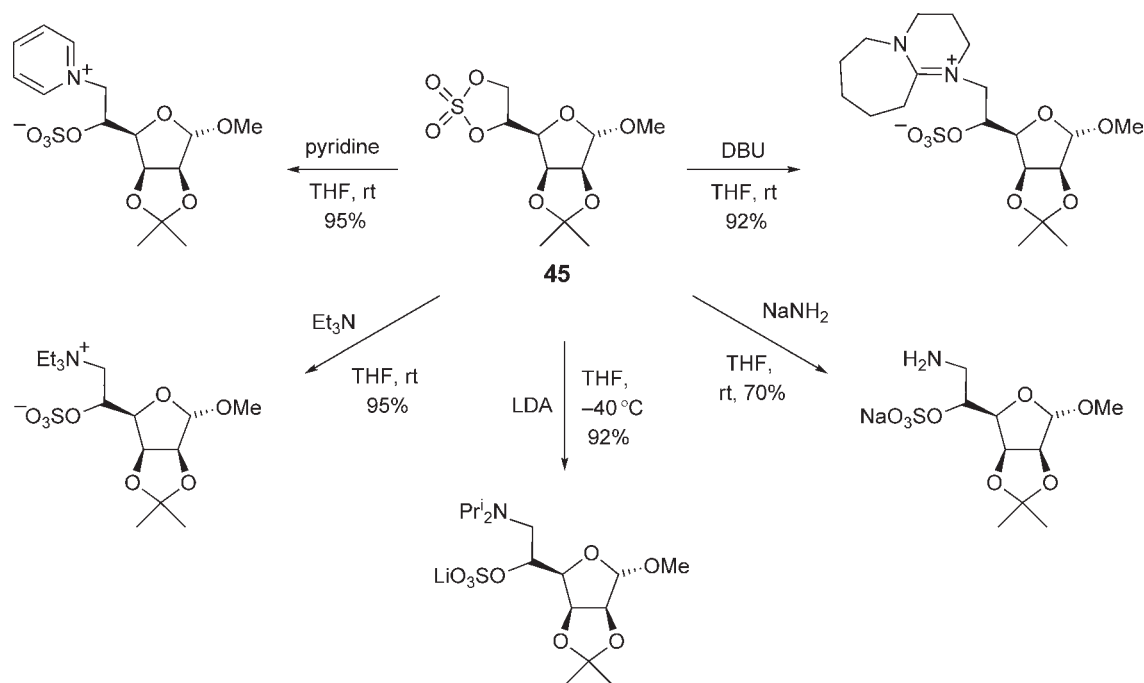
Table 3 (Continued)

Substrate ^a	Nucleophile	Conditions	Product(s)	Yield (%)	References
	NaN ₃	DMF, 80 °C, 5 h		91	2004TL7469
	 X = Br, NR ₂	KH, 18-crown-6, DMF, 0 °C to rt, 1 h	 X = Br, NR ₂	72–79	1997TL7839 1998TL6845 2003TA3487
 X = F, Cl	PhCH ₂ NH ₂	THF, rt, 2 h	 X = F X = Cl	75 65	1997CEJ517
	C ₁₆ H ₃₃ NH ₂	THF, rt		95	1998JOC5696

	BnNH ₂	THF, 28 °C, 8 h		94	2002IJB586
	BnNH ₂	i, BnNH ₂ , THF, 28 °C, 8 h; ii, LiAlH ₄ , 0 °C, 0.5 h		69	2002IJB586
		Morpholine, reflux		36	2004TL7469
		THF, rt overnight, then reflux 24 h		93	2006JOM3201
		NaH, DMF		58	2006OL5081

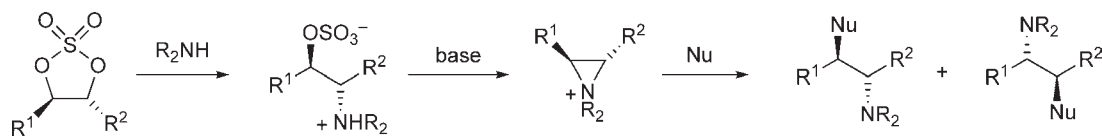
^aThe sulfates labeled with [O] were obtained by oxidation of the corresponding cyclic sulfites.

The synthetic approach via cyclic sulfites and sulfates has proved to be very useful in carbohydrate chemistry <1997JOC3944, 1999T14649, 2000TL659, 2004MI95, 2006T7455>. For example, the D-mannofuranose derivative **45** reacts with various N-nucleophiles to afford the corresponding substitution products in good to quantitative yields (Scheme 6) <2000TL659> (see also Table 2).



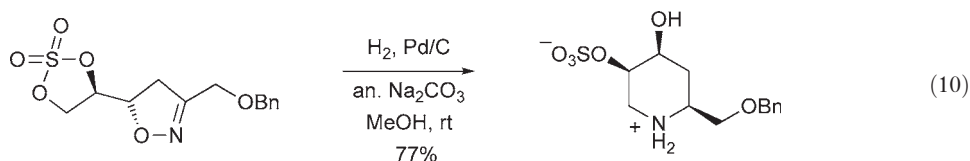
Scheme 6

A general strategy for the transformation of cyclic sulfates into vicinal diamines has been developed (Scheme 7) <1995TL9241>. This method has been extended to the synthesis of unsymmetrical diamines and various other amine derivatives by the controlled introduction of a second nucleophile into the reaction sequence <1995TL9241>.



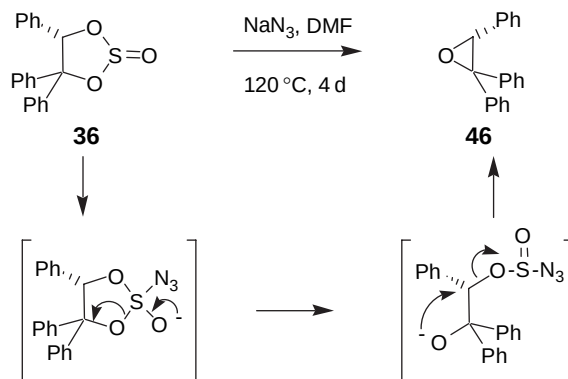
Scheme 7

An interesting example of intramolecular substitution by a reduction-generated amino group is presented in Equation (10) <2006JOC894>.



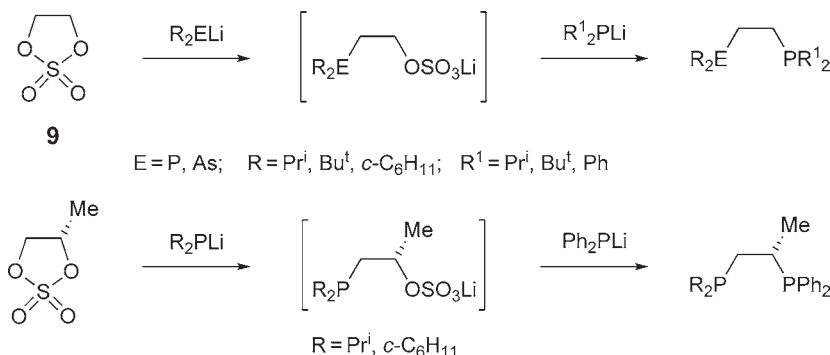
When a mixture of diastereomers of sterically hindered 4,4,5-triphenyl-1,3,2-dioxathiolane *S*-oxide **36** (*trans:cis* = 9:1) was treated with NaN_3 in dimethylformamide (DMF), a surprising reaction occurred: the enantiomerically

pure triphenyloxirane **46** was formed in 76% yield (Scheme 8) <1997LA1189>. The suggested explanation involves nucleophilic attack of azide ion at sulfur and cleavage of the S–O bond adjacent to the tertiary carbon, which allows a better relief of steric strain. The subsequent intramolecular S_N2 substitution led to the formation of epoxide **46** with inversion of configuration at the secondary carbon atom <1997LA1189>.



Scheme 8

Unsymmetrical 1,2-bis(phosphanyl)ethanes, the widely used chelating ligands in coordination chemistry, have been prepared with good yields in a simple and general one-pot synthesis starting from 1,3,2-dioxathiolane *S,S*-dioxide **9** and its chiral methyl derivative (Scheme 9) <2000AGE564, 2001DEP10033956, 2004JCD1873>. The cleavage of the cycle occurs rapidly and quantitatively when lithium phosphide is added to sulfate **9** in THF at $-70\text{ }^\circ\text{C}$. The subsequent addition of a second P-nucleophile leads to the substitution of the sulfate group. The same approach works well for As-nucleophiles (Scheme 9). It is important to add the stronger nucleophile first (e.g., LiPPr^{*i*}₂ or LiAsBu^{*t*}₂) and the weaker nucleophile second (e.g., LiPPh₂) to avoid the formation of mixtures of products <2000AGE564, 2001DEP10033956, 2004JCD1873>.



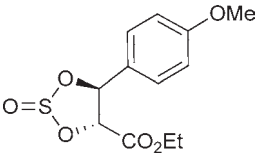
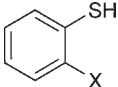
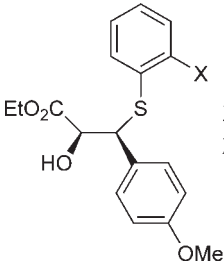
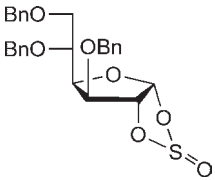
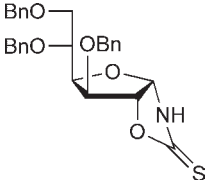
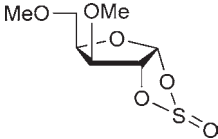
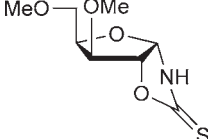
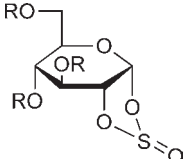
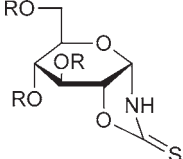
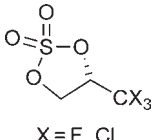
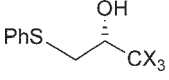
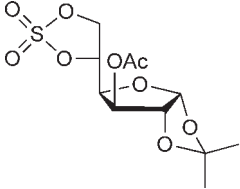
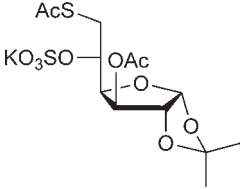
Scheme 9

6.05.5.3.3 S- and Se-nucleophiles

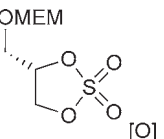
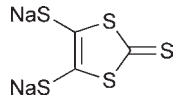
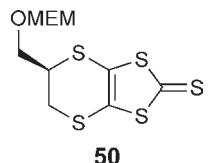
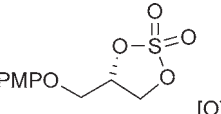
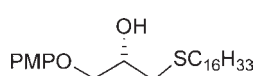
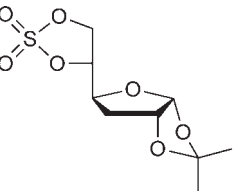
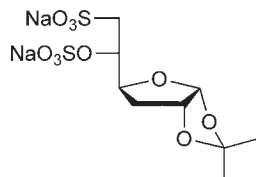
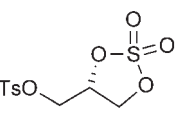
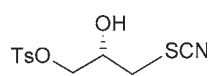
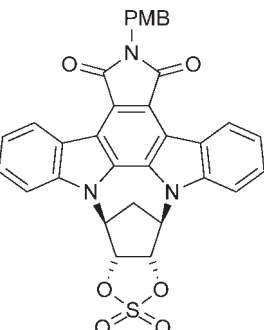
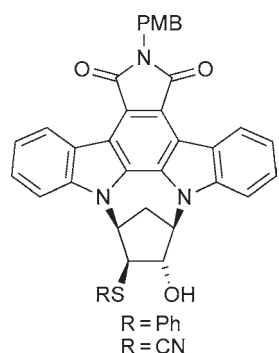
The cleavage of 1,3,2-dioxathiolane *S*-oxides and *S,S*-dioxides by S-nucleophiles occurs according to the general rules outlined earlier. Examples of such reactions are presented in Table 4.

Reaction of the carbohydrate-based cyclic sulfites with NaSCN was used for the synthesis of *cis*-1,2-fused oxazolidine-2-thiones (Table 4) <1995TL5347>. Seleno and oxo derivatives were obtained with KSeCN or NaOCN, respectively <2000MI397>. The stereochemistry of products can be explained by the intermediate isomerization of β -thiocyanates into α -isothiocyanates (Scheme 10) <1995TL5347, 2000MI397>.

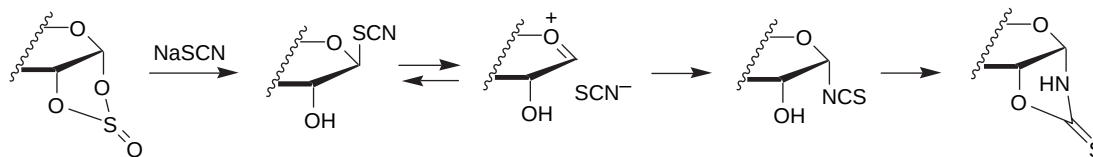
Table 4 Reactions of 1,3,2-dioxathiolane S-oxides (cyclic sulfites) and 1,3,2-dioxathiolane S,S-dioxides (cyclic sulfates) with S-nucleophiles

Substrate ^a	Nucleophile	Conditions	Product(s)	Yield (%)	References
		toluene, 110 °C	 X = NH ₂ X = H	60 10	1995JOC5983
	NaSCN	toluene, 90 °C, 2–8 h; or Me ₂ CO, crown ether		80	1995TL5347
	NaSCN	toluene, 90 °C, 2–8 h; or Me ₂ CO, crown ether		70	1995TL5347
 R = Ac, Bn	NaSCN	toluene, 90 °C, 2–8 h; or Me ₂ CO, crown ether	 R = Ac R = Bn	60 90	1995TL5347
 X = F, Cl	PhSH	THF, Bu ^t OK, rt, 2 h	 X = F X = Cl	90 94	1997CEJ517
 [O]	AcSK	Me ₂ CO, rt		97	1995CC461 1997JOC3944

(Continued)

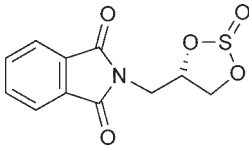
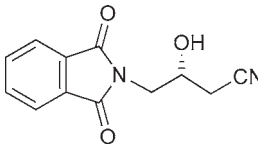
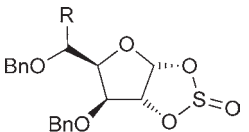
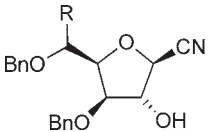
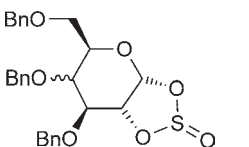
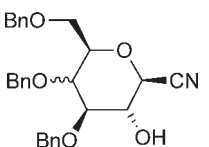
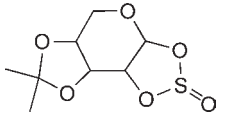
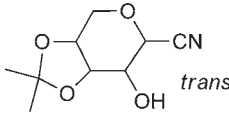
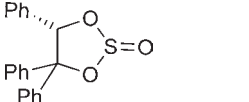
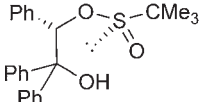
Substrate ^a	Nucleophile	Conditions	Product(s)	Yield (%)	References
 [O]	 NaS	MeOH, rt, overnight, then THF, 60 °C, 36 h	 50	54	1997J(P1)3173 2001T5015 2004TL5103
 [O]	C ₁₆ H ₃₃ SLi	THF, rt		94	1998JOC5696
 [O]	Na ₂ SO ₃	Me ₂ CO-H ₂ O, rt, 16 h, reflux, 4 h		85	1999T14649
 [O]	NH ₄ SCN	Me ₂ CO/H ₂ O, 28 °C, 2 h		88	2002IJB586
	PhSH, or NH ₄ SCN	NaH, THF, rt; or DMF, 70 °C	 R = Ph R = CN	91 64	2004TL7469

^aThe sulfates labeled [O] were obtained by oxidation of the corresponding cyclic sulfites.



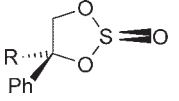
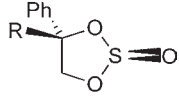
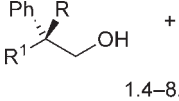
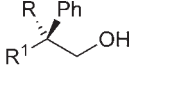
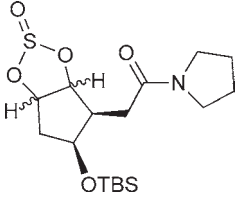
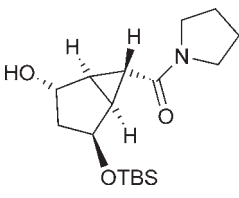
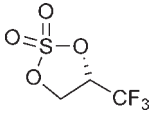
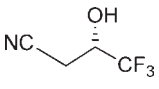
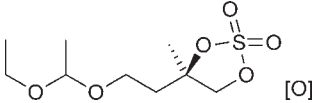
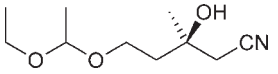
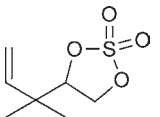
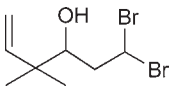
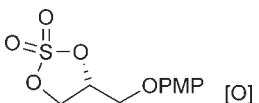
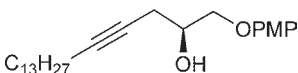
Scheme 10

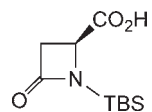
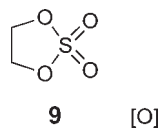
Table 5 Reactions of 1,3,2-dioxathiolane S-oxides (cyclic sulfites) and 1,3,2-dioxathiolane S,S-dioxides (cyclic sulfates) with C-nucleophiles

Substrate ^a	Nucleophile	Conditions	Product(s)	Yield (%)	References
	KCN	DMF, 100 °C, 2 d		70	1996TA2411
 R = H, CH ₂ OBn	NaCN	HMPA, 90 °C, 4 h Yb(OTf) ₃	 R = H R = CH ₂ OBn	70 78	2004OL3913
	NaCN	HMPA, 90 °C, 4 h Yb(OTf) ₃		70–76	2004OL3913
	NaCN	HMPA, 90 °C, 4 h Yb(OTf) ₃	 <i>trans</i>	63–79	2004OL3913
 36	Bu ^t MgCl	THF, –90 °C	 7:3	53 (major)	1997LA1189

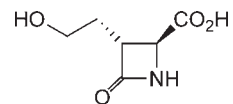
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Table 5 (Continued)

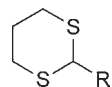
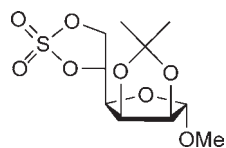
Substrate ^a	Nucleophile	Conditions	Product(s)	Yield (%)	References
 or  $R = \text{Me}, \text{Pr}^n, \text{Pr}^i, \text{Bu}^n$	R^1_3Al $\text{R}^1 = \text{Me}, \text{Et}$	hexane, -20°C , 1 h	 +  $1.4\text{--}8.6:1$ $\text{R} = \text{Me}, \text{Pr}^n, \text{Pr}^i, \text{Bu}^n; \text{R}^1 = \text{Me}, \text{Et}$	85–98	1998TL3007 2000TL2945
	LHMDS	THF, -78°C		38	2004TL7261
	NaCN	$\text{Me}_2\text{CO}/\text{H}_2\text{O}$ rt, overnight		50	1997CEJ517
	NaCN	DMF, 80°C , 8 h		85	1999TA4349
	LiCHBr_2	-90°C		89–97	1995TL4595
	$\text{C}_{13}\text{H}_{27}\text{C}\equiv\text{CLi}$	THF, cat. CuI, -23°C to rt		90	1998JOC2560



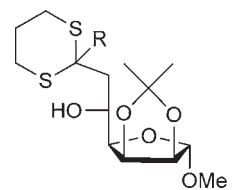
LDA,
THF, -78 °C
to rt



1995T5169



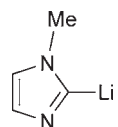
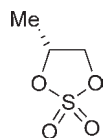
BuLi, THF-
HMPA,
-40 °C, 2 h



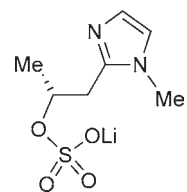
R = H
Bu
C₈H₁₇
C₁₂H₂₅

92
51
42
38

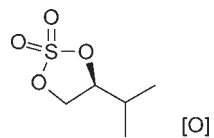
2000CAR66



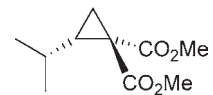
THF, -78 °C



2006TL1473



NaH, DME,
85 °C

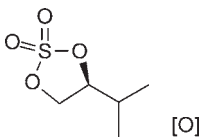
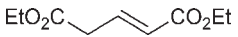
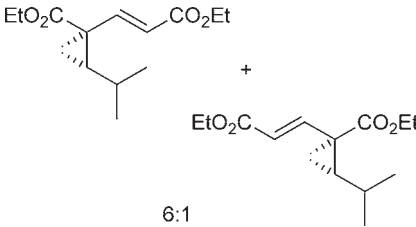
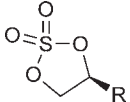
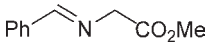
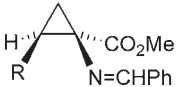
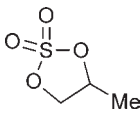
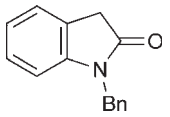
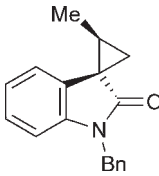


95

1995TL2725

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Table 5 (Continued)

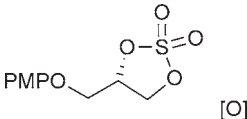
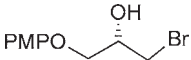
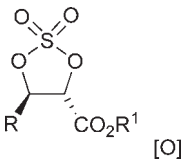
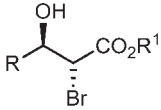
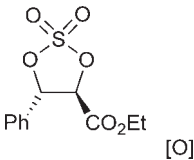
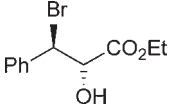
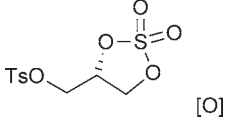
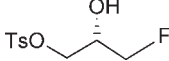
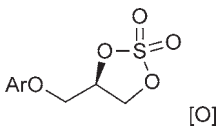
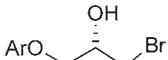
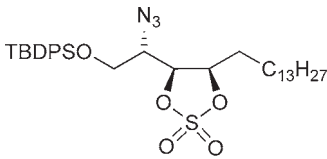
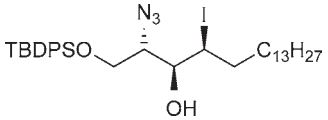
<i>Substrate^a</i>	<i>Nucleophile</i>	<i>Conditions</i>	<i>Product(s)</i>	<i>Yield (%)</i>	<i>References</i>
		NaH, DME, 85 °C	 6:1	61 (major)	1995TL2725
		NaH, DME, rt to 50 °C, 4 h	 R = Me, Cl(CH ₂) ₃	100	1996TA283 1996TL4529
		NaH, DME, rt		54	2005JA11505

^aThe sulfates labeled [O] were obtained by oxidation of the corresponding cyclic sulfites.

6.05.5.3.5 Halide ions

Several recent publications describe cleavage of 1,3,2-dioxathiolane *S,S*-dioxides (cyclic sulfates) by halide nucleophiles that furnish halohydrines, which can be used as synthetic intermediates, primarily for preparation of corresponding epoxides or for further reactions with nucleophiles (Table 6). Similar reactions with chloride have been studied for 1,3,2-dioxathiolane *S*-oxides (cyclic sulfites) <1996ACS832>.

Table 6 Reactions of 1,3,2-dioxathiolane *S,S*-dioxides (cyclic sulfates) with halide nucleophiles

Substrate ^a	Nucleophile	Conditions	Product(s)	Yield (%)	References
	LiBr	THF, rt			1998JOC5696
	LiBr	THF, rt	 R = Bu ^t , CO ₂ Pr ⁱ , OPMP, C ₁₅ H ₃₁ , Ph, <i>c</i> -C ₆ H ₁₁ R ¹ = Et, Pr ⁱ		1998TL2071
	MgBr ₂ ·Et ₂ O	Et ₂ O, 12 h, rt		70	1999IJB283
	Bu ₄ NF	Me ₂ CO/ H ₂ O, 28 °C, 8 h		81	2002IJB586
	LiBr	THF, rt, 2–3 h	 Ar = 1-naphthyl, 2-MeOC ₆ H ₄ , 3-MeC ₆ H ₄ , 2-NCC ₆ H ₄ , 4-AcNHC ₆ H ₄		2005T2831
	Bu ₄ NI	THF, 40 °C, 1 h, then H ₂ SO ₄		94	2006JOC8661

^aThe sulfates labeled [O] were obtained by oxidation of the corresponding cyclic sulfites.

6.05.5.3.6 Strong bases

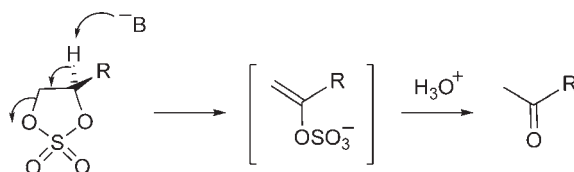
It has been shown that 4-decyl-1,3,2-dioxathiolane *S,S*-dioxide unexpectedly reacts with BuLi to give dodecanal in 99% yield <1994JOC520>. A few other examples of this base-mediated rearrangement of 1,3,2-dioxathiolane *S,S*-dioxides (cyclic sulfates) to ketonic products have been described (Table 7). The reaction may start with

Table 7 Reactions of 1,3,2-dioxathiolane *S,S*-dioxides (cyclic sulfates) with strong bases

Substrate ^a	Base	Conditions	Product(s)	Yield (%)	References
	BuLi or Bu ^t ONa	THF, -40 °C to rt or THF, 0 °C to rt		40 79	2000TL659
	Bu ^t ONa	THF, 0 °C to rt		77	2000TL659
	Bu ^t ONa	THF, 0 °C to rt		73	2000TL659
	Bu ^t ONa	THF, 0 °C to rt		72	2000TL659
	Bu ^t OK	THF, rt, 1.5 h		86	2000EJO1285
		THF, -78 °C, 4 h		39	2004TL7469

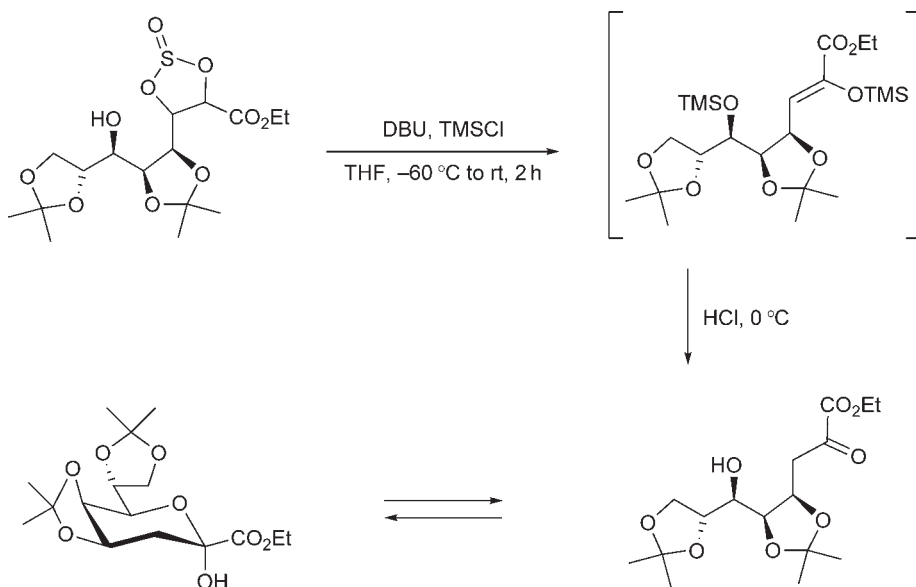
^aThe sulfates labeled [O] were obtained by oxidation of the corresponding cyclic sulfites.

β -elimination to give an intermediate vinyl bisulfate, which on acidification gives the ketone product (**Scheme 13**) <1994JOC520, 2000TL659, 2004TL7469>. As an alternative, an α -lithiation–carbenoid C–H insertion mechanism might operate <2004TL7469>. On treatment with a chiral lithium amide base, an asymmetric rearrangement to a chiral ketone has been achieved (**Table 7**) <2004TL7469>.



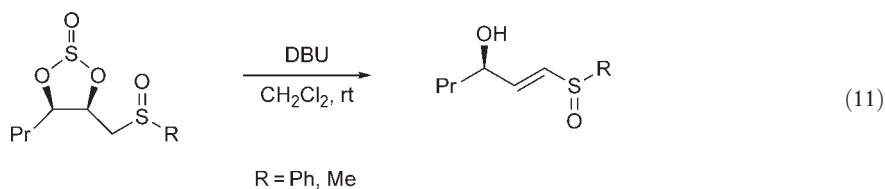
Scheme 13

Similar elimination from 1,3,2-dioxathiolane *S*-oxides (cyclic sulfites) has been studied and used along with an *in situ* trap (DBU/TMSCl) to obtain a tautomeric equivalent of α -oxocarboxylic acid ester (**Scheme 14**) <2004TL4545>.



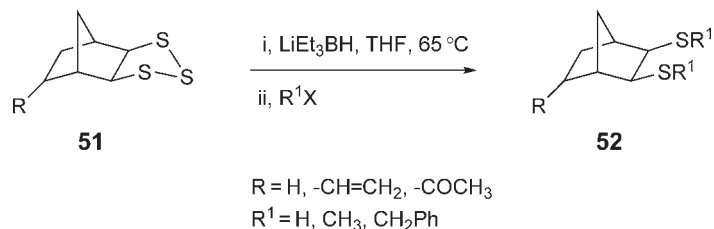
Scheme 14

A different type of elimination may also occur for cyclic sulfites and sulfates leading to allylic alcohols <1995J(P1)847, 2006JOC8661>. Thus, 2,3-dihydroxy sulfoxides have been converted via the reaction of corresponding cyclic sulfites with DBU to (*E*)- γ -hydroxy- α,β -unsaturated sulfoxides (**Equation 11**). Exclusive (*E*)-selectivity was observed for the new double bond <1995J(P1)847>.



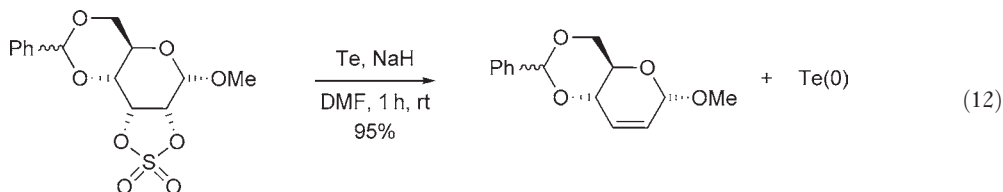
6.05.5.4 Reduction

In the context of 1,2-functionalization of alkenes by sulfur reagents, the selective transformation of norbornene and its derivatives with elemental sulfur in presence of a nickel complex into *exo*-1,2,3-trithiolanes **51** in good yields (75–82%) has been studied (Scheme 15) <2005TL7077>. The trithiolanes **51** were reduced with LiEt_3BH in refluxing THF followed by addition of MeI or PhCH_2Br to produce 71–91% yields of the corresponding disulfides **52**. The vicinal dithiol was isolated when the reaction was quenched with H_2O <2005TL7077>.

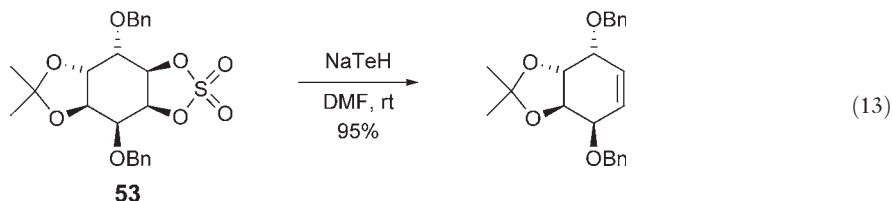


Scheme 15

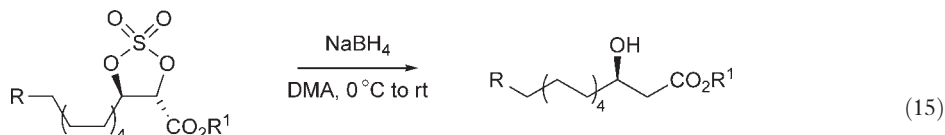
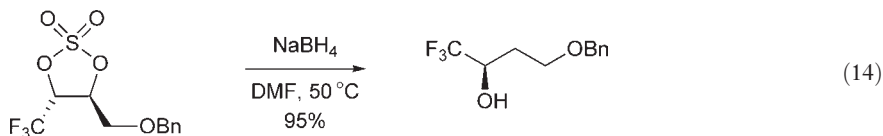
Treatment of 1,3,2-dioxathiolane *S,S*-dioxides with telluride ion, generated *in situ* by reduction of the elemental Te, yields alkenes rapidly (10 min–2 h) under mild conditions (0 °C to rt) <1995TL7209>. The reduction may be performed with 0.1 equiv or less of Te in the presence of a stoichiometric amount of LiEt_3BH or NaH. The reaction is stereospecific, for example, *meso*-2,3-diphenylethane-2,3-diol produces *cis*-stilbene, and *d,l*-2,3-diphenylethane-2,3-diol gives *trans*-stilbene. The sulfates of *cis*-diols are readily converted to *cis*-alkenes, as shown in Equation (12) <1995TL7209>.



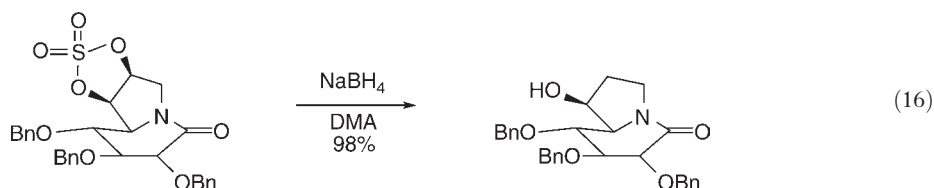
The *D-allo*-inositol-based cyclic sulfate **53** has been reduced with sodium hydrogen telluride to the protected condiritol (Equation 13) <2000EJO1285>.



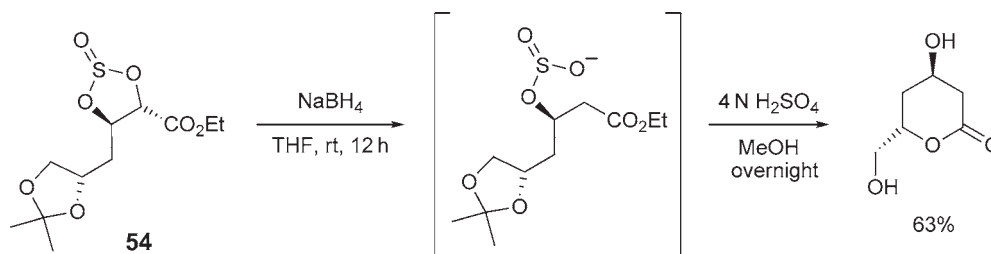
Alcohols can be obtained from cyclic sulfates by a regioselective reduction with sodium borohydride, as shown in Equation (14) <2006JFC580>, Equation (15) <2006BML3855, 2006T3221>, and Equation (16) <1996TL547>.



$\text{R} = \text{H}, \text{R}^1 = \text{Et}$ (72%); $\text{R} = \text{OCOBu}^t, \text{R}^1 = \text{Me}$ (55%)



Similar reductions can be used for cyclic sulfites [<2004TL5877>](#). The reduction of compound [54](#) and a longer subsequent acidification led to cyclization ([Scheme 16](#)) [<2002EJO2921>](#).



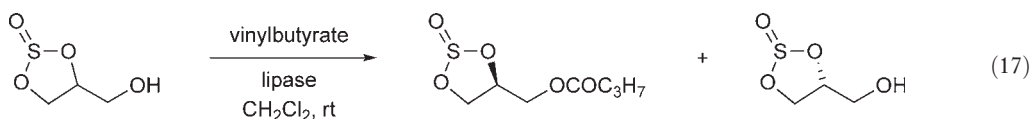
Scheme 16

6.05.5.5 Reactions with Radicals and Carbenes

No significant developments have been reported since the publication of [<1996CHEC-II\(4\)545>](#).

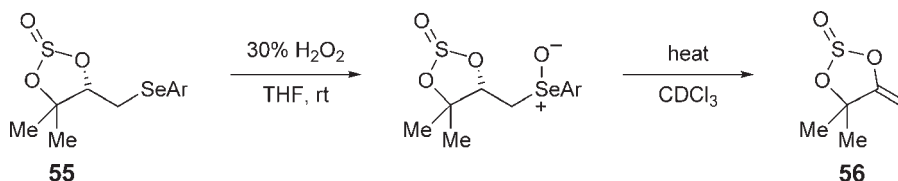
6.05.6 Reactivity of Substituents Attached to Ring Carbon Atoms

The first enzymatic resolution of 1,3,2-dioxathiolane *S*-dioxides (cyclic sulfites) was achieved via lipase-catalyzed acylation with vinyl butyrate ([Equation 17](#)) [<1999TA4755>](#). For the *cis*-alcohol, 91% ee has been observed after 21% conversion for the ester. However, the enantioselectivity is too low for the resolution of the *trans*-alcohol [<1999TA4755>](#).



Nucleophilic substitution in a side chain occurs for 4-chloromethyl-1,3,2-dioxathiolane *S*-oxide [33](#) with sodium 1-naphthyloxyde [<1999MC236, 2001IZV417, 2001RCB436>](#), 3-hydroxy-4-morpholino-1,2,5-thiadiazole [<2001IZV417, 2001RCB436>](#), and sodium phenoxide ([Scheme 3](#)) [<2000IZV1774, 2000RCB1753>](#), whereas a harder nucleophile (ethoxide anion) preferably attacks the sulfur atom causing ring cleavage (see [Section 6.05.5.3.1](#)).

The oxidation of selenide [55](#) with subsequent thermolysis of the intermediate, unstable selenoxide yielded 4-methylene-1,3,2-dioxathiolane *S*-oxide [56](#) (28%), which is a synthetic equivalent of allene oxides ([Scheme 17](#)) [<1999T10845>](#).



Scheme 17

A sulfoxide group in a side chain can also be selectively oxidized (by *m*-chloroperbenzoic acid (MCPBA)) without oxidation of cyclic sulfite to sulfate <2003HAC587>. On the other hand, the standard oxidation of cyclic sulfite to sulfate by NaIO₄ in the presence of RuCl₃ (Section 6.05.10.3) leads simultaneously to *cis*-dihydroxylation of a double bond in a substituent <1999TL2235>.

6.05.7 Reactivity of Substituents Attached to Ring Heteroatoms

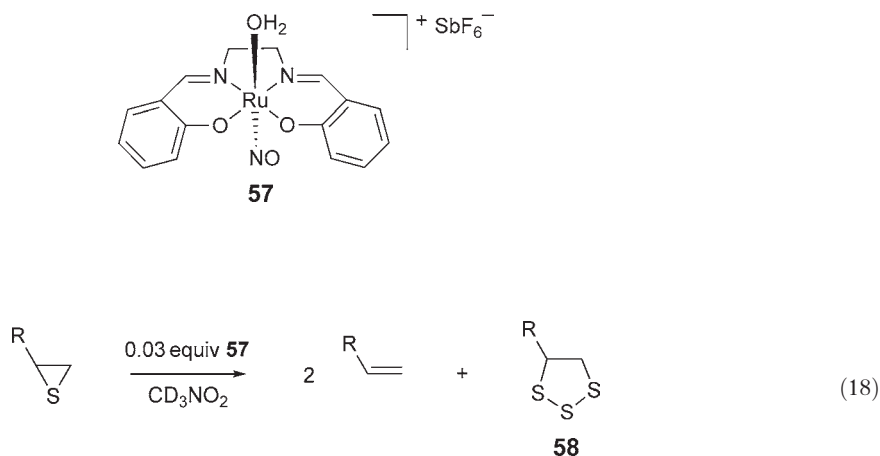
No significant developments have been reported since the publication of <1996CHEC-II(4)545>. The photochemical rearrangement of 1,2,3-benzotrithiole *S*-2-oxide into the corresponding *S*-1-oxide probably remains the only example <1993TL673, 1996CHEC-II(4)545>.

6.05.8 Ring Synthesis

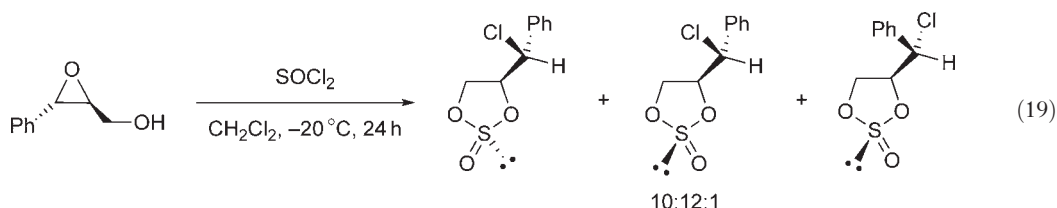
According to a comprehensive classification suggested in the previous chapter in CHEC-II(1996) <1996CHEC-II(4)545>, the synthesis of five-membered heterocycles containing three oxygen and/or sulfur atoms in the 1,2,3-positions can be classified into three groups: (1) one-component syntheses, in which a suitable precursor molecule is cyclized by linkage of two heteroatoms; (2) two-component syntheses, in which the ring is built up either by a [3+2] or [4+1] cyclization; and (3) syntheses by transformation of another heterocyclic ring. Many versatile synthetic approaches were described in CHEC(1984) <1984CHEC(6)851> and CHEC-II(1996) <1996CHEC-II(4)545>. Less diverse information is presented in this chapter due to little new development in the area.

6.05.9 Synthesis by Transformations of Another Ring

Monosubstituted 1,2,3-trithiolanes **58** (R=Me, Ph) were obtained in 91% and 90% yield, respectively, by a disproportionation of the corresponding episulfides catalyzed by the ruthenium complex **57** (Equation 18) <2002JA4770>.



A novel approach to 1,3,2-dioxathiolane *S*-oxides (cyclic sulfites) and 1,3,2-dioxathiolane *S,S*-dioxides (cyclic sulfates) has been developed recently by Bredikhin and co-workers via reaction of 2,3-epoxyalcohols (glycidols) with thionyl chloride or sulfonyl chloride, respectively <1999MC236, 2000IZV1586, 2000IZV1774, 2000RCB1575, 2000RCB1753, 2002RJO213, 2002ZOR233>. The configuration of C-4 in the resulting 4-chloroalkyl-1,3,2-dioxathiolane *S*-oxides is the same as of C-2 in the starting glycidol, whereas the configuration of the exocyclic carbon is inverted compared to C-3 of the precursor (Equation 19).



Similarly, 4-acetoxymethyl-1,3,2-dioxathiolane *S*-oxide was obtained in the reaction of glycidyl acetate with sulfur dioxide <1996MM826>.

Boronic esters of (*R,R*)-1,2-dicyclohexyl-1,2-ethanediol or pinanediol react with thionyl chloride and excess imidazole in acetonitrile on a borosilicate glass surface to form the corresponding cyclic sulfites of diols <2001OM2920>. Similarly, cyclic sulfites and sulfates have been prepared from silicates of diols <1997TL4841>.

6.05.10 Syntheses of Particular Classes of Compounds

6.05.10.1 Parent Systems

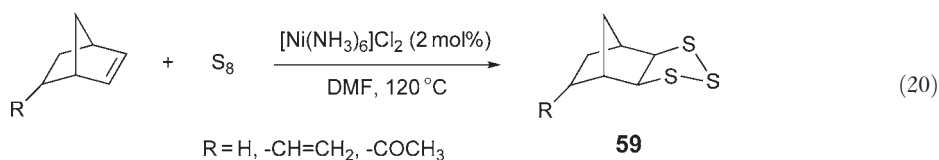
The reaction of ozone with ethene remains the only available method for the generation of 1,2,3-trioxolane **1**. The formation of 1,2,3-trioxolane (the primary ozonide) and of 1,2,4-trioxolane (the secondary ozonide) was observed by IR spectroscopy at much lower temperatures than previously reported: as low as 25 K in the amorphous CO₂ matrix <1996JA3687>. There was no indication of Criegee intermediates – carbonyl oxide and formaldehyde. No reaction was found in an argon matrix at temperatures up to 35 K. The identification of the primary ozonide was supported by an *ab initio* calculation of the IR spectrum <1996JA3687, 1996SAA1479>.

6.05.10.2 Benzo Derivatives

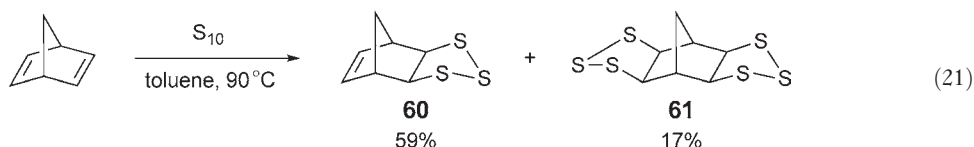
The formation of 1,2,3-benzotrithiole with very low yield (1.3%) was detected by gas chromatography–mass spectrometry (GC/MS) in a mixture of other polysulfides produced by the reaction of elemental sulfur with benzyne generated either by treatment of *o*-Cl₂C₆H₄ with BuLi in Et₂O at –60 °C, or by decomposition of benzenediazonium-2-carboxylate at 83 °C <2004JOC5483>.

6.05.10.3 C-Linked Substituents

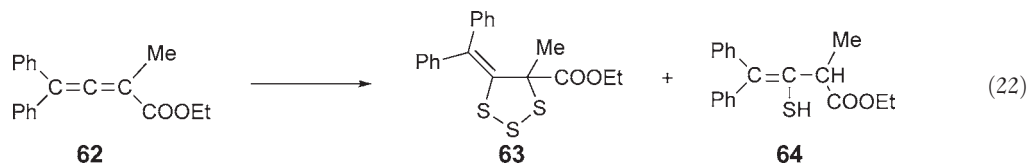
Norbornene reacts with elemental sulfur to give a mixture of 1,2,3-trithiolane **59** (R=H) and pentathiepane (Equation 20) <2005TL7077>. The use of Ni(NH₃)₆Cl₂ in DMF as a catalytic system allowed the selective transformation of norbornene and its derivatives into *exo*-1,2,3-trithiolanes **59** in good yields (75–82%). The reaction selectivity was maximal at an alkene:S₈ ratio of 1:3/8 <2005TL7077>.



Another sulfur allotrope – cyclodecasulfur (S₁₀) – also reacted with norbornene under milder conditions to furnish the trithiolane **59** (R=H) as the unique reaction product in 85% yield <1999TL7961>. Similarly, the reaction of S₁₀ with norbornadiene produced a trithiolane adduct **60** in good yield as well as a new bis-sulfurated compound **61** (Equation 21) <1999TL7961>. Reactions with S₈ under the same conditions produced only traces of the expected products.



In an electrochemical reduction in acetonitrile with a sacrificial sulfur/graphite electrode for generation of the anions S_x^{2-} , the allene **62** afforded a trithiolane **63** (77%) along with an enethiol **64** (8%) (Equation 22) <1996MI1987>. However, allenes with different structure gave different products or remained unchanged.

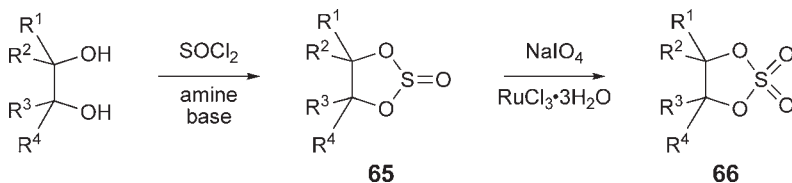


In another electrochemical experiment, the sacrificial sulfur/carbon electrode was a source of cations S^{2+} , which reacted in organic media with thiols or thiolates to give polysulfides, for example, 1,2,3-trithiolane (11%) <1996BSF273>.

Thionosulfite **21** and other thionosulfites have been synthesized by reaction of corresponding 1,2-diols with 1,1'-thio- or 1,1'-dithiobisbenzimidazole <2003JOC7059>.

The syntheses and reactions of 1,3,2-dioxathiolane *S*-oxides and 1,3,2-dioxathiolane *S,S*-dioxides have been discussed in comprehensive reviews <1997AHC89, 2000T7051>. In publications on organic synthesis these compounds are usually named cyclic sulfites and cyclic sulfates, respectively (Sections 6.05.5 and 6.05.6; Tables 1–7).

The most widely used method for the preparation of 1,3,2-dioxathiolane *S*-oxides (cyclic sulfites) **65** bearing C-linked substituents is the reaction of the corresponding 1,2-diols with thionyl chloride in presence of pyridine or Et_3N (Scheme 18). More reactive 1,3,2-dioxathiolane *S,S*-dioxides (cyclic sulfates) **66** are usually obtained by oxidation of sulfites **65** with sodium periodate, which is mediated by ruthenium tetroxide generated *in situ* from a catalytic amount of ruthenium trichloride. Numerous derivatives **65** and **66** were obtained via this approach and its modifications for further transformations, mostly as the synthetic equivalents of epoxides <1997AHC89, 2000T7051> (see also Sections 6.05.5 and 6.05.6, and Tables 1–7).

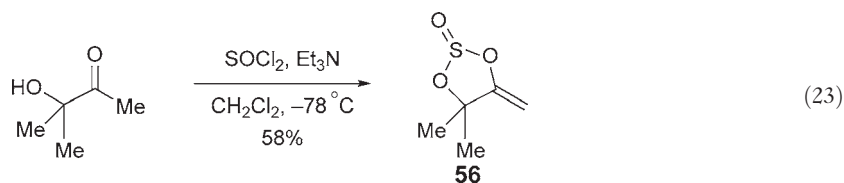


Scheme 18

One of the modifications is an acid-catalyzed transesterification of 1,2-, 1,3-, and 1,4-diols with diisopropyl sulfite for the efficient preparation of corresponding cyclic sulfites, even in cases when reaction with thionyl chloride does not give good results <1997SC701>. In a more popular method, thionyl bis(imidazole) is used, which is more reactive than thionyl chloride <1995JA12873, 1995TL5347, 1997CEJ517, 1997T16391, 1999TL2235, 2000MI397, 2004MI95, 2004OL3913, 2004TL7469, 2005CCC487, 2005JOC7715>.

Synthesis of cyclic sulfites and sulfates from epoxides is described in Section 6.05.9.

4-Methylene-1,3,2-dioxathiolane *S*-oxides, potential equivalents of allene oxides, can be obtained by treatment of α -hydroxyketones with thionyl chloride (Equation 23) <1999T10845>.



6.05.10.4 N-Linked Substituents

No significant developments have been reported since the publication of <1996CHEC-II(4)545>.

6.05.10.5 O-Linked Substituents Including Keto Derivatives

No significant developments have been reported since the publication of <1996CHEC-II(4)545>.

6.05.10.6 Halogens Attached to Ring

No significant developments have been reported since the publication of <1996CHEC-II(4)545>.

6.05.10.7 S- and Si-Linked Substituents

No significant developments have been reported since the publication of <1996CHEC-II(4)545>.

6.05.11 Important Compounds and Applications

6.05.11.1 Applications in Research and Industry

1,3,2-Dioxathiolane *S*-oxides (cyclic sulfites) and 1,3,2-dioxathiolane *S,S*-dioxides (cyclic sulfates) have been widely used in organic chemistry, mostly as the synthetic equivalents of epoxides (Sections 6.05.5 and 6.05.6; Tables 1–7).

1,3,2-Dioxathiolane *S*-oxide, benzo-1,3,2-dioxathiolene *S*-oxide, and other cyclic sulfites have been studied as secondary antioxidants <1997MI209>. They decompose hydroperoxides in a nonradical way at a faster rate than phosphites, and may be used for the protection of polymers against aging.

Industrial applications for 1,3,2-dioxathiolane *S*-oxides and 1,3,2-dioxathiolane *S,S*-dioxides include their use as components of the nonaqueous solvent of electrolyte solutions in lithium secondary batteries <2000JPP2000188127, 2002JPP2002237331, 2002JPP2002319430, 2003JPP2003157900, 2003JPP2003173821, 2004JPP2004055502, 2004JPP2004185931, 2004JPP2004228010, 2004USP2004072080, 2004USP2004137332, 2005JPP2005011762, 2005JPP2005050671, 2006JPP2006120460, 2006JPP2006140115>, as stabilizers for the cyanoacrylate adhesives <1999DEP19750802>, as reagents for preparation of surfactants <1995DEP4404728> and cross-linkable polymers <1995JPP07002950, 1995JPP07062027>.

6.05.11.2 Biological Activity

1,2,3-Benzotrithiole *S*-oxide is capable of causing efficient DNA cleavage in the presence of 2-mercaptoethanol or glutathione and exhibited potent cytotoxicity against certain cancer cell lines <2002BML3259>.

The carbohydrate-based 1,3,2-dioxathiolane *S,S*-dioxide **23** (Section 6.05.3.1) has demonstrated an exceptional anticonvulsant activity in the standard maximal electroshock seizure test. Compound **23** is much more potent than structural analogs, and approximately 8 times more potent than the isosteric topiramate <1998JME1315>.

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6.06

Five-membered Rings with Three Oxygen or Sulfur Atoms in 1,2,4-Positions

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6.06.1	Introduction	192
6.06.2	Theoretical Methods	193
6.06.3	Experimental Structural Methods	195
6.06.3.1	Electron and X-Ray Diffraction	195
6.06.3.2	Microwave Spectroscopy	197
6.06.3.3	Nuclear Magnetic Resonance Spectra	197
6.06.3.3.1	Carbon-13 and proton NMR	197
6.06.3.3.2	Oxygen-17 NMR	197
6.06.3.4	Mass Spectrometry, Infrared and Raman Spectroscopy	198
6.06.3.5	Photoelectron Spectroscopy	201
6.06.3.6	Other Physical Methods	202
6.06.4	Thermodynamic Aspects	202
6.06.5	Reactivity of Ring Aspects	202
6.06.5.1	Thermal and Photochemical Reactions Formally Involving No Other Species	202
6.06.5.1.1	Rearrangements	202
6.06.5.1.2	Thermolysis	202
6.06.5.1.3	Photolysis	204
6.06.5.1.4	Polymerization	204
6.06.5.2	Reactions with Electrophiles	204
6.06.5.2.1	Reactions with Lewis acids and Brønsted acids	204
6.06.5.2.2	Reactions at double bonds	208
6.06.5.2.3	Oxidation	208
6.06.5.3	Reactions with Nucleophiles	208
6.06.5.3.1	Reactions with O-nucleophiles and halogens	208
6.06.5.3.2	Reactions with N-nucleophiles	210
6.06.5.3.3	Reactions with C-nucleophiles	210
6.06.5.3.4	Reactions and reductive ring cleavage	211
6.06.6	Reactivity of Substituents Attached to Ring Carbons	212
6.06.6.1	H-Substituents	212
6.06.6.2	C-Substituents	212
6.06.6.3	O-Substituents	212
6.06.7	Ring Syntheses Classified by the Number of Rings Atoms in Each Component	212
6.06.8	Syntheses by Ring Transformation	212
6.06.8.1	Introduction	212
6.06.8.2	The Ozonolysis Reaction	213
6.06.8.2.1	The co-ozonolysis reaction	213
6.06.8.2.2	Ozonolysis of alkynes	217
6.06.8.2.3	Trapping of carbonyl oxides with acyl cyanides	219

6.06.8.2.4	Co-ozonolysis of polycyclic aromatic hydrocarbons	221
6.06.8.2.5	Trapping of intermediate carbonyl oxides with methyl pyruvate	223
6.06.8.2.6	Domino reaction: Tandem ozonolysis–aldol sequence	225
6.06.8.2.7	Cryo-ozonolysis	227
6.06.8.2.8	Ozonolysis of terpenes and implications for ecology	229
6.06.8.2.9	Regioselective fragmentation of molozonides	232
6.06.8.2.10	Grob fragmentation and Baeyer–Villiger rearrangement	236
6.06.8.2.11	Formation of unsaturated hydroperoxy acetals	236
6.06.8.2.12	Fragmentation with Fe(II) compounds	238
6.06.9	Syntheses of Particular Classes of Compounds	238
6.06.9.1	Parent Systems Including S-Oxides and S,S-Dioxides	238
6.06.9.1.1	<i>endo</i> -Peroxides	238
6.06.9.1.2	Sulfur compounds	240
6.06.9.2	C-Linked Substituents	245
6.06.9.3	N-Linked Substituents	245
6.06.9.4	O-Linked Substituents	245
6.06.9.5	Halogens Attached to the Ring	245
6.06.10	Important Compounds and Applications	245
6.06.10.1	Applications in Research and Industry	245
6.06.10.1.1	Synthesis of porphyrinobilinogen	245
6.06.10.1.2	Synthesis of clerodane and 4-alkyl-4-ketoglutaric acids	245
6.06.10.1.3	Analysis of LDL by mass spectrometry after ozonolysis	246
6.06.10.1.4	Synthesis of β -lactams	246
6.06.10.1.5	Synthesis of oxetanocin analogues	247
6.06.10.1.6	Toxicities of ozonides	247
6.06.10.1.7	Synthesis of jasplakinolide	247
6.06.10.1.8	Ozonolysis in asymmetric synthesis	247
6.06.10.2	Natural Occurrence	247
6.06.10.3	Biological Activity	248
6.06.10.3.1	Ozonides with antimalarial activity	248
6.06.11	Further Developments	252
References		252

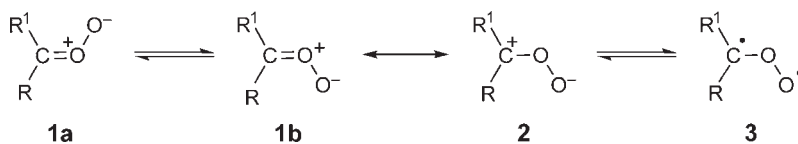
6.06.1 Introduction

In the decade since the publication of CHEC-II(1996) <1996CHEC-II(4)581>, two outstanding developments have taken place in the field of 1,2,4-trioxolanes: (1) isolation of many stable 1,2,4-trioxolanes (secondary ozonides), and their facile synthesis by alternative methods to ozonation; (2) most significantly, technological advances in the industrial synthesis of 1,2,4-trioxolanes by co-ozonolysis for preparing on an industrial scale the first fully synthetic antimalarial medicines. Earlier work has been excellently summarized <1984CHEC(6)851>.

The mechanism of ozonolysis has been firmly proved to follow Criegee's three-step pathway involving (1) the reaction of π -electrons in alkenes, alkynes, or oximes with ozone yielding a 1,2,3-trioxolane (primary ozonide); (2) its spontaneous splitting into a carbonyl and a carbonyl oxide fragment; and (3) rearrangement to a 1,2,4-trioxolane, in a succession of [2+3] cycloadditions or cycloreversions. Details of this mechanism in solution have been refined by taking into account thermodynamic data and the influence of the solvent cage.

A marked difference exists between the ozonolysis of C=C or C=N double bonds and C $\equiv$ C triple bonds as indicated in the formulas; in the latter case, the fragments remain attached, and the carbonyl oxide couples intra- or intermolecularly with another partner.

A review of the recent synthetic progress on ozonides at the Karlsruhe University has appeared <1997MI145>. Two older reviews on the structure of the reactive intermediates 1–3 involved in these reactions deserve to be mentioned: "Carbonyl oxides: zwitterions or diradicals?" <1990AGE344> and "Preparation, properties, and reactions of carbonyl oxides" <1991CRV335>. Reviews on cyclic peroxides <1995COS225> and dioxiranes <1989CRV1187> are also relevant.

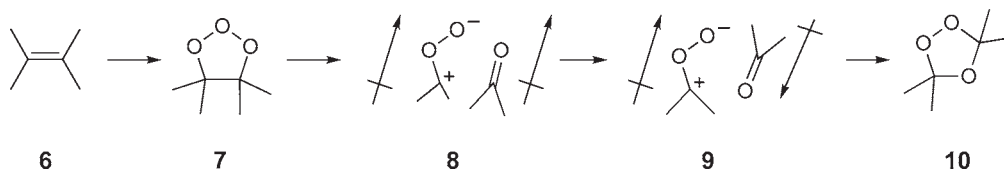


Since there have been some confusions in the nomenclature [<1990AGE344, 1991CRV335>](#), it must be emphasized that (1) 1,2,3-trioxolanes are primary ozonides or moloxides; (2) 1,2,4-trioxolanes are secondary or final ozonides; and (3) Criegee's 'carbonyl oxide' intermediate **1, 2** has been found theoretically to have a pronounced diradical character **3**, not only in the gas phase, but also in solution in nonpolar solvents; only its reaction with carbonyl compounds in solution has a polar character. Nevertheless, the name 'carbonyl oxide' is so well entrenched that it will continue to be used for intermediates **1–3**.

Dioxiranes **4** have equivalent oxygens (attested by isotopic labeling and ¹⁷O NMR; NMR – nuclear magnetic resonance) and an *sp*³-hybridized carbon (of course, the exact hybridization is influenced by the 3-membered ring), whereas carbonyl oxides **1–3** have an *sp*²-hybridized carbon atom and give rise to diastereomers **1a** and **1b** when R ≠ R¹.



Calculations of thermodynamic data [<1991CPL\(187\)491>](#) using MP(SDQ)/6-31G(d,p) software for the splitting of the primary ozonide in the ozonolysis of ethylene (**6** → **8**) have found that this process is endothermic by 12 kcal mol⁻¹; the dipoles in the pair of products **8** are parallel, repelling each other. When one of the fragments rotates in solution without destroying the solvent cage, the dipoles in complex **9** become parallel attracting each other and leading to the formation of the secondary ozonide **10**. The reaction **6** → **9** is endothermic by only 3.1 kcal mol⁻¹; therefore, the authors concluded that the Criegee mechanism needs to be changed slightly in order to include the dipolar complex **9**, which is more stable by 9 kcal mol⁻¹ than the separated independent fragments.



Stereoviews of the optimized structures of primary **7** and secondary ozonides **10** of ethylene without hydrogen atoms and lone pairs (molecular mechanics) are shown in [Figure 1](#).

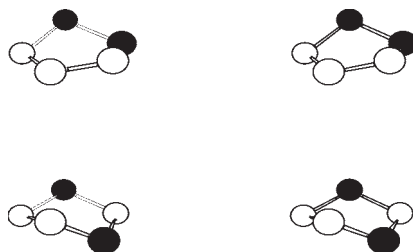
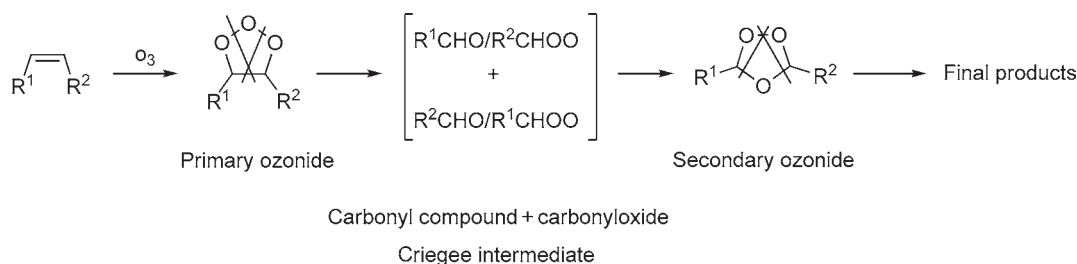


Figure 1 Stereoviews of the primary (top row) and secondary ozonide of ethylene (bottom).

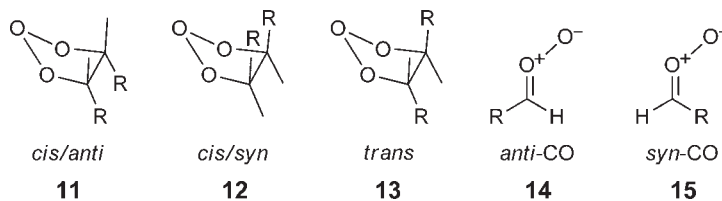
6.06.2 Theoretical Methods

A thorough theoretical analysis of the Criegee mechanism for the ozonolysis of *cis*- and *trans*-symmetrical alkenes RHC=CHR has been performed by semiempirical AM1 calculations [<1997JOC2757>](#). The experimentally observed stereoselectivity for bulky groups (e.g., R = Bu^t) is that from the *cis*-alkene a *cis/trans* ratio of 7:3 is encountered while from a *trans*-alkene a 3:7 ratio for the *cis/trans* secondary ozonides resulted. With smaller R groups (e.g., R = Me) both *cis*- and *trans*-alkenes lead preferentially to the *trans* secondary ozonide ([Scheme 1](#)).

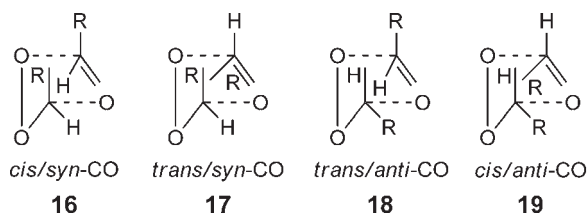


Scheme 1

While both the primary and secondary ozonides have been isolated and characterized, the pair formed by the carbonyl oxide (CO) and the carbonyl compound (CC) has never been directly put into evidence. This elusive intermediate, called also Criegee intermediate zwitterion (CZ), according to this AM1 study which did not take into account solvent effects, forms a tight pair or a dipolar complex (DC). The primary ozonide has an O-envelope half-chair conformation and as such two conformers are possible from a *cis*-alkene **11** and **12** and only one **13** from the *trans*-alkene. The splitting of the primary ozonide can lead either to an *anti* **14** or *syn* **15** CO and has a determining role for the stereochemical outcome of the reaction <1997JOC2757>.



The final step of the Criegee mechanism involves a retrocycloaddition of the CO to the carbonyl compound and it was calculated to be very exothermic (*c.* 50 kcal mol⁻¹). Several tightly bound Criegee intermediates **16–19** can be formed with relatively small activation barriers (1–10 kcal mol⁻¹), the *anti*-isomer **18** being significantly favored (Figure 2).



The calculated barriers determine the final structure of the secondary ozonide but as can be seen from Figure 2, the differences between different routes tend to be rather small. The dipolar complex, a slight modification to the Criegee mechanism, when tightly bound, seems to explain well the stereochemical outcome although different product ratios may be encountered in ozonolysis reactions where for instance the heating rates are varied.

Ab initio calculations of the normal vibrational frequencies for the primary and secondary ozonides of ethylene allowed making a few modifications of the earlier assignments, and will serve for assisting in assigning vibrational bands of larger ozonides <1996SAA1479>.

Semi-empirical calculations for the geometry and dipole moment of tetrasubstituted bis-spiro-1,2,4-trithiolanes derived from adamantane-1-thione were reported <2004JMT(668)179>. Satisfactory agreement with X-ray data was obtained with the PM3 method.

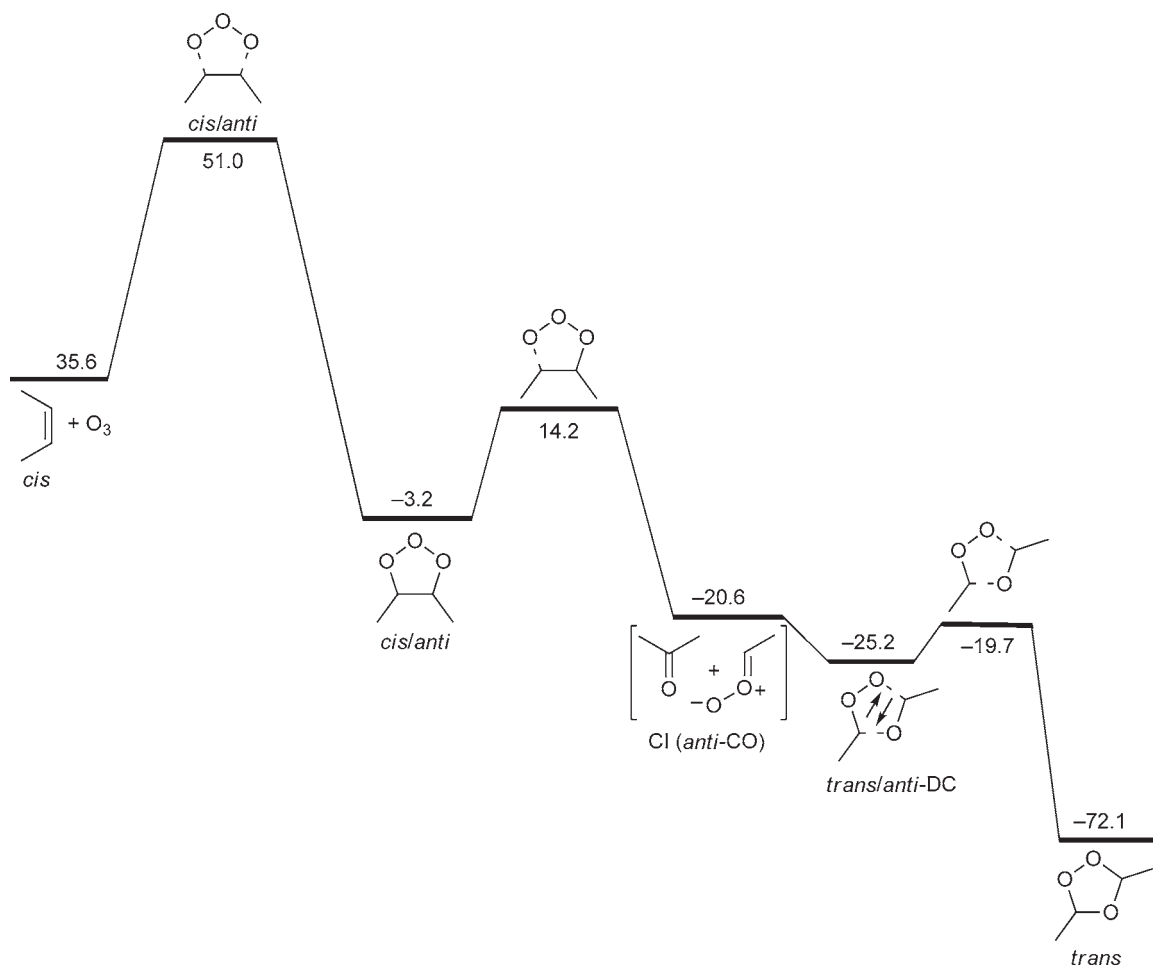
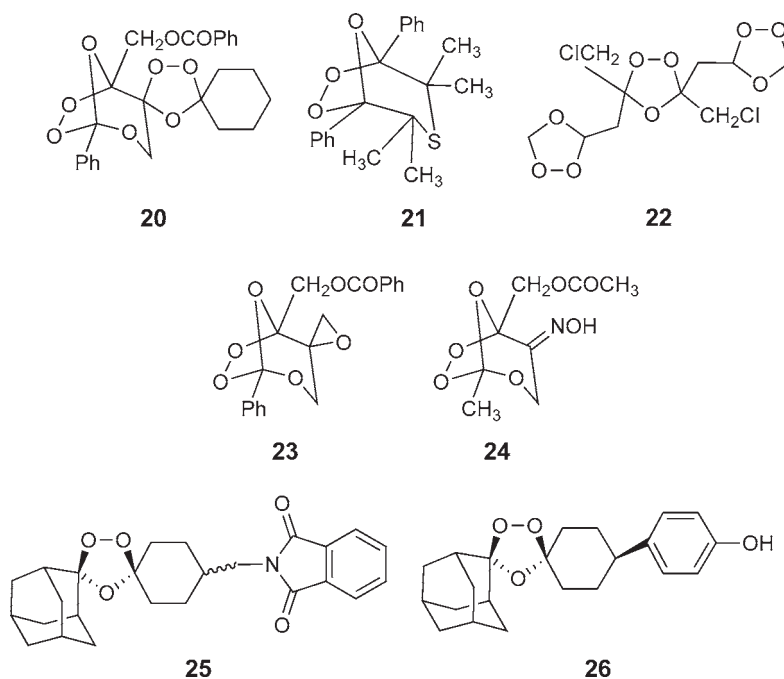


Figure 2 AM1-calculated energy profile for the ozonolysis of *cis*-2-butene, which includes the DC. Numbers represent the heats of formation (in kcal mol^{−1}) for the intermediates and transition states.

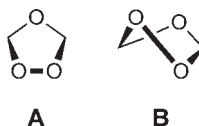
6.06.3 Experimental Structural Methods

6.06.3.1 Electron and X-Ray Diffraction

A January 2007 search in the Cambridge Structural Data Base (CSD) yielded a total of 52 single crystal structures of 1,2,4-trioxolanes and most of these have been described in CHEC-II(1996). The compounds **20–26** are examples of newer entries, several of these being part of a considerable synthetic effort toward identifying new antimalarial drugs related to artemisinin (see also [Section 6.06.10.3](#) and [<2004EJO3657>](#)). Co-ozonolysis of *O*-methyl-2-adamantanone oxime and 4-substituted cyclohexanones afforded a mixture of achiral *cis*- (major product) and *trans*-ozonides (minor product). The *cis*-configuration corresponds to the peroxidic oxygens and phthalimidomethylene carbon being *cis* to one another in the chair-shaped cyclohexanic ring. For the phthalimidomethyl-cyclohexyl- and adamantyl-substituted ozonide **25**, both *cis*- and *trans*-isomers could be crystallized and analyzed by X-ray diffraction [<2004JOC6470>](#). Two independent molecules (one of which has one disordered peroxide oxygen) are encountered in the unit cell for the *cis*-compound. In both stereoisomers the methylenic carbon atom bearing the bulky phthalimido group is equatorial. In the *cis*-isomer the epoxidic (ethereal) oxygen is also equatorial. For the *trans*-compound only one independent molecule is encountered in the unit cell and again the methylenic carbon is equatorial as is one of the two peroxide oxygen atoms; the ‘ethereal’ oxygen is in an axial position. In the related phenolic compound **26**, the peroxidic substituent is in the axial position. This can have important differences on the reactivity and/or biological activity of these adamantyl ozonides (see [Section 6.06.10.3](#)).



Generally, the 1,2,4-trioxolane ring can adopt either an envelope (**A**) or a puckered (**B**) conformation.

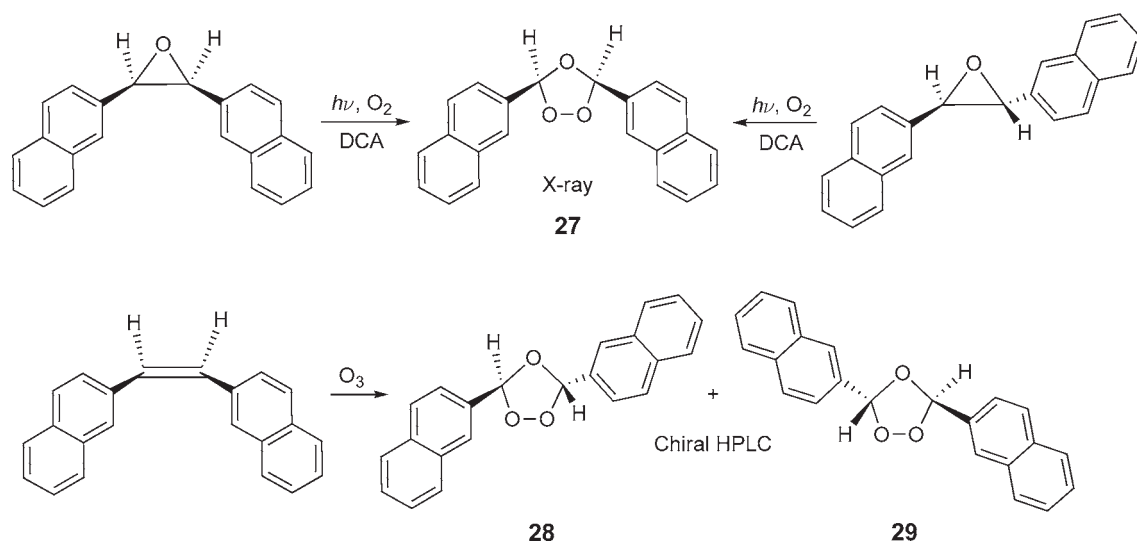


In the envelope conformation (**A**) the peroxide bond and the two carbon atoms are all coplanar (with the C–O–O–C dihedral angle being close to 0°) while the ethereal oxygen atom can be displaced by as much as 0.65 Å to either side of this plane. In conformation **B** the peroxide bond straddles the plane of the remaining three atoms and this dihedral is around 50°. While conformation **A** is achiral, **B** has C_s symmetry. Usually ozonides crystallize in chiral space groups; however, both enantiomorphic forms of **B** are usually encountered in the crystal lattice. Furthermore, disorder of the peroxide oxygen atoms over several occupancies is frequent, and in recent analyses, due mostly to improvement in the structure refinement algorithms, this disorder could be taken into account and suitably refined models could be built from the diffraction data.

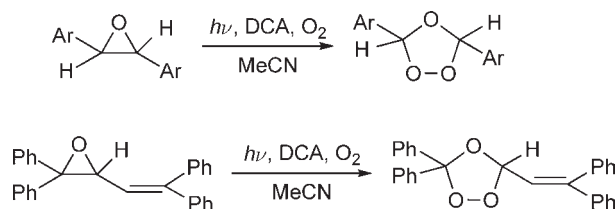
The substituents at C-3 and C-5 may also have stacking interactions in the crystal and thus packing forces can dictate the preferential conformation of the 1,2,4-trioxolane ring as the C-5 and peroxide envelope or even the half chair conformations are energetically close. For instance in the 6,7,8-trioxa-3-thiabicyclo[3.2.1]octane **21**, centrosymmetrical pairs are formed by π – π stacking between two phenyl rings combined with two weak C–H $\cdots$ π interactions <2000AXC1510>.

In an earlier study <1984JA6087>, the product of photosensitized oxygenation with 9,10-dicyanoanthracene (DCA) of 1- and 2-naphthyl *cis*- and *trans*-substituted epoxides could be proved by X-ray crystallography to be the *cis*-trioxolane **27**, which is a *meso* form. The corresponding *trans*-trioxolane was obtained by the ozonation of *cis*-1,2-bis(2-naphthyl)ethene and it could be resolved into enantiomers **28** and **29** on a chiral high-performance liquid chromatography (HPLC) stationary phase (Scheme 2).

Photo-oxygenation of oxiranes sensitized by DCA was reported to afford 1,2,4-trioxolanes quantitatively, but with 2,2-diaryl-3-(2,2-diarylvinyl)oxirane a 1,2,4-trioxepine was claimed to be the product <1988CC1053>. It was now established by reduction of the ozonide with Ph_3P that the reaction afforded a 1,2,4-trioxolane along with other products, and that no 1,2,4-trioxepine resulted <2001TL9203>. Similar reactions were also observed with *para*-tolyl groups instead of phenyl (Scheme 3).



Scheme 2



Scheme 3

A survey of the 47 crystallographically unique fragments of 1,2,4-trioxolanes deposited in the CSD prior to 2000 was published [<2000AXC1510>](#) and shows that the average value for the O–O bond length is 1.473 (11) Å, with the majority of O–O bond lengths being between ~1.46 and 1.50 Å with a relatively wide range of torsion angles spanning from 0° to ~50°. Apparently, no correlation exists between the C–O–O–C torsion angle and the O–O bond length.

6.06.3.2 Microwave Spectroscopy

No newer studies using microwave spectroscopy have been published for the parent system. The previous edition of CHEC(1984) should be consulted for ground state rotational constants and dipole moments.

6.06.3.3 Nuclear Magnetic Resonance Spectra

6.06.3.3.1 Carbon-13 and proton NMR

Routine ^1H and ^{13}C NMR characterization of 1,2,4-trioxolanes and 1,2,4-trithiolanes has been performed. In the case of fluorine substituted ozonides, Teflon NMR tubes had to be employed as glass catalyzes gradual decomposition at room temperature and above.

6.06.3.3.2 Oxygen-17 NMR

Oxygen-17 chemical shifts at natural abundance promise to be among the best tools for discriminating among peroxidic materials, including primary and secondary ozonides, 1,2,4,5-tetroxanes, and acyclic polymeric peroxides [<1991CC816>](#). As shown in [Tables 1–3](#) the epoxidic (ether) oxygen in 3,3- R_2 -5,5- R'_2 -1,2,4-trioxolanes resonates at 120–170 ppm, whereas the peroxidic oxygens resonate at much lower field, 285–330 ppm. Slight differences occur between *cis/trans*-diastereomers [<1994MR150>](#).

Table 1 ^{17}O Chemical shifts (ppm) [in C_6D_6] for 3,3- R_2 -5,5- R^1_2 -1,2,4-trioxolanes

<i>R</i>	<i>R</i> ¹	<i>cis</i>		<i>trans</i>	
		<i>O</i>	<i>O–O</i>	<i>O</i>	<i>O–O</i>
CH_3	CH_2Cl	125.6	293.4	126.5	297.9
Cl	CH_2Cl	172.0	327.0	162.0	319.0
F	CH_2Br			155.6	303.1
CH_3	CN			143.8	327.7

3,3-Dimethyl-5-cyano-5- R -1,2,4-trioxolanes have no diastereomers, but their peroxidic oxygens are not equivalent, as indicated in [Table 2](#).

Table 2 ^{17}O Chemical shifts (ppm) [C_6D_6] for 3,3- Me_2 -5-CN-5- R -1,2,4-trioxolanes

<i>R</i>	<i>O</i>	<i>O–O</i>
CN	139.2	288.6, 336.4
Cl	159.6	291.4, 329.2

Carbonyl groups attached to 1,2,4-trioxolanes lower their stability, but the corresponding *O*-methyl-oximes are quite stable. [Table 3](#) presents some of their ^{17}O NMR data.

Table 3 ^{17}O Chemical shifts (ppm) [C_6D_6] for 3- R -3- R^1 -*O*-methyl-acetoxime-1,2,4-trioxolanes

<i>R</i>	<i>R</i> ¹	<i>O</i>	<i>O–O</i>
H	CH_3	123.8	312.2
H	OCH_3	125.9	303.0
CH_3	CF_3	110.7	282.0, 302.3
CH_3	CH_2Cl	127.5	302.3
CH_3	CH_3	131.9	307.9
CH_3	CN	134.1	299.7, 322.4

Some other typical examples of 1,2,4-trioxolanes with nonequivalent peroxidic oxygen atoms are shown in [Figure 3](#) <1995LA1571>.

Finally, several *cis*- and *trans*-diastereomers with their ^{17}O chemical shifts are presented in [Figure 4](#).

6.06.3.4 Mass Spectrometry, Infrared and Raman Spectroscopy

Electrospray-ionization mass spectra (ESI-MS) and tandem mass spectrometry of unsaturated glycerophosphocholine lipids revealed ω - and ω -carboxylic acid direct products <1996ANC3224>. For polyunsaturated glycerophosphocholine lipids (even with conjugated double bonds), the ESI-MS fragment ions are indicative of the position of the double bonds. The major decomposition pathway involves charge remote fragmentation of the 1,2,4-trioxolane ring with homolytic cleavage of the peroxide bridge <2000JMP224>.

The high-resolution infrared (IR) absorption spectrum of gaseous 1,2,4-trioxolane was measured at 185 K with a spectral resolution of 0.003 cm^{-1} <2005PCA8719>.

A mechanistic study related to low-temperature gas-phase ozonation of alkenes has been performed using gas chromatography-Fourier transform infrared (GC-FTIR) and gas chromatography-mass spectrometry (GC-MS) <1999J(P2)239>. [Table 4](#) presents the FTIR and electron-impact (EI-MS) data for four ozonides derived from primary alkenes and three ozonides derived from secondary alkenes. In the case of ethene, when gas-phase ozonation was performed at -120 , -50 , -20 , and 0°C , four products could be detected, namely formaldehyde, formic acid, carbon dioxide, and the secondary ethene ozonide. The yield of secondary ethene ozonide decreases with increasing temperature, this species being hardly detectable at 0°C . The energy-rich carbonyl oxide H_2COO decomposes

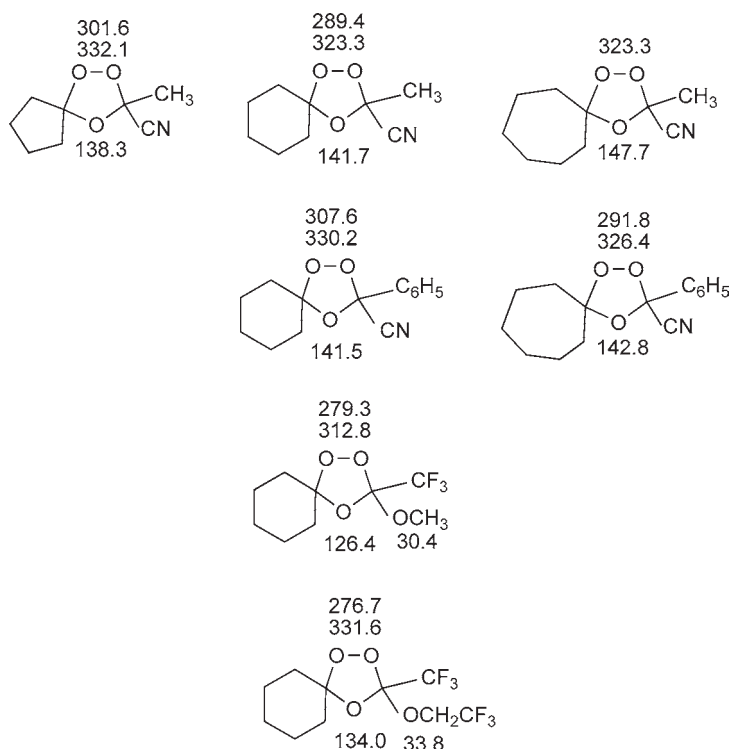


Figure 3 ^{17}O chemical shifts of some 1,2,4-trioxolanes with nonequivalent oxygen atoms within the peroxy bridge.

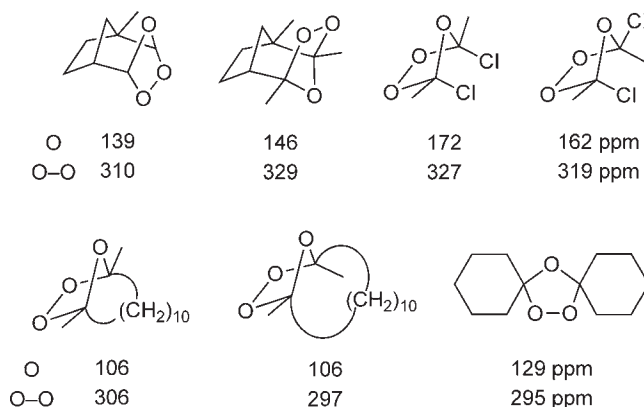
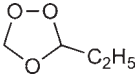
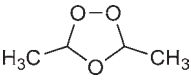
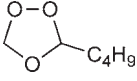
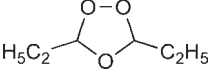
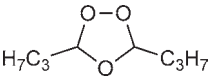
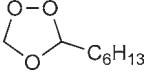


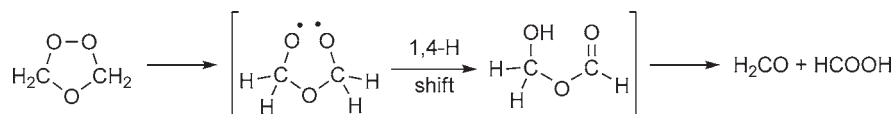
Figure 4 ^{17}O chemical shifts of some 1,2,4-trioxolanes with (almost) equivalent oxygen atoms within the peroxy bridge.

unimolecularly or reacts with H_2CO to form the 'hot' secondary ozonide, which may further decompose or be stabilized by collisions. The fact that equimolar amounts of HCOOH and H_2CO are formed upon decomposition of ethene ozonide may be mechanistically formulated via scission of the peroxide bond followed by a 1,4-H shift to give hydroxymethyl formate (Scheme 4). However, the latter could not be detected by FTIR.

Gas-phase ozonation of terminal alkenes $\text{RCH}=\text{CH}_2$ ($\text{R}=\text{C}_2\text{H}_5$ and $n\text{-C}_4\text{H}_9$) at -40 , -20 , 0 , and 20°C gave a series of compounds among which the secondary ozonides are stable in the gaseous mixture but their yields steeply decrease with increasing temperature. The R group length does not influence the formation of the secondary ozonide. From the product distribution, which also includes CO , CO_2 , H_2CO , RCHO , and RCOOH among others, one can conclude that a CO species of type H_2COO is more efficiently stabilized at low temperatures than an RHCOO species. Due to the low vapor pressure of 1-octene ($\text{RCH}=\text{CH}_2$, $\text{R}=n\text{-C}_6\text{H}_{13}$), gas-phase ozonolysis could be performed only at 20°C when no secondary ozonide could be detected by GC-MS or GC-FTIR in the gas or liquid

Table 4 Infrared and mass spectral data of 1,2,4-trioxolanes according to <1999J(P2)239>

Ozonide	ν (in cm^{-1}) (relative intensity)	m/z (rel. int. %)	Highest peak, m/z
	948 (0.45), 955 (0.45), 468 (0.46), 1082 (1.00), 1092 (0.80), 2887 (0.39), 2897 (0.74), 2908 (0.36), 2956 (0.11), 2970 (0.47), 2984 (0.26)	29 (100), 30 (92), 28 (74), 46 (67), 45 (52), 44(31), 18 (16), 76 (10)	76 (10), M^+
	967 (0.39), 973 (0.42), 984 (0.41), 1066 (0.76), 1103 (0.87), 1117 (0.85), 1391 (0.29), 1470 (0.15), 2894 (1.00), 2963 (0.50), 2980 (0.193)	29 (100), 27 (38), 28 (36), 31 (23), 30 (17), 57 (12), 26 (12), 75 (10)	104 (1.2), M^+
	900 (0.14), 1128 (1.00), 1349 (0.12), 1386 (0.27), 1394 (0.28), 1452 (0.05), 2908 (0.28), 3005 (0.18)	43 (100), 45 (41), 44 (34), 29 (34), 89 (16), 15 (15), 60 (11), 31 (10)	104 (5.0), M^+
	984 (0.26), 1065 (0.62), 1107 (0.82), 1209 (0.04), 1325 (0.07), 1390 (0.24), 1466 (0.12), 2890 (0.85), 2967 (1.00)	29 (100), 44 (60), 41 (57), 27 (41), 28 (26), 43 (25), 39 (23), 57 (23)	104 (0.8), $\text{M} - 28$
	896, (0.09), 959 (0.33), 1017 (0.29), 1122 (0.92), 1297 (0.09), 1386 (0.35), 1470 (0.27), 2894 (0.83), 2950 (0.55), 2979 (1.00)	29 (100), 57 (43), 28 (33), 27 (27), 31 (23), 103 (17), 41 (11)	132 (1.5), M^+
	957 (0.07), 993 (0.09), 1024 (0.11), 1088 (81.00), 1125 (0.19), 1191 (0.06), 1294 (0.069), 1364 (0.14), 1395 (0.23), 1476 (0.23), 2887 (0.50), 2938 (0.25), 2972 (0.65)	43 (100), 41 (26), 27 (17), 29 (10), 72 (8), 73 (7), 39 (7), 55 (7)	117 (0.9), $\text{M} - \text{C}_3\text{H}_7$
	963 (0.49), 1057 (0.82), 1103 (0.91), 1200 (0.12), 1225 (0.09), 1325 (0.16), 1380 (0.34), 1395 (0.28), 1463 (0.35), 2855 (0.82), 2953 (1.00)	43 (100), 41 (62), 29 (56), 44 (47), 55 (45), 70 (35), 57 (29), 45 (27)	132 (1.4), $\text{M} - 28$

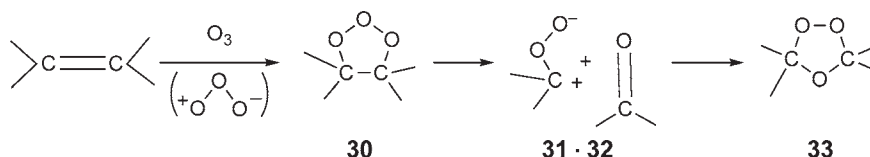
**Scheme 4**

phase formed by condensation. Products were in this case CH_2O , heptanal, hexane, hexyloxirane, and hexyl formate. Nevertheless, the secondary 1-octene ozonide (3-hexyl-1,2,4-trioxolane) was formed in the gas phase and it decomposed into heptanal and formic acid.

The gas-phase ozonation of internal alkenes $\text{RHC}=\text{CHR}$, with $\text{R}=\text{CH}_3$, C_2H_5 , and $(\text{H}_3\text{C})_2\text{CH}$, at -40 , -20 , 0 , and 20°C gave among other products secondary ozonides in relatively high yields. The combined yields in *cis*- and *trans*-ozonides increase considerably with the steric bulk of the R group but show less temperature dependence than in the case of terminal alkenes $\text{RCH}=\text{CH}_2$. This behavior is again explained by a more efficient stabilization of the H_2COO intermediate at low temperatures, this species being not formed in the ozonation of $\text{RHC}=\text{CHR}$. Similarly to the ozonation reactions in solution, the gas-phase reaction of *trans*- $\text{RHC}=\text{CHR}$ is stereoselective showing a preference for the *trans* secondary ozonide.

Ozonation of 2,3-dimethyl-2-butene in the gas phase at -40°C failed to give an isolable ozonide; instead, acetone (major product) and acetone peroxide with other minor products were formed. This parallels the behavior in solution when tetramethylethene ozonide could not be obtained. However, by performing the reaction on the surface of finely divided polyethylene (maximum particle diameter $20\text{ }\mu\text{m}$), this ozonide could be obtained and it proved to be stable <1985JA5309>.

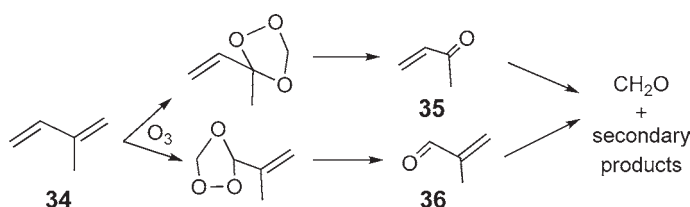
The original Criegee mechanism <1957RCP111, 1957RCP111, 1975AGE745> with its more recent refinement <1991CPL(187)491, 1991CPL(187)491, 1997JOC2757> can thus be extended to operate also in the gas phase. The initially formed primary ozonide **30** rearranges to form an electrostatically stabilized dipolar complex composed of the carbonyl oxide **31** and a carbonyl component **32** that subsequently decays into the secondary ozonide **33** (Scheme 5).



Scheme 5

The carbonyl component can be externally supplied as in the co-ozonolysis reactions (see Section 6.06.8.2) and other dipolarophiles can be used to trap the intermediate CO. Two types of rotations of the carbonyl component can take place relative to the CO <1997JOC2757>: one type is in the plane of the heavy atoms which leads to the same stereochemistry as in the original alkene; the other type is a rotation in a plane perpendicular to it leading to inversion. The preference of *trans*-alkenes to furnish in the gas phase the *trans*-ozonides indicates a preference for the ‘in-plane rotation’ and geminate pair recombination within the dipolar complex. At low temperatures this complex appears to be stabilized.

Gas-phase ozonolyses of ethene, *cis*- and *trans*-but-2-ene, isoprene, as well as several monoterpenes such as α -pinene, β -pinene, 3-carene, limonene, and β -myrcene have been performed by trapping the reaction products in O_2 -doped argon matrices and recording the IR spectra <2000SAA2605>. Bands characteristic for the secondary ozonides were identified after bleaching by broad-band UV-Vis photolysis. In the case of isoprene **34**, a secondary ozonide appears to be formed more likely at the more substituted double bond; however, the two possible carbonyl compounds **35** and **36** could not be put into evidence by infrared (IR) in the reaction condensate as these reacted further with O_3 (Scheme 6).



Scheme 6

On studying the ozonolysis of *cis*- or *trans*-2-butene in gas phase at 295 K and 730 torr, it was found by FTIR spectroscopy <1997IJK461> that the Criegee intermediate $\text{H}_3\text{C}-\text{CH}-\text{OO}$ behaves similarly in gas and liquid phase. With HCOOH it yields hydroperoxymethyl formate $\text{O}=\text{CH}-\text{O}-\text{CH}_2-\text{OOH}$ (which had previously been assumed <1994IJK1975, 1995CPL(246)150> to be hydroxymethyl formate). Also, this Criegee intermediate reacts with added $\text{H}_3\text{C}-\text{CH}=\text{O}$ forming butene ozonide, and with added formaldehyde forming propene ozonide. A minor product is acetoin.

6.06.3.5 Photoelectron Spectroscopy

No significant developments have been reported since the publication of CHEC-II(1996) <1996CHEC-II(4)581>.

6.06.3.6 Other Physical Methods

No significant developments have been reported since the publication of CHEC-II(1996) <1996CHEC-II(4)581>.

6.06.4 Thermodynamic Aspects

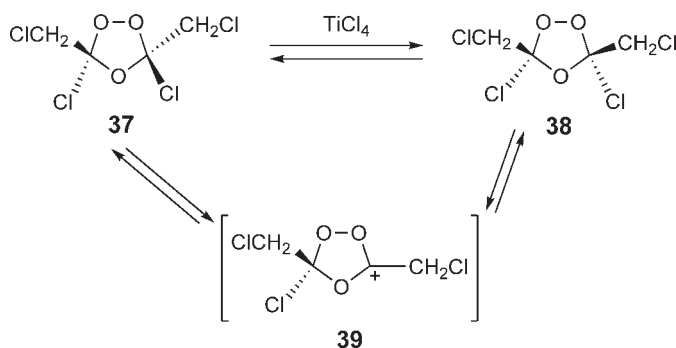
No other experimental significant developments have been reported since the publication of CHEC-II(1996) (see Section 6.06.2) <1996CHEC-II(4)581>.

6.06.5 Reactivity of Ring Aspects

6.06.5.1 Thermal and Photochemical Reactions Formally Involving No Other Species

6.06.5.1.1 Rearrangements

1,2,3,4-Tetrachloro-2-butene forms upon ozonation two stereoisomeric ozonides that can be separated by crystallization and HPLC. The *trans*-form **37** crystallizes from the mother liquor and can be thus separated in pure form. Its structure could be unambiguously proved by single crystal X-ray diffraction <1997AXC911>. The HPLC separation of the 1:1 mixture of stereoisomers **37** and **38** provides the *cis*-isomer as a colorless oil at room temperature in pure form. Caution should be exercised as the elution order is dependent on the solvent system used: with pentane–dichloromethane (98:2) the *cis*-ozonide is eluted first, while with *n*-hexane–ethyl ether (97:3) the *trans*-ozonide has a shorter retention time on silica gel <1997JPR650>. Interestingly, an isomerization reaction was put into evidence upon treatment with TiCl_4 at -40°C in dichloromethane. From the *cis*-ozonide a 8:92 mixture of *cis*–*trans* was obtained while from the *trans*-ozonide a 10:90 mixture resulted in over 90% yield. No by-products were isolated. The *trans*-ozonide is thus the thermodynamically favored form. Most probably, a carbenium ion **39** and not an oxonium ion coordinating a Ti atom, which could ring-open, is formed as an intermediate (Scheme 7).



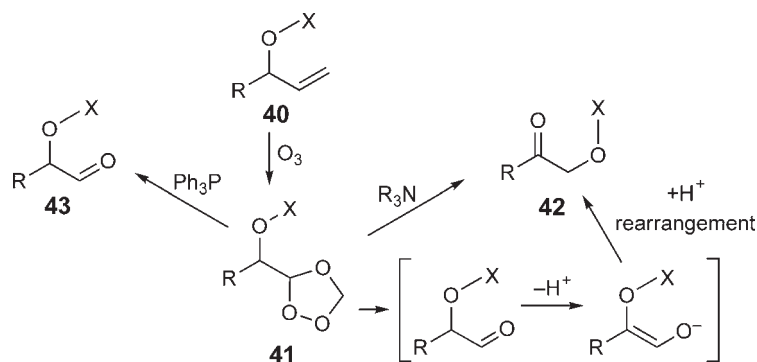
Scheme 7

An interesting rearrangement was reported on treating ozonides **41** of allyl esters (**40**, $\text{X} = \text{Ac}$, Bz , Me_3CCO) or silyl ethers ($\text{X} = \text{SiMe}_2\text{Bu}^t$) with tertiary amines (but not with triphenylphosphine, which affords the expected aldehydes). Thus, when $\text{R} = \text{Ph}$, triethylamine is sufficiently basic to deprotonate the resulting aldehyde which rearranges to the ketonic product **42**, but with aliphatic R groups more basic tertiary amines have to be used for this deprotonation, such as 1,8-diazabicyclo[5.3.0]undec-7-ene (DBU) (Scheme 8) <2005TL1365>.

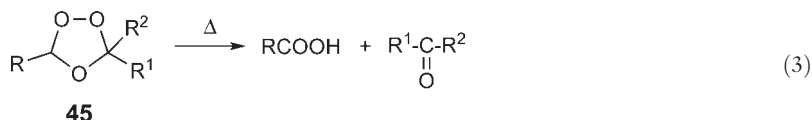
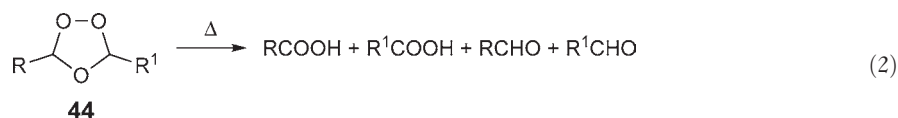
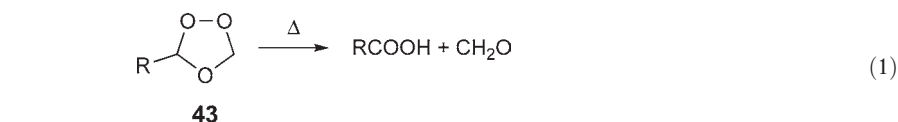
6.06.5.1.2 Thermolysis

Most ozonides decompose upon heating although highly substituted ones can have sharp melting points. Handling of peroxidic materials should be done with caution and work with large quantities should be avoided.

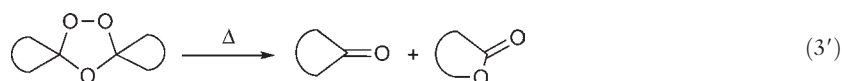
Monosubstituted ozonides **43** decompose to formaldehyde and the corresponding carboxylic acid. Unsymmetrical disubstituted ozonides **44** form a mixture of the two possible acids and two aldehydes. Trisubstituted ozonides **45** give a ketone and a carboxylic acid (Equations 1–3) <1996CHEC-II(4)581>.



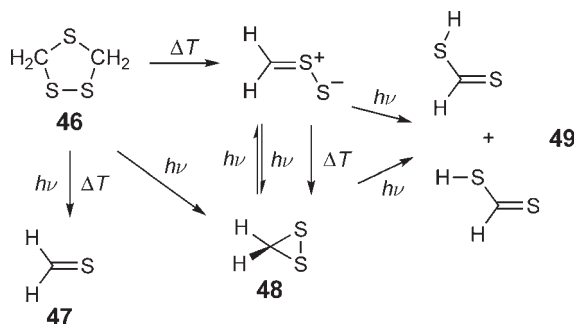
Scheme 8



An earlier study had shown that tetrasubstituted ozonides decompose thermally to ketones and esters (Equation 3') <1991CB391>.



Unlike 1,2,4-trioxolane, 1,2,4-trithiolane **46** is a stable, easily accessible substance. On heating it at 950°C in high vacuum followed by condensation of the products on a CsI window at 10 K and examination of the IR spectrum, one could detect, along with unreacted material and thioformaldehyde **47**, the presence of thiosulfine (thioformaldehyde-*S*-sulfide) and dithiirane **48** <2001AGE393>. The calculated spectral data from their calculated geometry <1998SR1> allowed to estimate their formation ratio as 67:33, and only 80:20 at 850°C . Below 650°C no pyrolysis products can be detected. Photochemical interconversions of these compounds, including the formation of the two diastereomers of dithioformic acid **49**, are indicated in Scheme 9. Remarkably, irradiation of 1,2,4-trithiolane ($\lambda = 313\text{ nm}$) affords only decomposition products of thiosulfine. It was concluded that thiosulfine is a dipolar ylide



Scheme 9

rather than a singlet diradical. Its isomerization into the more stable dithiirane (by $5.9 \text{ kcal mol}^{-1}$) must overcome an activation barrier of $28.6 \text{ kcal mol}^{-1}$ <2002SR209, 2003CCR167>.

The labile unsubstituted system thiosulfine (thiocarbonyl *S*-sulfide/dithiirane) was obtained by matrix isolation techniques from the unsubstituted 1,2,4-trithiolane <2001AGE393>. On the other hand, it was reported that tetra-substituted dithiiranes were quite stable <2005T6693>. In contrast to sulfines $\text{R}_2\text{C}=\text{S}=\text{O}$ which are stable compounds, thiosulfines with one ($\text{MeCH}=\text{S}^+-\text{S}^-$) or two methyl groups ($\text{Me}_2\text{C}=\text{S}^+-\text{S}^-$) had to be generated by flash vacuum pyrolysis of the corresponding 2,5-dimethyl- and 2,2,5,5-tetramethyl-1,2,4-trithiolanes at $500\text{--}700^\circ\text{C}$ and trapped in an argon matrix at 10 K on a CsI window. A small amount of the isomeric dimethyldithiirane was formed by isomerization of the thiosulfine. The conversion is complete upon irradiation for 4 min ($\lambda = 366 \text{ nm}$) at 10 K. Monomethyl derivatives present diastereoisomerism and rearrange further photochemically into dithioacetic acid or thermally into stereoisomeric propen-2-yl-disulfanes <2006EJO3721>.

6.06.5.1.3 Photolysis

No significant developments have been reported since the publication of CHEC-II(1996) <1996CHEC-II(4)581>.

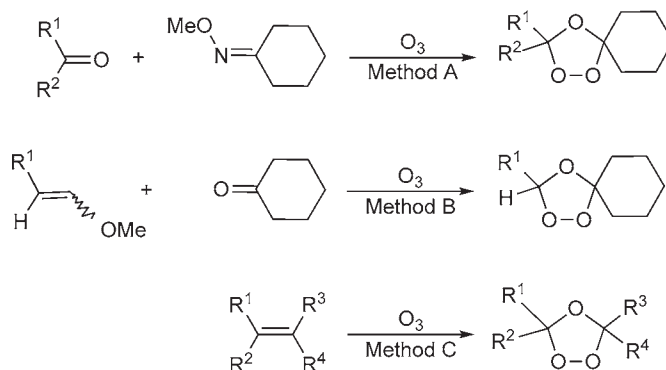
6.06.5.1.4 Polymerization

No significant developments have been reported since the publication of CHEC-II(1996) <1996CHEC-II(4)581>.

6.06.5.2 Reactions with Electrophiles

6.06.5.2.1 Reactions with Lewis acids and Brønsted acids

Three methods were used for making tri- or tetra-substituted 1,2,4-trioxolanes in the investigations of the reaction between these secondary ozonides and Lewis acids: co-ozonolysis of oximes and ketones (method A), co-ozonolysis of enol ethers and ketones (method B), and ozonolysis of alkenes (method C, **Scheme 10** and **Table 5**) <2000J(P1)3006>.

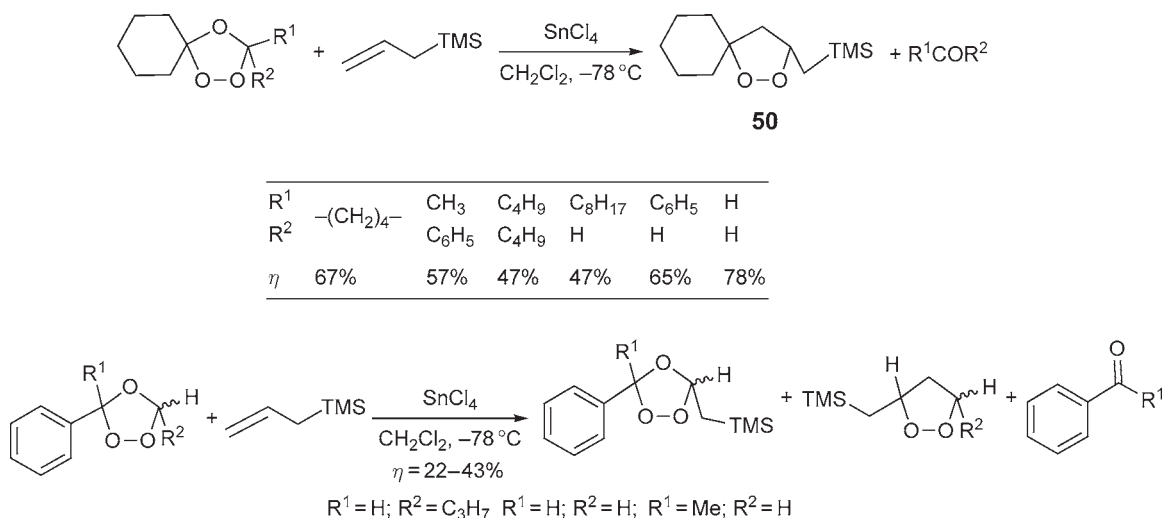


Scheme 10

Table 5

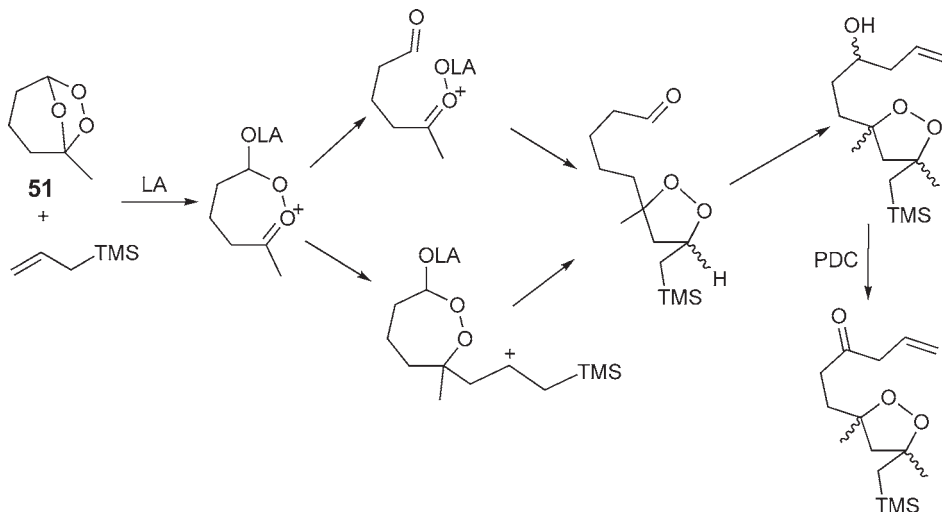
Ozonide	R^1	R^2	R^3	R^4	Method	Yield (%)
		$-(\text{CH}_2)_4-$		$-(\text{CH}_2)_5-$	A	60
		$-(\text{CH}_2)_5-$		$-(\text{CH}_2)_5-$	A	67
		$-(\text{CH}_2)_6-$		$-(\text{CH}_2)_5-$	A	63
	CH_3	Ph		$-(\text{CH}_2)_5-$	A	57
	C_4H_9	C_4H_9		$-(\text{CH}_2)_5-$	A	47
	C_8H_{17}	H		$-(\text{CH}_2)_5-$	B	47
	Ph	H		$-(\text{CH}_2)_5-$	B	65
	H	H		$-(\text{CH}_2)_5-$	C	78
	CH_3	$\text{C}(\text{CH}_3)_3$		$-(\text{CH}_2)_5-$	A	53
	H	Ph	H	C_3H_7	C	73
	H	Ph	H	H	C	77
	CH_3	Ph	H	H	C	61
	H		$-(\text{CH}_2)_3-$	CH_3	C	73

Tin tetrachloride mediates the reaction of ozonides with electron-rich alkenes such as allyltrimethylsilane forming 1,2-dioxolanes **50** in moderate yields (**Scheme 11**) <1999TL6553>.



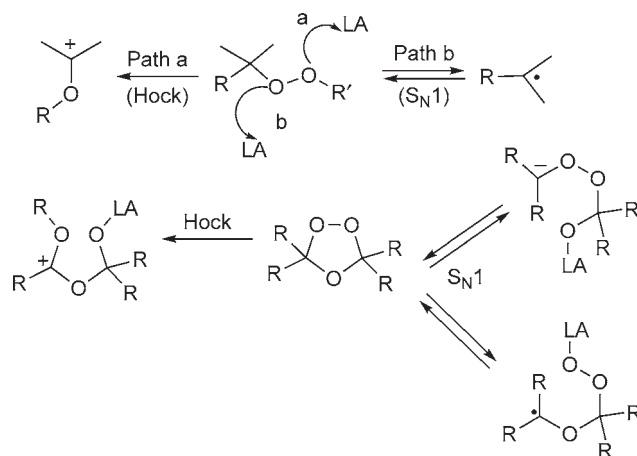
Scheme 11

Allylation of 1-methylcyclopentene ozonide **51**, at the most-substituted ozonide carbon, with SnCl₄ as a Lewis acid (LA) and an excess of allyltrimethylsilane was regiospecific but the stereoselectivity was modest with a 30:70 mixture of *cis/trans*-isomers, each a 1:1 mixture of epimers at the exocyclic carbinol. On oxidation with pyridinium dichromate (PDC), the stereogenic center due to the secondary alcohol vanishes and only the two diastereomeric ketones in a 30:70 ratio are obtained. The probable mechanism involves regiospecific attack of the LA at the ether bridge leaving a tertiary carbocationic center at the carbonyl oxide; this peroxycarbenium ion is then trapped by the allyltrimethylsilane (**Scheme 12**) <1999TL6553, 2000J(P1)3006>.



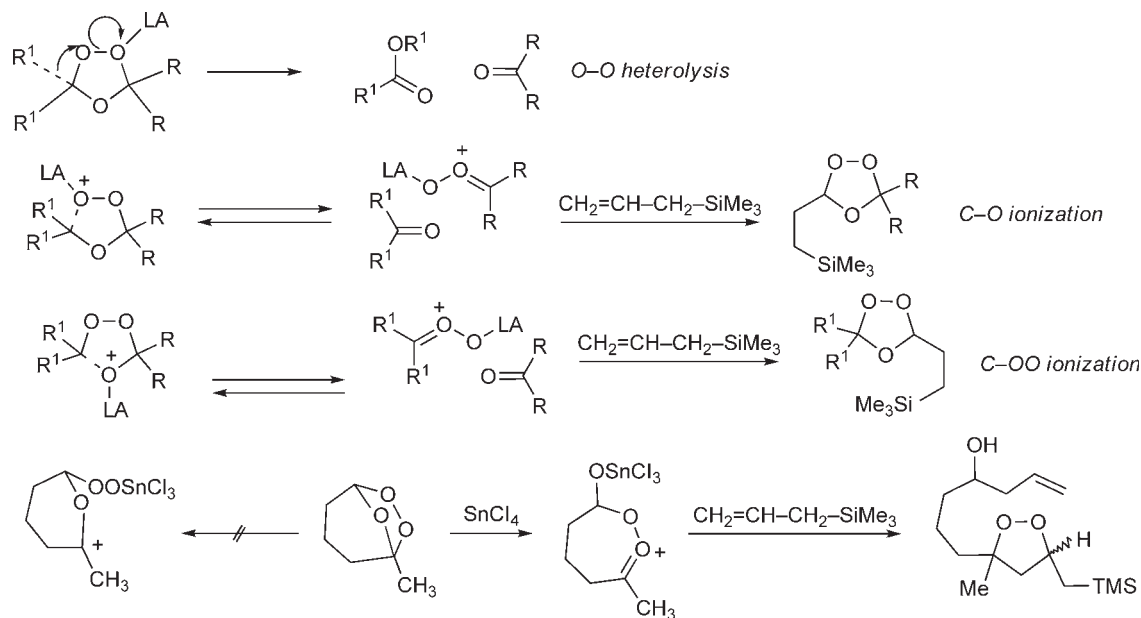
Scheme 12

Whereas TiCl₄ interacts with the peroxide bridge yielding ethers, SnCl₄ promotes a selective displacement of the alkoxide to form peroxides. Heterolysis of an O–O bond (Hock reaction) furnishes oxycarbenium ion intermediates via 1,2-shifts (path a), whereas acid-catalyzed C–O ionization affords carbenium ions (path b, **Scheme 13**).



Scheme 13

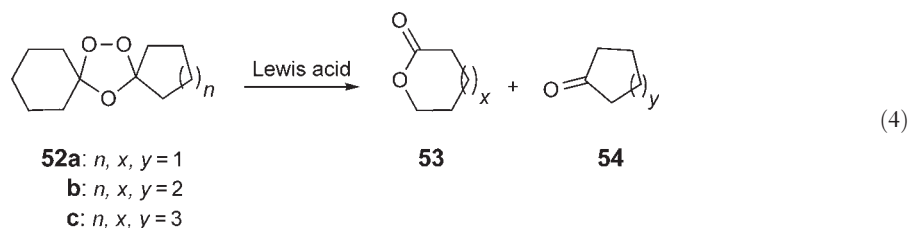
In more detail these pathways and their coupling with Lewis-acid-catalyzed allylation using allyltrimethylsilane are shown in [Scheme 14](#) <2000J(P1)3006>.



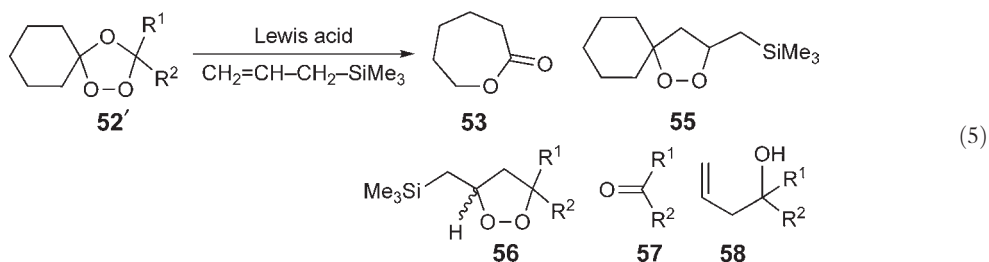
Scheme 14

Spiro-ozonides **52** undergo fragmentation under the influence of Lewis acids. The spiro-6,6-ozonide **52b** underwent Hock-type fragmentation yielding a 1:1 mixture of caprolactone and cyclohexanone. The spiro-6,5- **52a** and -6,7-ozonides **52c** reacted similarly favoring the product derived from migration of a cyclohexyl C-C bond; TiCl₄ promoted reactions at lower temperatures than those required by SnCl₄ or Me₃SiO-SO₂-CF₃ (Equations 4-6 and Tables 6-8) <2000J(P1)3006>.

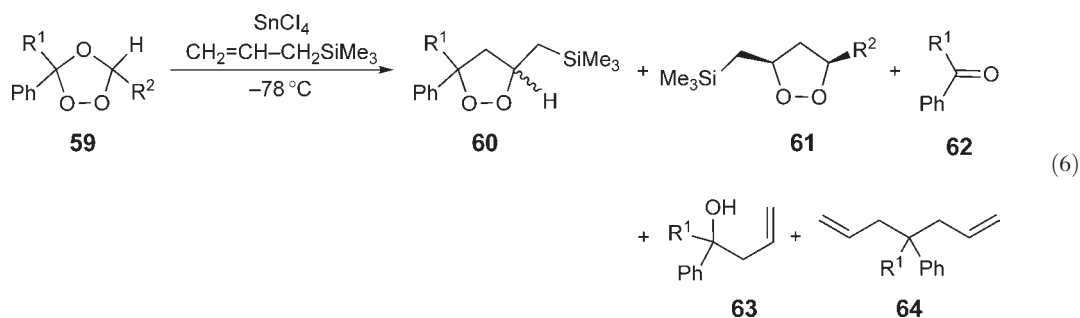
1-Methylcyclopentene ozonide **51** can also be allylated via this S_N1-type reaction forming in good yields a 3,5,5-trisubstituted dioxolane **65** as a single regioisomer constituted by two separate *cis*- (35% each) and two *trans*- (15% each) isomers. The assignments were confirmed by transformation of the secondary alcohol into the acetate **66** or by its oxidation with PDC to the corresponding ketone **67** (Scheme 15).

**Table 6** Fragmentations of spiro-ozonides with Lewis acids

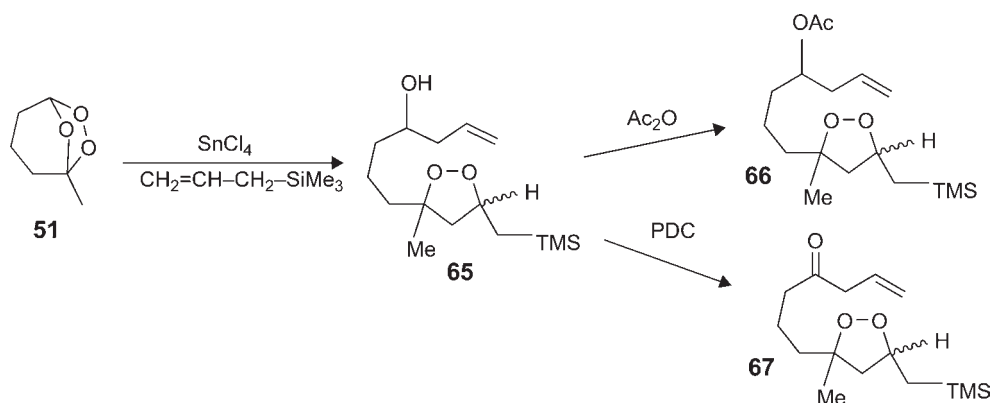
Ozonide	Lewis acid	Temperature (°C)	Yield (%)					
			53a	53b	53c	54a	54b	54c
52a	TiCl ₄	−78	18	32		30	20	
52a	SnCl ₄	0	5	39		4	11	
52a	TMSOTf	rt	14	36		36	14	
52b	TiCl ₄	−78		52			48	
52b	SnCl ₄	0		49			51	
52b	TMSOTf	rt		50			50	
52c	TiCl ₄	−78		43	5		11	41
52c	SnCl ₄	0		44	5		6	45
52c	TMSOTf	rt		49	1		1	49

**Table 7** Reactions of spiro-ozonides with Lewis acids and allyltrimethylsilane

Ozonide	R ¹	R ²	Lewis acid	Temp. (°C)	Yield (%)				
					53	55	56	Ketones 57	58
52'a	−(CH ₂) ₄ −		SnCl ₄	−78 to 0	11	50		trace	
52'b	−(CH ₂) ₅ −		TiCl ₄	−78	9	0		35,comb	
52'b	−(CH ₂) ₅ −		SnCl ₄	−78 to 0	17	57		trace	
52'b	−(CH ₂) ₅ −		TMSOTf	−78 to 0		NR			
52'b	−(CH ₂) ₅ −		SbCl ₅	−78 to rt	major	decomp.		major	
52'c	−(CH ₂) ₆ −		SnCl ₄	−78 to 0	39	24		trace	
52'd	CH ₃	Ph	SnCl ₄	−78 to 0	25	61		93	
52'e	C ₄ H ₉	C ₄ H ₉	SnCl ₄	−78 to 0	40	14		70	75
52'f	H	C ₈ H ₁₇	SnCl ₄	−78		56			50
52'g	H	Ph	SnCl ₄	−78		79			13
52'h	H	H	SnCl ₄	−78		10			
52'i	CH ₃	C(CH ₃) ₃	SnCl ₄	−78 to 0	31	21	9 (cis)		

**Table 8** Reactions of ozonides with Lewis acids and allyltrimethylsilane

Ozonide	R ¹	R ²	60 (%; <i>cis:trans</i>)	61 (%)	Ketones 62 (%)	63 (%)	64 (%)
59a	H	C ₃ H ₇	15 (1:1)	7	39	29	
59b	H	H	15 (1:1)		22	24	
59c	CH ₃	H	9 (1:1)		43		2.5

**Scheme 15**

It was shown [<1999BML3255>](#) that a crystalline ozonide obtained by ozonolysis of the *N*-allylamide of Cbz-L-phenylalanine inhibits papain, a cysteine protease. Reduction of that ozonide in excess dimethyl sulfoxide (DMSO) generates *in situ* a peptide aldehyde, as proved by coupling with a stabilized Wittig ylide forming thereby an unsaturated ester.

6.06.5.2.2 Reactions at double bonds

No significant developments have been reported since the publication of CHEC-II(1996) [<1996CHEC-II\(4\)581>](#).

6.06.5.2.3 Oxidation

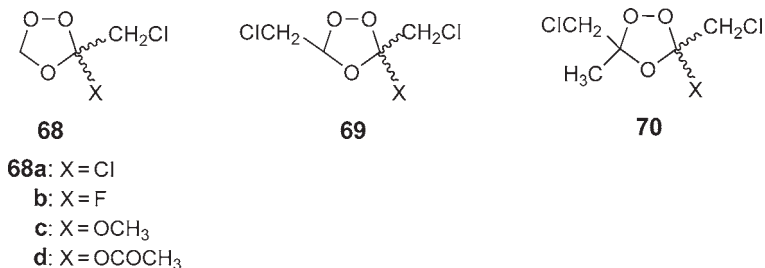
No significant developments have been reported since the publication of CHEC-II(1996) [<1996CHEC-II\(4\)581>](#).

6.06.5.3 Reactions with Nucleophiles

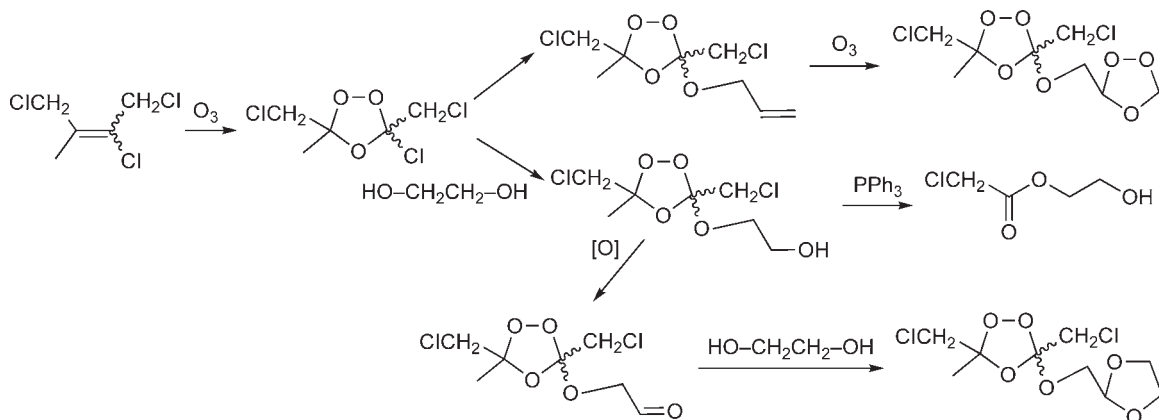
6.06.5.3.1 Reactions with O-nucleophiles and halogens

As it is well known, acyloxy, alkoxy, or phenoxy groups connected to sp²-hybridized carbon atoms in alkenes or aromatics are unreactive to nucleophilic substitution. However, after alkene ozonolysis such groups become attached to sp³-hybridized carbon atoms and become reactive. It was shown [<1989TL1511>](#) that such substitutions have to be carried out at 40 °C when they compete with thermolytic reactions of the ozonides, lowering the yields. However, if 2,3-dichloropropene and *cis*- or *trans*-1,2,4-trichloro-2-butene are ozonized, one obtains stable ozonides **68a–70**

<1993CB1843>. Then in the presence of silver tetrafluoroborate, it is possible to replace chloro by fluoro groups (to give **68b**), and the products may be kept in Teflon vials (but not in glass). Even more stable are the methoxy substitution products **68c** obtained similarly in methanol in the presence of potassium carbonate, or the acetoxy substitution products obtained in acetic acid with AgBF_4 <1995JOC8062>.

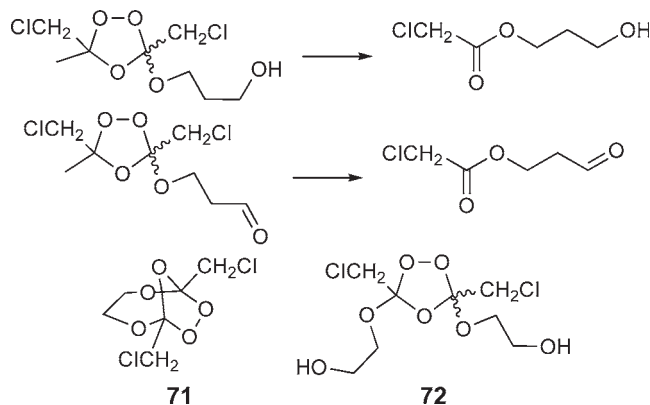


Starting from 1,2,4-trichloro-3-methyl-2-butene, a mixture of stable stereoisomeric ozonides was obtained. After substitution with allyl alcohol at room temperature, the two diastereoisomers could be separated by HPLC. A second ozonation in pentane afforded the diozonide, which is stable at room temperature but explodes on heating <1997LA2581>. Structures of ozonides were proved by ¹H, ¹³C, and ¹⁷O NMR, and by reactions with triphenylphosphine opening the ozonide ring to the corresponding carbonyl compounds. Swern oxidation at -60 °C with dimethylsulfoxide and oxalyl chloride gave an aldehyde-ozonide that underwent intermolecular condensations at room temperature, but could be stabilized with ethylene glycol into its cyclic acetal (Scheme 16).



Scheme 16

Similar reactions were carried out with 1,3-propanediol (Scheme 17). The same paper describes the reaction of ethylene glycol with the tetrachloro-ozonide mentioned in the previous formulas leading to a mixture of a bicyclic



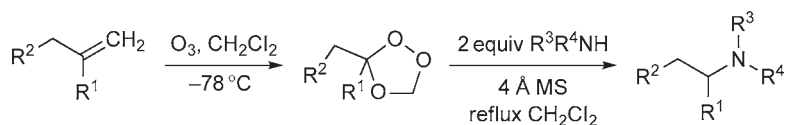
Scheme 17

ozonide **71** formed by equimolar amounts of ozonide and glycol, together with a monocyclic ozonide-diol **72** from 1 mol of ozonide and 2 mol of glycol.

Substitution of chlorine by acetate increases tremendously the stability of the 1,2,4-trioxolane. Thus, whereas *trans*-2,3-dichloro-2-butene ozonized on polyethylene and then dissolved in ether gave no signal for any ozonide left after removal of the solvent at room temperature, if the same product on polyethylene was extracted by acetic acid with sodium acetate, the crystalline 3,5-dimethyl-3,5-diacetoxy-1,2,4-trioxolane with unknown stereochemistry was identified by its ^{17}O and ^{13}C NMR spectra, elemental analysis, and reduction with Ph_3P to 2 molar equivalents of acetic anhydride. This ozonide cannot be obtained by ozonizing the corresponding alkene. A similar nucleophilic replacement of bromo substituents from the ozonides of *cis*- and *trans*-2,3-dibromo-1,4-dichloro-2-butene by fluoro (on treatment with AgBF_4 and LiF at -70°C in diethyl ether) or by methoxy (on treatment with AgBF_4 in methanol at -70°C) proved the existence of the elusive bromo-substituted ozonides <1996JPR307>.

6.06.5.3.2 Reactions with N-nucleophiles

On reacting with secondary amines, ozonides from terminal alkenes form tertiary amines in over 80% yield (Scheme 18) <1993TL5309, 1993TL5309, 1995T5019>. Molecular sieves (4 Å) are needed in this reaction, reminiscent of the Leuckart–Wallach reductive amination. In experiments involving the bicyclic secondary ozonide of 1-phenylcyclopentene, it was found <1995T5019> that tertiary amines act as bases abstracting the proton and yielding only 5-oxo-5-phenylvaleric acid in an E1cb mechanism; triphenylphosphine becomes oxidized and affords only 5-oxo-5-phenylvaleraldehyde; dimethyl sulfide furnishes mostly the aldehyde (92%) along with a small amount of the acid (7%).



Scheme 18

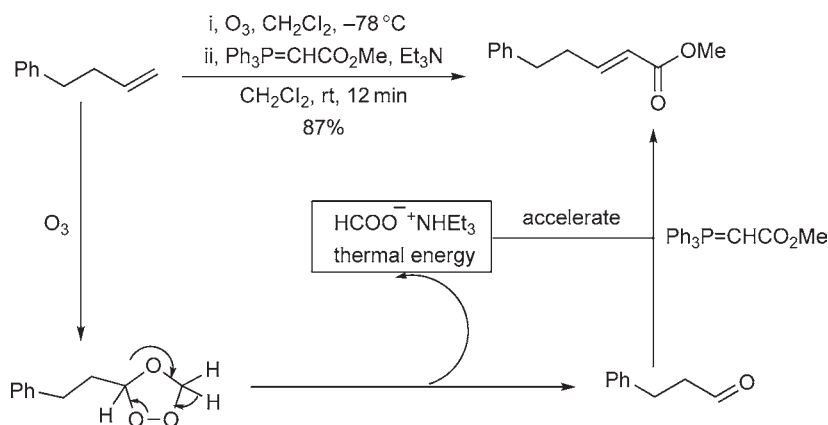
On stirring at room temperature ozonides of terminal alkenes (prepared in dichloromethane at -70°C) with a polymer-supported tertiary amine obtained from chloromethylated poly(styrene/divinylbenzene) and piperidine, followed by filtration and concentration under reduced pressure, the products (aldehydes or ketones) can be obtained easily in almost pure form in high yields <2003T493>. However, yields are low for cycloalkenes because apparently they form monomeric and polymeric ozonides.

An analogous soluble liquid-phase reagent with two triphenylphosphine groups tethered to poly(ethylene glycol) gave better yields of aromatic aldehyde products in the reduction of ozonides than with triphenylphosphine in solution-phase or supported on solid-phase <1999JOC5188>. The comparison was made with two substituted styrenes, α -vinylpyridine and 4-phenyl-1-butene; also 1,2-dihydronaphthalene gave a higher yield of 2-propanal-benzaldehyde. However, the regeneration of the reagent with lithium aluminium hydride in tetrahydrofuran for a new reduction cycle provided only a 75% yield.

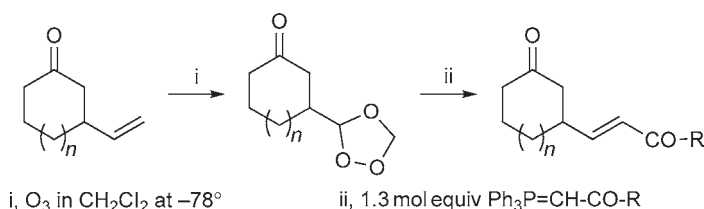
6.06.5.3.3 Reactions with C-nucleophiles

The reaction of ozonides with ester-substituted phosphorane ylides affording unsaturated esters had been mentioned earlier <1996CHEC-II(4)581>. It was now found <1993TL5309, 1995T7937> that a one-pot procedure could convert terminal alkenes by ozonolysis at -78°C in the presence of $\text{Ph}_3\text{P}=\text{CH}-\text{CO}_2\text{Me}$ and Et_3N into *trans*-unsaturated esters. The reaction mechanism involves the ammonium formate by-product as catalyst, and thermal energy, as proved by separate experiments (Scheme 19).

The tandem ozonolysis plus Wittig–Horner reaction can be carried out also with terminal alkenes that have carbonyl groups, and can also be used for preparing *trans*-unsaturated ketones ($\text{R}=\text{CO}-\text{Ph}$, $\text{CO}-\text{Me}$) or aldehydes ($\text{R}-\text{CO}=\text{CHO}$), but the yields are in this case lower than for unsaturated esters ($\text{R}=\text{CO}_2\text{Me}$, $\text{CO}_2\text{CH}_2\text{Ph}$, CO_2-Bu^t) as shown in Scheme 20 <2000T9269>. If the phosphorane is treated with D_2O , the result is $\text{Ph}_3\text{P}=\text{CD}-\text{CO}-\text{R}$, and it yields a deuterated unsaturated carbonyl compound <2000SC97>.



Scheme 19



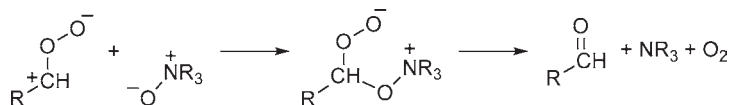
Scheme 20

Allyl trimethylsilane can be used to displace the reactive chlorine atom in ozonide **70** and further treatment with ozone gives a diozonide. Similarly, a triozone can be obtained from the corresponding 2,4-bis-allyl ozonide [\[2004EJO3657\]](#).

6.06.5.3.4 Reactions and reductive ring cleavage

6.06.5.3.4(i) Reductive ozonolysis with aminoxides

An older paper [\[1971MI873\]](#) reported that ozonolysis of alkenes in the presence of tertiary amines resulted in the formation of aldehydes. A recent reinvestigation [\[2006OL3199\]](#) has shown that amine oxides were responsible for this 'reductive ozonolysis'. Indeed, pretreatment of the tertiary amines with ozone, giving rise to amine oxides, accounted for this phenomenon. A preparative method emerged, by treating the alkene (e.g., 1-decene) at 0°C with a solution of 2% O_3/O_2 in dichloromethane (2 equiv of ozone relative to the alkene) in the presence of an excess (about threefold molar excess) of *N*-methylmorpholine *N*-oxide, pyridine *N*-oxide, or 1,4-diazabicyclo[2.2.2]octane *N*-oxide (DABCO *N*-oxide). Yields of aldehydes (nonanal in the above example) were 80–96%, and the excess of amine oxide ensured the absence of residual ozonide (**Scheme 21**).

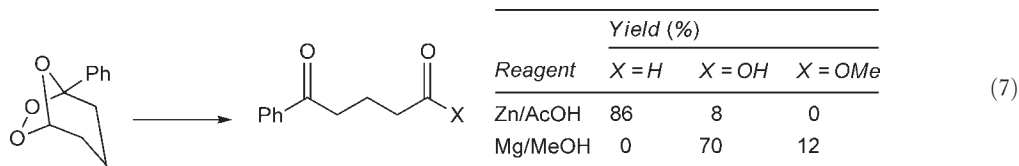


Scheme 21

This method can also be used in tandem reaction sequences, by adding to the crude reaction mixture after completion of the reaction a Grignard reagent (such as ethylmagnesium bromide) to prepare a secondary alcohol (3-undecanol in an overall yield of 53% in the above example).

6.06.5.3.4(ii) Reduction of ozonides to keto-acids

For reducing ozonides or sterically hindered peroxides, magnesium and methanol proved to be a better and mild reducing agent [<2004JOC2851>](#). Thus, the bicyclic ozonide prepared from 1-phenylcyclopentene, which is prone to base-mediated cleavage, was cleanly reduced by Mg/MeOH to the keto-acid with the ketonic methyl ester as a by-product, whereas reduction with zinc and acetic acid affords mainly the keto-aldehyde with the keto-acid as a by-product ([Equation 7](#)).



6.06.6 Reactivity of Substituents Attached to Ring Carbons

6.06.6.1 H-Substituents

No significant developments have been reported since the publication of CHEC-II(1996) [<1996CHEC-II\(4\)581>](#).

6.06.6.2 C-Substituents

No significant developments have been reported since the publication of CHEC-II(1996) [<1996CHEC-II\(4\)581>](#).

6.06.6.3 O-Substituents

No significant developments have been reported since the publication of CHEC-II(1996) [<1996CHEC-II\(4\)581>](#).

6.06.7 Ring Syntheses Classified by the Number of Rings Atoms in Each Component

The syntheses of five-membered rings containing three oxygen and/or sulfur atoms have been classified according to the precursor fragments [<1996CHEC-II\(4\)581>](#). The CHEC-II(1996) should be consulted for a complete description of these synthetic approaches.

6.06.8 Syntheses by Ring Transformation

6.06.8.1 Introduction

Since the publication of CHEC-II(1996), in the field of 1,2,4-trioxolane chemistry (also commonly known as ozonide chemistry), two research directions have been pursued. First, mechanistic investigations on how the primary ozonide is fragmenting have led to predictive rules that show that both steric and electronic factors need to be considered. Second, and more importantly, a relatively large number of chemical transformations have been performed on ozonides, remote from the heterocyclic moiety. This is of interest as the ozonide has proved to be stable in a number of chemical transformations and can thus function as a masked or protected aldehyde.

The mechanism proposed by Criegee for the ozonolysis of alkenes [<1975AGE745>](#) considers an initial π -complex between the alkene and ozone which decays via a 1,3-dipolar cycloaddition into a 1,2,3-trioxolane or primary ozonide, known also as the 'molozonide'. These compounds are unstable, even at low temperatures, and due to cycloreversion decompose into a carbonyl fragment and a CO, which may recombine by another 1,3-dipolar cycloaddition step to form the more stable 1,2,4-trioxolane ('secondary ozonide' or 'final ozonide' (see also [Section 6.06.2](#)).

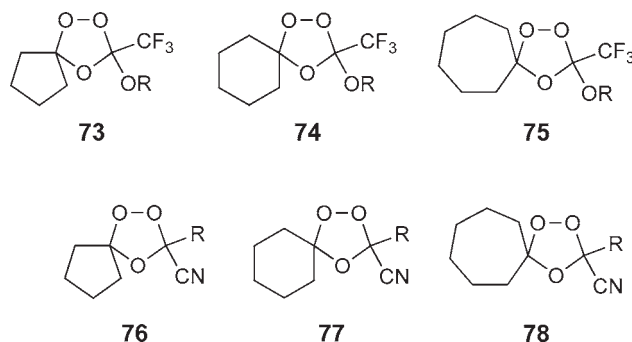
6.06.8.2 The Ozonolysis Reaction

6.06.8.2.1 The co-ozonolysis reaction

An important advancement has been the *in situ* generation of a CO, which is then trapped by an added carbonyl species. Substituted ozonides are thus quite easily made available without the need to prepare the parent alkenes. Especially ozonides from tetrasubstituted alkenes are not readily accessible so that this co-ozonolysis has preparative advantages.

O-Alkyl oximes are excellent precursors of COs as they react more slowly with ozone than alkenes. Initially <1995LA1571>, as added carbonyl species, acyl cyanides and esters of trifluoroacetic acid were used and the ozonides could be isolated usually in 25–60% yields. In an extension of this reaction, trapping could be performed by a variety of carbonyl compounds.

Although the ozonolysis of C=N-containing compounds has been reported repeatedly <B-1982MI(2)225>, it proceeded slowly and usually did not afford peroxidic compounds, except for a tetraoxa-dioxane obtained from the *O*-methyloxime of pivalophenone. However, as shown in <1995LA1571>, *O*-methyloximes of cycloalkanones do furnish satisfactory yields of 1,2,4-trioxolanes when ozonolyzed in the presence of reactive carbonyl compounds such as alkyl trifluoroacetates (R = Me, CH₂CF₃, or *p*-O₂N-C₆H₄) or acyl cyanides (R = Me or Ph). The spirocyclic ozonides **73–78** thus obtained are stable at room temperature and have been characterized by reduction with Ph₃P and by ¹H, ¹³C, and ¹⁷O NMR spectra.

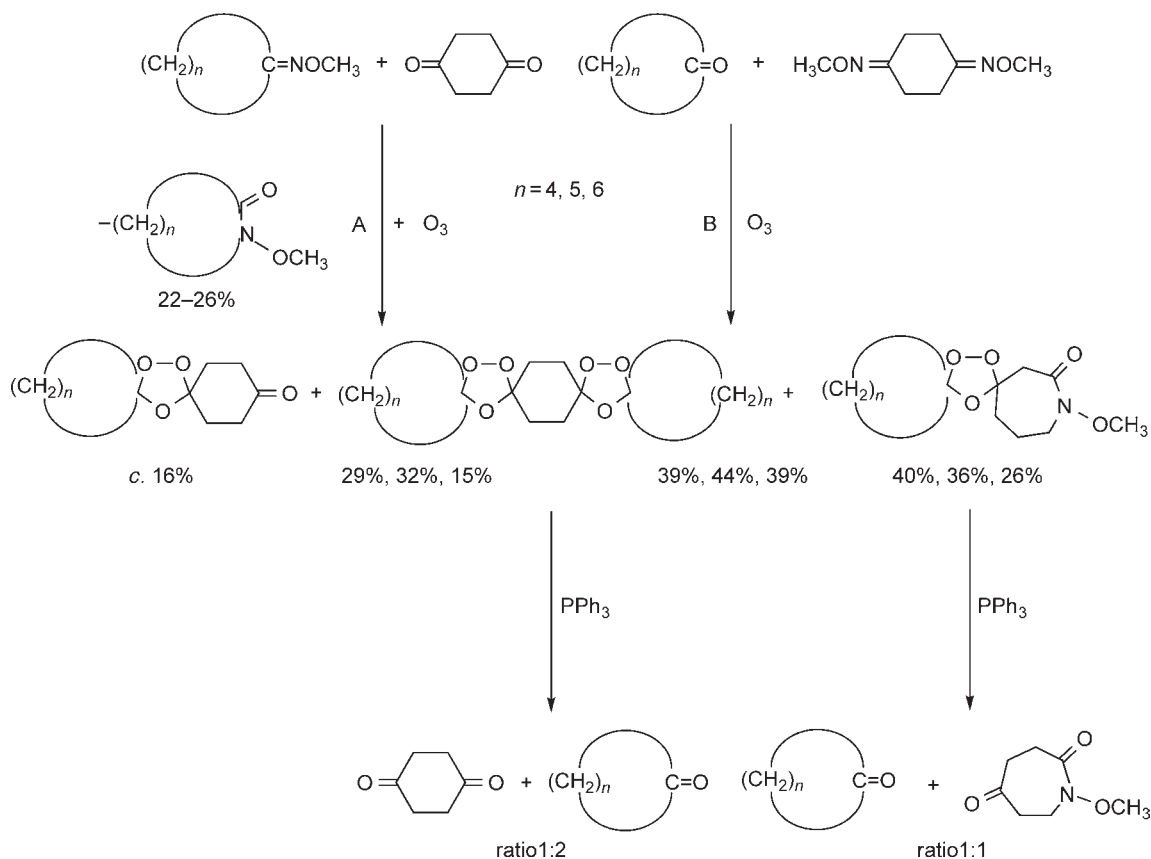


When starting co-ozonolyses either with a diketone and the *O*-methyloxime of a monoketone (route A), or with a monoketone and the bis-*O*-methyloxime of a diketone (route B), interesting results were obtained operating with cyclanone derivatives with ring sizes 5, 6, or 7 (Scheme 22) <1997T5463>. The diozonides are crystalline compounds, characterized by ¹H and ¹³C NMR spectra and by reduction to expected products using triphenylphosphine (PPh₃). Lower yields are shown for each of the ring sizes on the left-hand side for route A (when also a lactam derivative was obtained), and higher yields on the right-hand side for route B. Lactam formation is ascribed to oxidation of a C=N double bond yielding an oxaziridine which then rearranges leading to ring enlargement (Scheme 22).

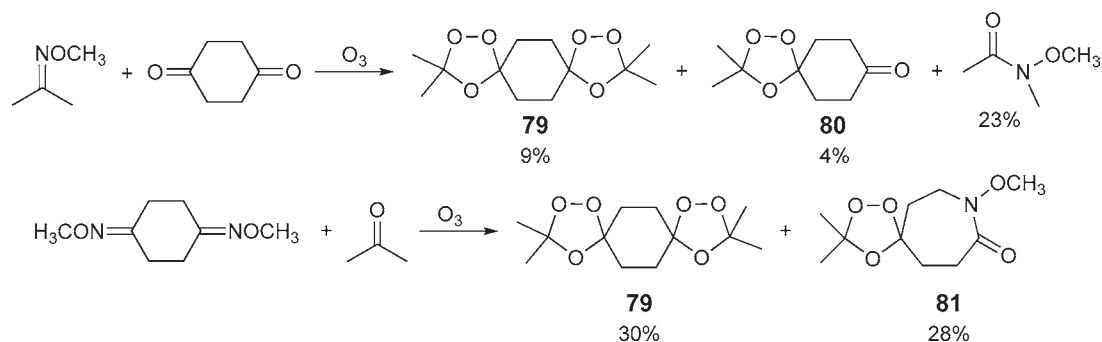
When 1,4-cyclohexanedione was ozonized in the presence of the *O*-methyloxime of acetone, a stable crystalline diozonide **79** was obtained along with a mono-ozonide **80** and amide. Vice versa, ozonolysis of the bis-*O*-methyloxime of 1,4-cyclohexanedione in acetone afforded a higher yield of the same diozonide **79** and a spiro-mono-ozonide-*N*-methoxy-lactam **81** (Scheme 23) <1997T5463>.

When the *O*-methyloxime of acetone was co-ozonided with diacetyl, the known stereoisomers of the α-diozonide (the achiral meso and the racemic) were obtained. A similar result was obtained when the *O*-methyloxime of cyclohexanone was co-ozonided with diacetyl. Reduction with Ph₃P afforded the expected products plus acetic anhydride, whose formation may be explained by the formation of a diradical or the corresponding dioxirane **82** that rearranged to an anhydride (Scheme 24) <1997T5463>.

The primary ozonide formed from cycloalkene derivatives (5- to 8-membered, or 12-membered) and aromatic polycyclic hydrocarbons under usual conditions (ozonolysis in dichloromethane at temperatures between 0 and –78 °C, depending on the solubility of the substrate) splits spontaneously according to Criegee's mechanism yielding a normal carbonyl group (aldehyde or ketone) and a CO, which may join together into a dipolar pentaatomic chain ⁺C–O–C–O–O[–] that cyclizes into the secondary ozonide. However, co-ozonolysis can take place in the presence of an excess of a different carbonyl compound. In the following paragraphs, a series of results are presented for such co-ozonolysis reactions <2000EJO335>.



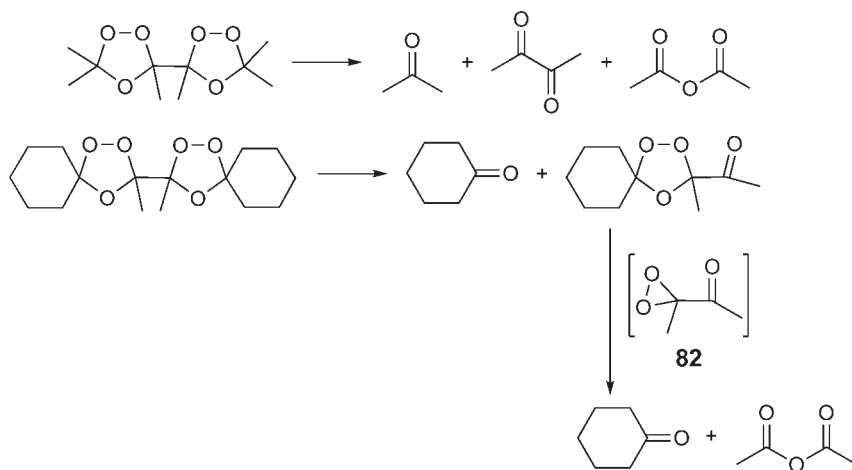
Scheme 22



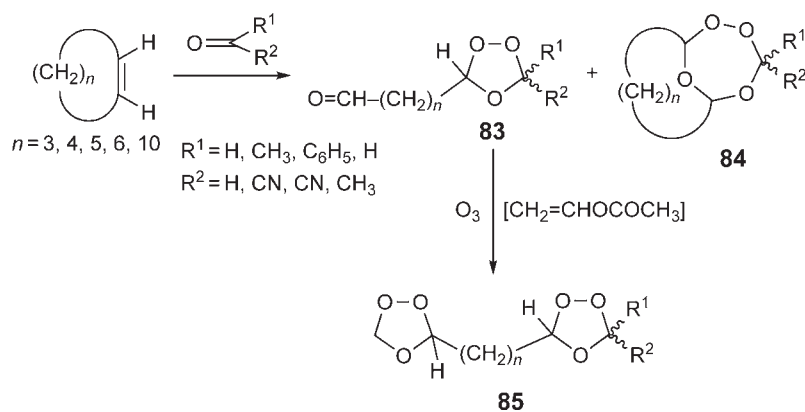
Scheme 23

When a twofold molar excess of an aldehyde, ketone, ketonitrile, or vinyl acetate (the latter provides formaldehyde oxide $^+\text{CH}_2\text{--O--O}^-$) is co-ozonolyzed with various cycloalkene derivatives, three main products are obtained: (1) an ozonide **83** with an aldehydic group tethered via an n -carbon chain; (2) a bicyclic tetraoxepane compound **84** formed from the above dipolar chain and the added carbonyl derivative; and (3) a diozonide **85** resulted from the formaldehyde oxide and the aldehydic compound **83**. Structures and yields of these products are presented in [Scheme 25](#) and [Table 9](#).

1-Methylcyclopentene co-ozonolyzed with formaldehyde, acetyl cyanide, or benzoyl cyanide afforded only the normal 1,2,4-trioxolane (secondary ozonide, **88**); by contrast, 1-methylcyclohexene co-ozonolyzed with formaldehyde or acetyl cyanide gave no such ozonide, but almost equal amounts of the aldehyde-ozonide **86** and the diozonide **87**, as shown in [Equation \(8\)](#) and [Table 10](#).



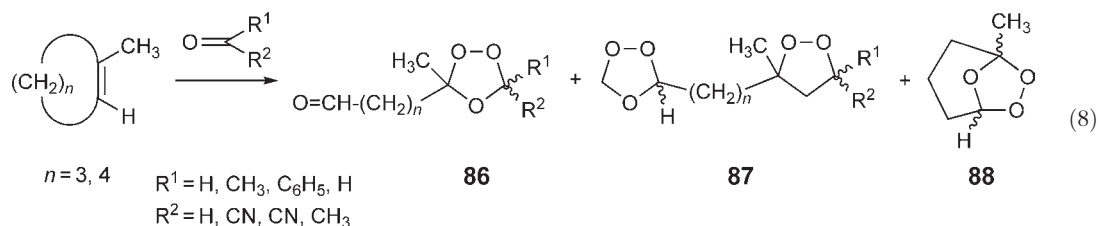
Scheme 24



Scheme 25

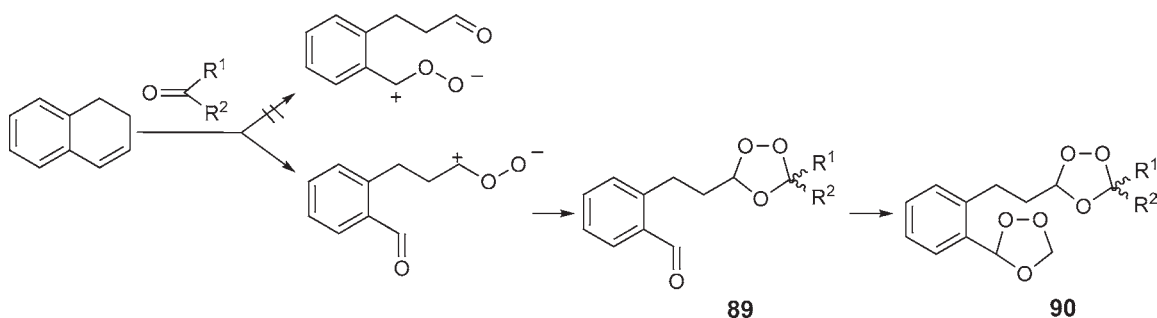
Table 9 Co-ozonolyses of cycloalkenes

	Structural units			Yields (%)		
	<i>n</i>	<i>R</i> ¹	<i>R</i> ²	83	84	85
a	3	H	H	46		29
b	4	H	H	68	36	10
c	5	H	H	74	19	33
d	6	H	H	36	16	57
e	10	H	H	17	10	32
f	3	H	CH ₃	37		21
h	5	H	CH ₃	17	8	10
i	6	H	CH ₃	19	8	9
j	10	H	CH ₃	17		10
k	3	CH ₃	CN	47		19
l	4	CH ₃	CN	70		32
m	5	CH ₃	CN	61		53
n	3	C ₆ H ₅	CN	42		25
o	4	C ₆ H ₅	CN	62		26
p	5	C ₆ H ₅	CN	33		34

**Table 10** Co-ozonolyses of 1-methylcycloalkenes

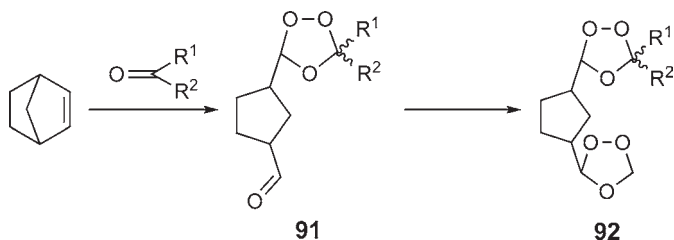
	Structural units			Yields (%)		
	<i>n</i>	<i>R</i> ¹	<i>R</i> ²	86	87	88
a	3	H	H			74
b	3	CH ₃	CN			63
c	3	C ₆ H ₅	CN			61
d	4	H	H	50	38	
e	4	CH ₃	CN	42	32	

Co-ozonolysis of 1,2-dihydronaphthalene with formaldehyde, acetyl cyanide (pyruvonnitrile), benzoyl cyanide, or acetaldehyde afforded an ozonide attached to a benzaldehyde group **89** and none of the isomeric ozonide with a propionaldehyde group. This indicates the preference for scission of the molozonide so as to favor conjugation between the aromatic ring and the aldehyde group rather than with the carbonyl oxide group. Subsequent co-ozonolysis of products **89** with vinyl acetate produced diozonides **90**, as shown in **Scheme 26** and **Table 11**.

**Scheme 26****Table 11** Co-ozonolyses of 1,2-dihydronaphthalene

	Structural units		Yields (%)	
	<i>R</i> ¹	<i>R</i> ²	89	90
a	H	H	63	58
b	CH ₃	CN	80	77
c	C ₆ H ₅	CN	78	55
d	H	CH ₃	74	69

Norbornene co-ozonized with formaldehyde, acetyl cyanide, or benzoyl cyanide gave similarly the aldehydic ozonide **91**, which then on co-ozonolysis with vinyl acetate (i.e., the source of formaldehyde oxide) afforded a diozonide **92**, as indicated in **Scheme 27** and **Table 12**.

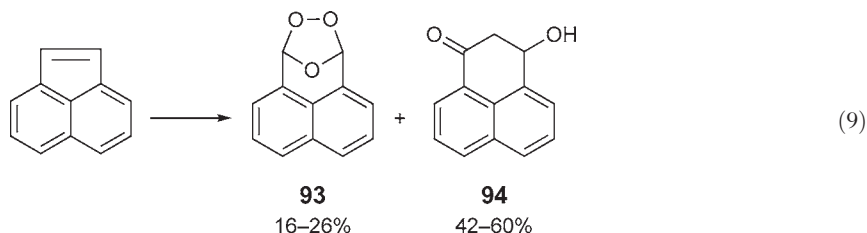


Scheme 27

Table 12 Co-ozonolyses of norbornene

	Structural units		Yields (%)	
	R^1	R^2	91	92
a	CH_3	CN	18	25
b	C_6H_5	CN	28	24
c	H	CH_3	48	37

Acenaphthene co-ozonized with formaldehyde, acetyl cyanide, or benzoyl cyanide gave no cross-product, but only the normal ozonide **93** (resulted by cleavage of the reactive double bond of the non-aromatic five-membered ring), together with a hydroxy-perinaphthanone **94** (Equation 9).



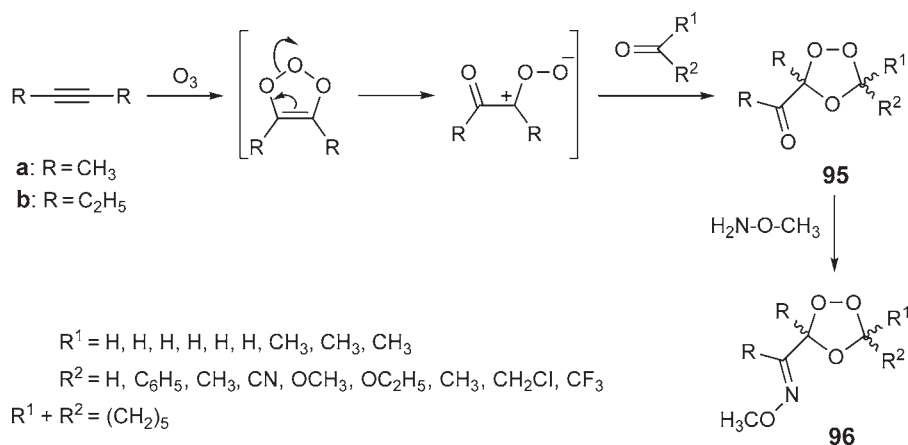
6.06.8.2.2 Ozonolysis of alkynes

Ozonolysis of alkynes can lead to stable ozonides if the intermediate unstable 3-acyl ozonide is derivatized to the more stable methoxyimino compounds. Thus, by treatment of alkynes admixed with a carbonyl compound (1:1 molar ratio) with ozone in dichloromethane at low temperatures, a 3-acyl-1,2,4-trioxolane **95** is formed. The cold crude reaction mixture was then quenched with a precooled solution of *O*-methylhydroxylamine in methanol affording in relatively modest to preparative useful yields the methoxyimino derivatives **96** (**Scheme 28**) <1997JOC6129>. In analogy with the Criegee mechanism, the initially formed primary ozonide ring opens to an α -acylcarbonyl oxide which reacts readily with the carbonylic species present in the reaction mixture forming the rather unstable 3-acyl-1,2,4-trioxolane. The reaction with an *O*-alkylated hydroxylamine gives isolable ozonides **96** (**Scheme 28**) <1995LA1571>.

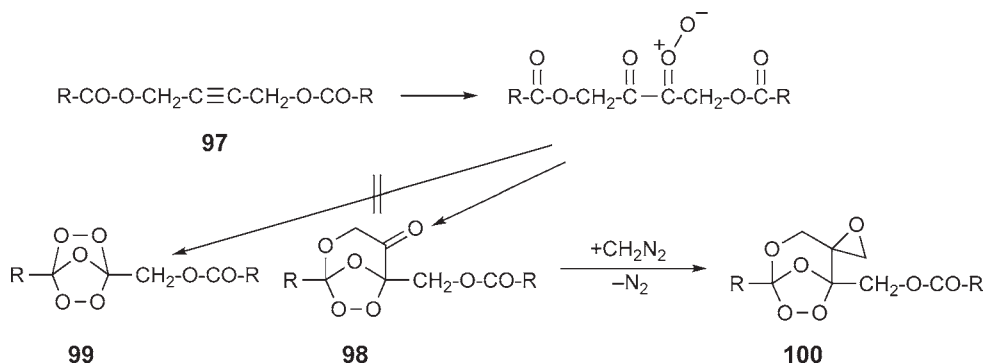
Both 2-butyne and 3-hexyne in the presence of various aldehydes or ketones gave isolable ozonides as one diastereoisomer only. However, the stereochemistry is uncertain as neither NMR chemical shifts nor HPLC retention factors give conclusive assignments <1997JOC6129>.

Bis-acyloxy-substituted 2-butyne **97** in the presence of added carbonyl compound (e.g., acetone) failed to give the corresponding cross-ozonides. Instead, the bicyclo[3.2.1]ozonides **98** were obtained in good yields by intramolecular cyclization of the CO intermediate with only one of the ester carbonyl groups. The bicyclo[2.2.1]ozonide **99** which

could have been formed by cyclization on the other ester carbonyl group was not formed, presumably due to its more strained conformation <1997JOC6129>. Reaction with diazomethane of the bicyclo[3.2.1]ozonide **98** afforded an ozonide-oxirane **100** whose structure was confirmed by X-ray crystallographic analysis (Scheme 29) <1997JOC6129>.

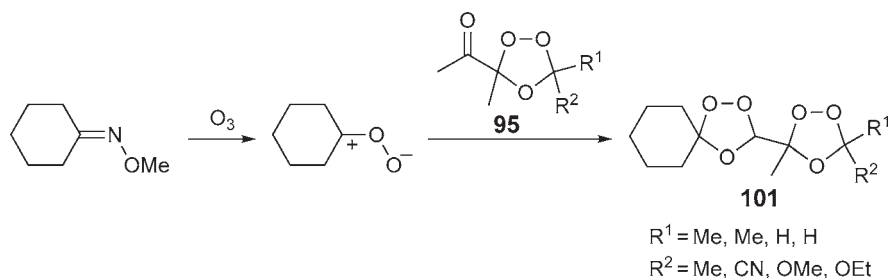


Scheme 28



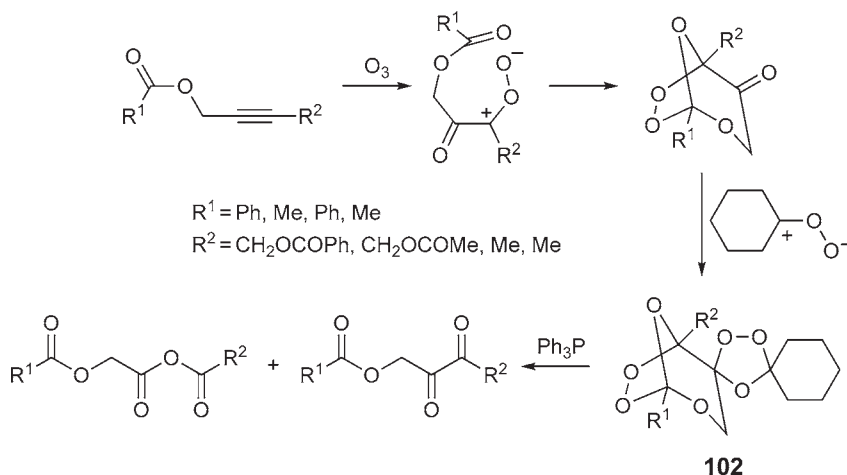
Scheme 29

Treatment of 2-butyne with ozone leads to unstable primary ozonides that cleave to α -oxo-carbonyl oxides; these could be trapped in the presence of aldehydes or ketones affording cross- α -oxo-1,2,4-trioxolanes. Subsequent cycloadditions between such α -oxo-ozonides and cyclohexanone oxide, generated *in situ* from *O*-methylcyclohexanone oxime (which affords methyl nitrite as a side-product), yield α -diozonides **101** (Scheme 30) <1997J(P1)1601>.



Scheme 30

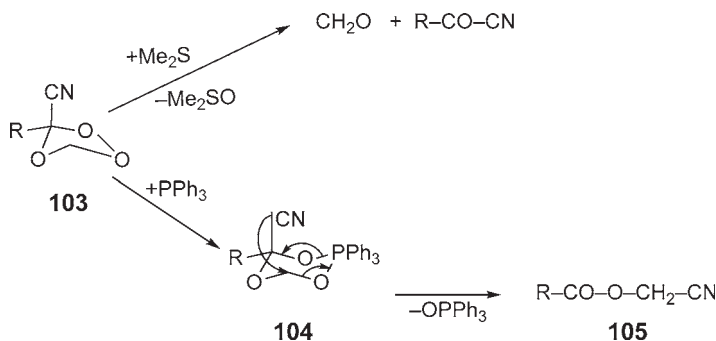
In a similar reaction various acyloxy-substituted alkynes were ozonolyzed in the presence of *O*-methylcyclohexanone oxime affording more complex α -dizonides. An X-ray crystallographic determination revealed that the compound with $R^1 = \text{Ph}$ and $R^2 = \text{CH}_2\text{O-CO-Ph}$ is a single diastereomer **102** formed by the approach of the cyclohexanone oxide to the carbonyl group of the intermediate bicyclic ozonide from the less hindered *exo*-face (**Scheme 31**) <1997J(P1)1601>.



Scheme 31

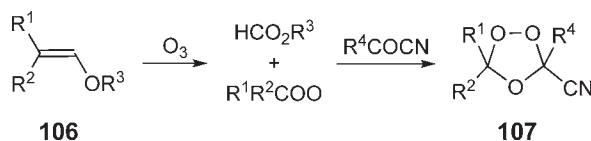
6.06.8.2.3 Trapping of carbonyl oxides with acyl cyanides

Ozonolysis of vinyl cyanides such as acrylonitrile produces in good yields the isolable 3-cyano-1,2,4 trioxolanes **103** which react readily with dimethyl sulfide or triphenylphosphine <1990TL3299>. Whereas the reduction products with Me_2S in CHCl_3 at -20°C are the usual ones, the increased reactivity of the ozonide due to the electron-attracting cyano substituent causes a rearrangement of the intermediate 2,4,6-trioxaphosphane **104** formed when the ozonide is reacted with Ph_3P below 0°C , affording an ester (an acylated cyanohydrin) **105** (**Scheme 32**).



Scheme 32

In an extension of this reaction, various carbonyl oxides could be generated by the ozonolysis at -70°C of enol ethers **106** in diethyl ether in the presence of acyl cyanides (**Scheme 33** and **Table 13**) <1996J(P1)871>.



Scheme 33

Table 13

107	R^1	R^2	R^4	Yield (%)	Ratio of the two isomers
a	Ph	H	Me	87	65:35
b	Ph	H	Ph	87	57:43
c	Ph	H	Bu ^t	90	66:34
d	Cyclohexyl	H	Me	84	53:47
e	Cyclohexyl	H	Ph	67	50:50
f	Cyclohexyl	H	Bu ^t	68	55:45
g	Ph	Ph	Me	59	
h	Ph	Ph	Ph	77	
i	Ph	Ph	Bu ^t	34	
j		-(CH ₂) ₅ -	Me	77	
k		-(CH ₂) ₅ -	Ph	79	
l		-(CH ₂) ₅ -	Bu ^t	81	
m	H	H	Ph	88	

When aldehyde *O*-oxides reacted with acyl cyanides, the resulting 3,3,5-trisubstituted 1,2,4-trioxolanes **107** were a mixture of stereoisomers.

Co-ozonolysis of *tert*-butylethene (3,3-dimethyl-1-butene) in the presence of benzoyl cyanide gave as major product (55%) 3-cyano-3-phenyl-1,2,4-trioxolane **103** along with 13% of the *tert*-butyl-substituted 1,2,4-trioxolanes **108** as a mixture of stereoisomers in 53:47 *Z/E* ratio which could be assigned from nuclear Overhauser effect (NOE) data, as only the (*Z*) compound shows an NOE enhancement (across the 1,2,4-trioxolane ring) of the *ortho*-phenyl protons upon irradiation of the Bu^t methyl groups (Equation (10) and Figure 5).

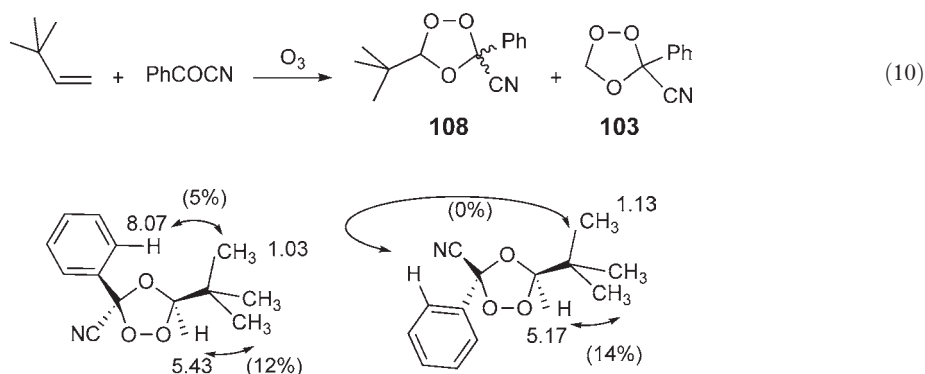
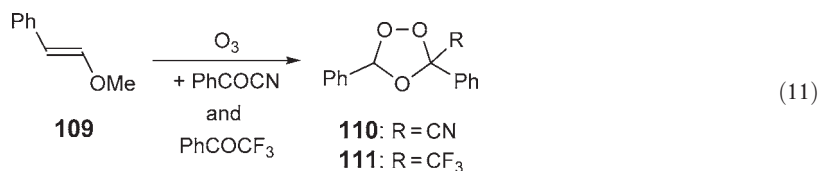


Figure 5 NOE enhancements used to assign the stereochemistry.

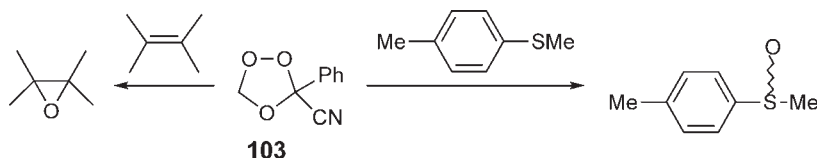
Furthermore, the two diastereoisomers reacted differently with substoichiometric amounts of triphenylphosphine. By treating a 1:1 mixture of the *Z/E* isomers **108** with 0.5 equiv of triphenylphosphine, the less sterically hindered (*E*)-isomer was rapidly reduced, whereas the (*Z*)-isomer remained unreacted. With 1 equiv of triphenylphosphine, however, both isomers are reduced forming a mixture of trimethylacetaldehyde and benzoyl cyanide. This contrasts with the behavior of 3-cyano-3-methyl-1,2,4-trioxolane shown above in Scheme 32.

The reactivity of acyl cyanides versus carbonyl oxides could be compared in competition experiments with other 1,3-dipolarophiles. Thus when enol ether **109** was ozonized in the presence of an equimolar amount of benzoyl cyanide and 2,2,2-trifluoroacetophenone in diethyl ether at -70°C , a mixture of two ozonides **110** and **111** was obtained in yields of 32% and 45%, respectively, as shown by Equation (11).



Other competition experiments allowed establishing an order of trapping reactivity for the carbonyl oxide as follows: $\text{PhCOCF}_3 > \text{Ph}_2\text{C}=\text{N}(\text{O})\text{Ph} > \text{PhCOCN} > \text{PhCOCOOMe} > \text{Ph}_2\text{C}=\text{NPh} \gg \text{PhCHO}$. Generally nitrones and imines are much more efficient trapping agents for the carbonyl oxides than benzaldehyde. However, carbonyl compounds with electron-withdrawing α -substituents have a much enhanced reactivity.

As cyano-substituted ozonides were easily reduced by triphenylphosphine, also *p*-tolyl sulfide can be used as a reducing agent and the corresponding sulfoxide could be isolated in quantitative yield. Alternatively, the 3-cyano-3-phenyl-ozonide **103** can oxidize 2,3-dimethyl-2-butene to the corresponding epoxide (Scheme 34).

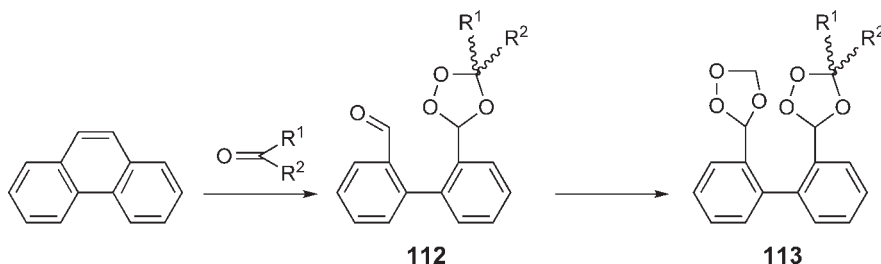


Scheme 34

This behavior parallels that of alkyl peroxides with electron-withdrawing substituents, compounds that are powerful epoxidizing agents.

6.06.8.2.4 Co-ozonolysis of polycyclic aromatic hydrocarbons

Phenanthrene has also a reactive 9,10-double bond, in agreement with the Clar structure having two aromatic sextets and a $\text{C}=\text{C}$ 'fixed' double bond in the median ring. On co-ozonolysis with formaldehyde, acetyl cyanide, or benzoyl cyanide, phenanthrene reacted accordingly, affording an aldehydic ozonide **112**, which in a separate co-ozonolysis with vinyl acetate that produced formaldehyde oxide ($\text{H}_2\text{C}-\text{O}-\text{O}$) gave rise to a diozonide **113** (Scheme 35 and Table 14).

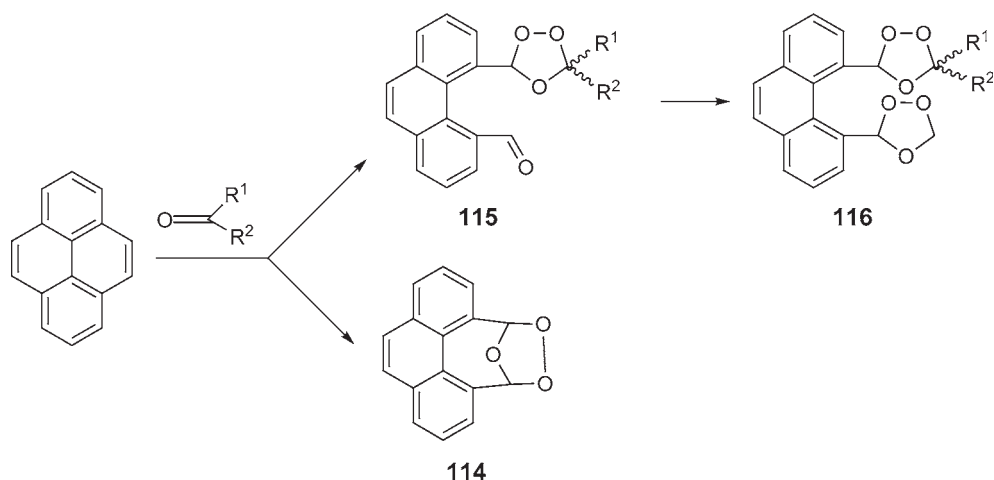


Scheme 35

Table 14 Co-ozonolyses of phenanthrene

	Structural units		Yields (%)	
	R^1	R^2	112	113
a	H	H	49	63
b	CH_3	CN	74	63
c	C_6H_5	CN	72	66

In the case of pyrene, there are two sextets and two fixed double bonds similar to the phenanthrenic double bond. In agreement with this argument and with the result for phenanthrene, co-ozonolysis of pyrene with formaldehyde or acetyl cyanide afforded the expected normal ozonide **114** and the cross-ozonide **115** with an aldehydic group. In a separate co-ozonolysis of **115** with vinyl acetate, diozonides **116** were prepared. No cross-ozonide was obtained in the presence of benzoyl cyanide, which afforded only the normal mono-ozonide **114** (Scheme 36 and Table 15).

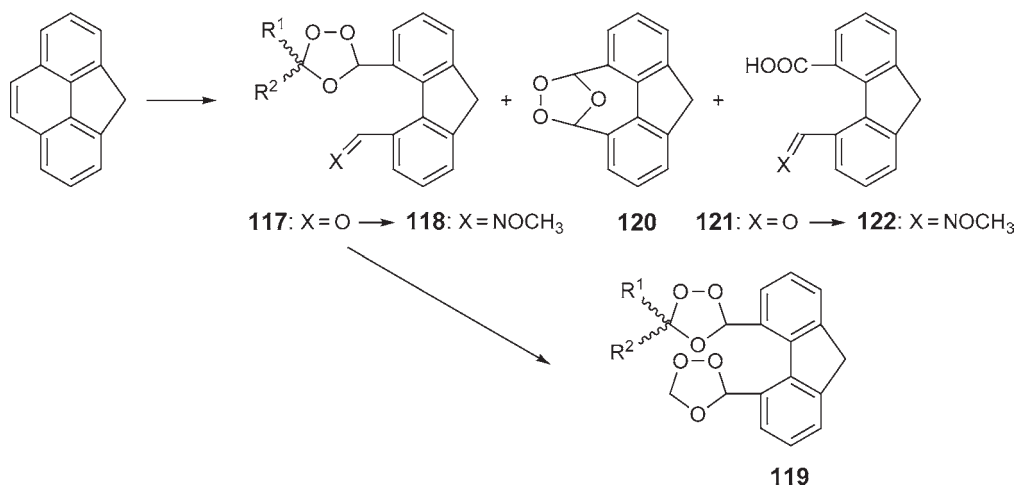


Scheme 36

Table 15 Co-ozonolyses of pyrene

	Structural units		Yields (%)		
	R ¹	R ²	115	116	114
a	H	H	52	41	17
b	CH ₃	CN	62	4	22
c	C ₆ H ₅	CN			24

The final polycyclic aromatic hydrocarbon that was investigated <2000EJO335> is benzo[def]fluorene which has a fixed double bond like phenanthrene. Its cross-ozonolysis with formaldehyde gave none of the normal ozonide **120**, but mainly the aldehydic ozonide **117**. At room temperature, a substantial amount of opening of the ozonide ring occurred with the formation of the acid aldehyde **121**. Both products **117** and **121** could be stabilized by treatment with *O*-methylhydroxylamine, yielding products **118** and **122**, respectively. The separate co-ozonolysis of compound **117** with vinyl acetate afforded the diozonide **119** (Scheme 37 and Table 16). The cross-ozonolysis with acetyl cyanide followed by treatment of the crude reaction mixture with *O*-methylhydroxylamine yielded the *O*-methyloxime of the cross-product. Cross-ozonolysis with benzoyl cyanide was not successful, and only the normal mono-ozonide **120** was formed.



Scheme 37

Table 16 Co-ozonolyses of benzo[def]fluorene

	Structural units		Yields (%)				
	R^1	R^2	117	118	119	120	121
a	H	H	82		26		46
b	CH ₃	CN		12		13	45
c	C ₆ H ₅	CN				64	

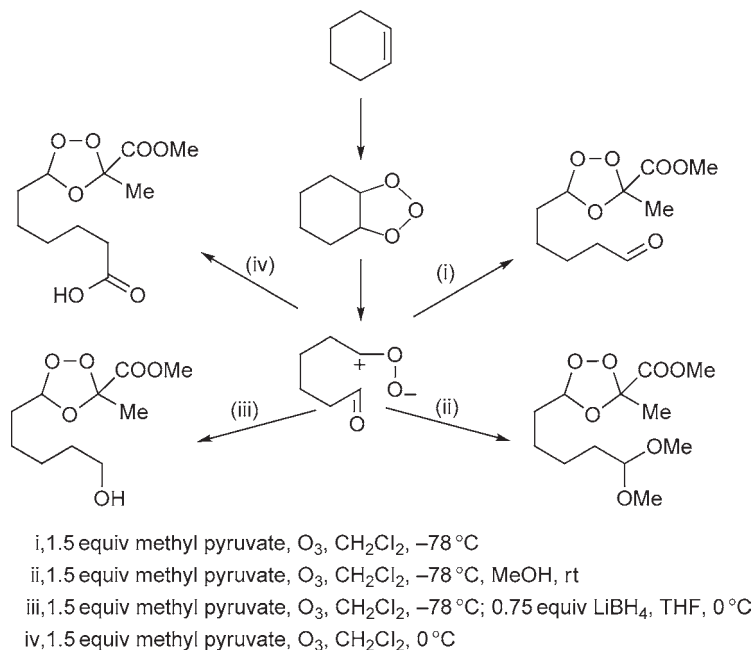
The supply of drinking water may become problematic as global warming becomes more acute. Chlorination and ozonation are at present the most widely used methods for sanitizing drinking water. The former method is less expensive but leads to the formation of foul-smelling chlorophenols when there are trace concentrations of phenolic products in the treated water. For destroying dangerous industrial wastes such as chlorinated hydrocarbons or polycyclic aromatic hydrocarbons (PAHs) that have a high persistency in the environment, combined or sequential use of gamma radiation and ozone have been proposed. The most resistant to radiation among PAHs are chrysene and fluorene <2006JRN679>. All traces of PAHs are destroyed by ozonolysis.

The World Health Organization recommends that the total concentration of PAHs in drinking water should not exceed 10 ng L⁻¹. The ozonation of the above two PAHs, plus benzo[*a*]pyrene, in water solution was examined experimentally as a function of pH and concentration of radical scavenger (*tert*-butanol). Acidic pH values accelerate the disappearance of the PAHs. At pH 2, the direct ozonolysis rates were approximately 33 000 M⁻¹ s⁻¹ for benzo-pyrene, 11 000 M⁻¹ s⁻¹ for chrysene, and 45 M⁻¹ s⁻¹ for fluorene <2004MI453>.

Density functional theoretical calculations were applied to the formation of 'internal primary ozonides' from three PAHs (pyrene, coronene, and 'circum-pyrene' C₄₂H₁₆) to simulate the atmospheric interaction between ozone and soot. No 1,2,4-trioxolane intermediate was considered in the conversion of the 1,2,3-trioxolane into aromatic epoxides via ring-opened trioxyl diradicals <2005PCA10929>.

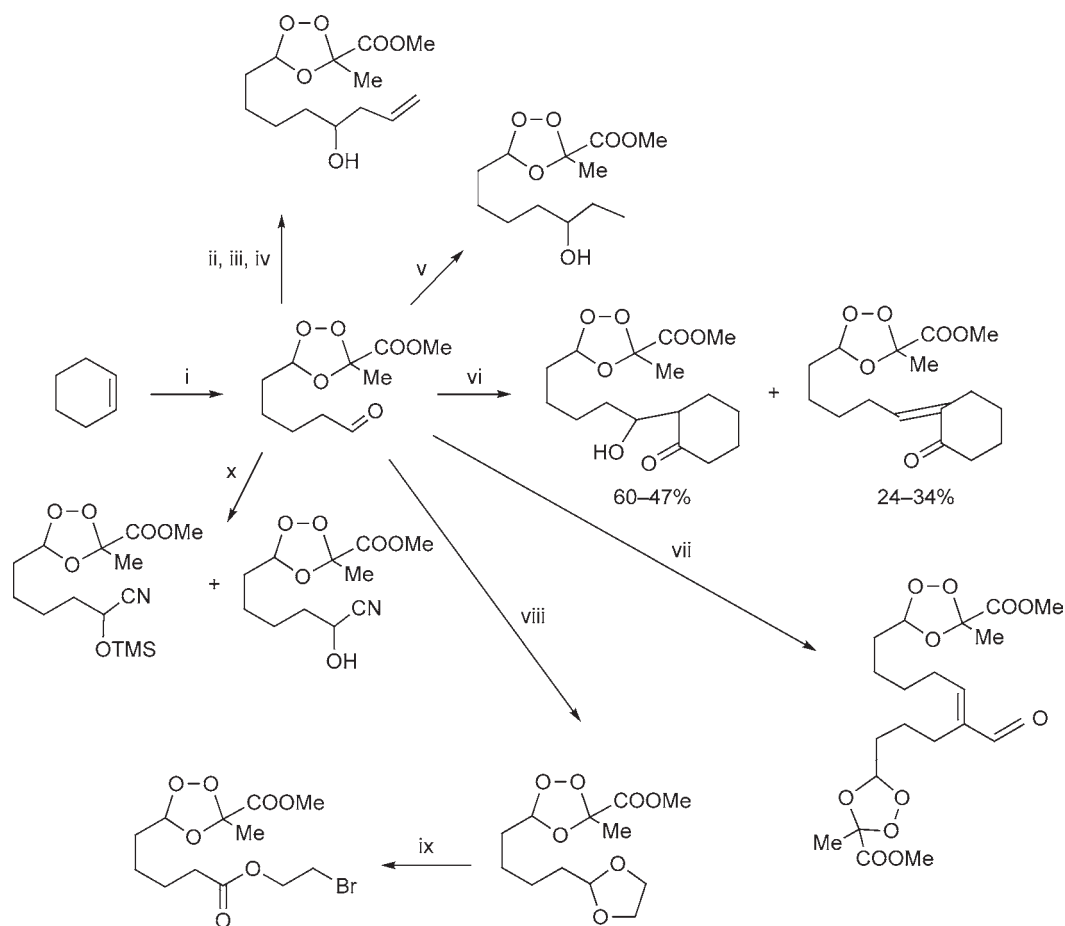
6.06.8.2.5 Trapping of intermediate carbonyl oxides with methyl pyruvate

This represents a particular case of the co-ozonolysis reaction when the intermediate carbonyl oxide can be trapped giving rise to other 1,2,4-trioxolanes having a remote functionality. **Scheme 38** shows the ozonolysis of cyclohexene

**Scheme 38**

in the presence of methyl pyruvate <1993TL6591, 1993TL6591, 1997T5217>. Depending upon the reaction conditions, the aldehyde function can be acetalized, reduced, or further oxidized to the corresponding carboxylic acid.

Further products containing the 1,2,4-trioxolane ring, which prove to be stable under a variety of reaction conditions, can be accessed by the same remote functionalization strategy (Scheme 39) <1994TL1743, 1994TL1743, 1998T8525>.

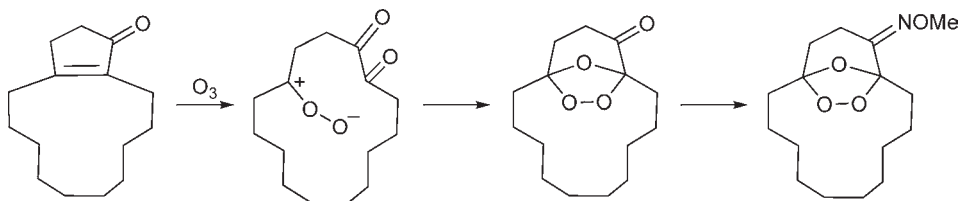


- i, O₃, –78 °C, CH₂Cl₂, 1.5 equiv MeCOCO₂Me, 74%
 ii, 1.1 equiv CH₂CH=CH₂SiMe₃, 0.5/1 equiv TiCl₄ or SnCl₄, –78 °C, CH₂Cl₂, 81–88%
 iii, 1.1 equiv CH₂CH=CH₂SnBu₃, 0.5/1 equiv TiCl₄ or SnCl₄, –78 °C, CH₂Cl₂, 77–87%
 iv, 2 equiv CH₂CH=CH₂ZnBr, THF, rt, 70%
 v, 1.5 equiv Et₂Zn, 1 equiv BF₃·Et₂O, CH₂Cl₂, –78 °C, 80%
 vi, 1.5 equiv TiCl₄, 1-trimethylsilyloxycyclohexene, –78 °C, CH₂Cl₂
 vii, 2.3 equiv BF₃·Et₂O, CH₂Cl₂, rt, 1 h, 51%
 viii, ethylene glycol, PPTS, acetone, rt, 79%
 ix, NBS, THF, AIBN, 60 °C, 65%
 x, TMSCN, cat. ZnI₂, –78 °C

Scheme 39

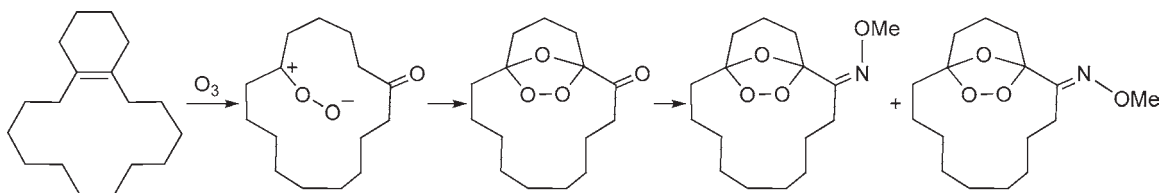
The reaction can be extended to other cycloalkenes such as cyclooctene, 1,5-cyclooctadiene, or 1,5-cyclooctadiene resulting in ozonides that have, in addition to the geminal 3-methyl-3-carbomethoxy substituents, a heptanal or *cis*-heptenal group at position 5 (in the case of 1,3-cyclooctadiene this side chain has the double bond in the non-conjugated position relative to the aldehydic group) <1993TL6591>.

The ozonolysis of bicyclo[10.3.0]pentadec-1(12)-en-13-one in pentane afforded a labile ozonide which was stabilized by conversion into the *N*-methyloxime by treatment with H₂N-OMe (Scheme 40) <1994TL1153>.



Scheme 40

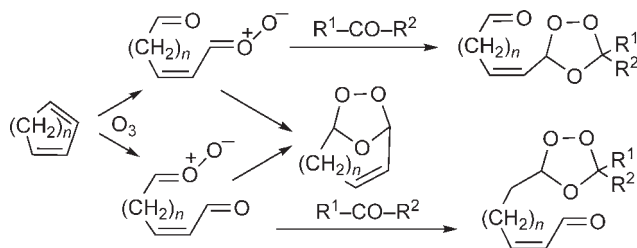
Similarly, two stable diastereomeric (*syn/anti*) tricyclic ozonides were obtained from bicyclo[9.4.0]pentadec-1(11)-en-12-one and ozone at -75°C in pentane followed by treatment of the ozonolysis product with H_2NOMe . Their structures were confirmed by X-ray crystallography (Scheme 41) <2006EJO1978>.



Scheme 41

Surprisingly, treatment of 1,2-dimethylcyclopentene and 2,6-heptanedione with ozone in the gas phase at room temperature gave in both cases low yields of 1,2-dimethylcyclopentene ozonide. The explanation is that in gas phase a diradicalic or dioxiranic rather than a zwitterionic carbonyl oxide is produced, and that the enol of the diketone is involved in the reaction <1998EJO627>.

Conjugated cyclodienes with five-, six-, seven-, and eight-membered rings were subjected to ozonolysis in the presence of formaldehyde or acetyl cyanide as trapping agents for the carbonyl oxides leading to cross-ozonolysis <2001EJO3083>. It is known that ozonolysis of dienes proceeds stepwise. Cyclopentadiene ($n = 1$) affords all three products in Scheme 42, in agreement with the known propensity of five-membered ring alkenes to form secondary ozonides easily. The configuration of the double bond tethering the aldehyde group was mainly (*Z*) but the isomer with (*E*)-configuration was also present.



Scheme 42

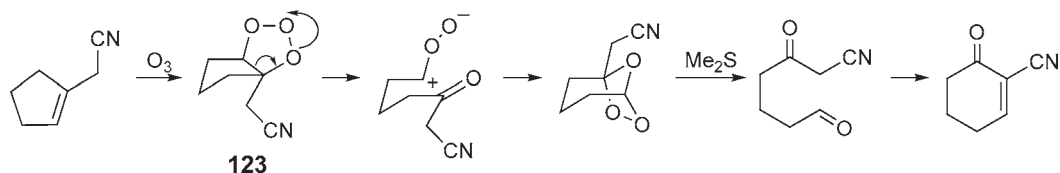
1,3-Cyclohexadiene yielded only the two (*Z*)-cross-ozonides with the upper one predominating. 1,3-Cycloheptadiene afforded the two (*Z*)-cross-ozonides with the lower one predominating, and 1,3-cyclooctadiene gave only the lower (*Z*)-cross-ozonide. At room temperature in CH_2Cl_2 , the *cis*-double bonds isomerize to *trans*-configurations.

The nonconjugated 1,5-cyclooctadiene and its 1,5-dimethyl homolog behave in this reaction normally, reacting at only one of the two double bonds and forming 1,2,4-trioxolanes having a tethered heptenal.

6.06.8.2.6 Domino reaction: Tandem ozonolysis–aldol sequence

It is known that two electron-withdrawing groups (EWGs) attached to the same carbon atom in an alkene increase substantially the reactivity of the alkene towards electrophiles. At the same time, ozonides with EWGs become too unstable. A compromise between stability and reactivity is attained with unsaturated

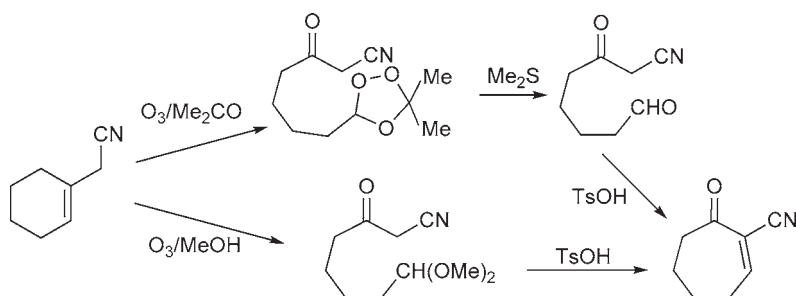
nitriles, which participate in an interesting domino (tandem) ozonolysis–aldol sequence, as shown with cyclopenteneacetonitrile in [Scheme 43](#) <1999JOC2830>.



Scheme 43

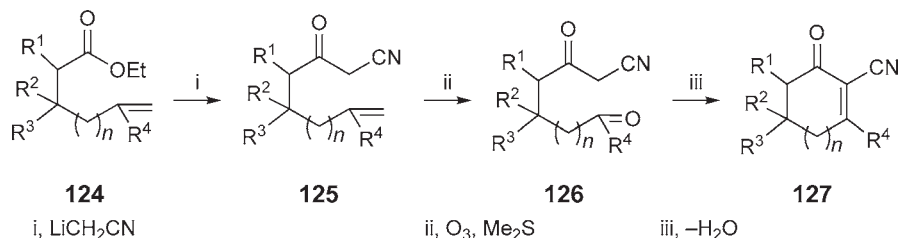
The crystalline 1,2,4-trioxolane derivative **123** is exceptionally stable. Its structure was determined by X-ray crystallography. Its reduction with dimethyl sulfide and intramolecular cyclization generates an oxonitrile with a six-membered ring; even simpler one-pot synthesis without isolating the ozonide gives a >90% yield.

If an acetone solution of cyclohexeneacetonitrile is submitted to ozonolysis, the mixed ozonide can be reduced with Me_2S and cyclized to an unsaturated seven-membered oxonitrile, but an alternative way is achieved if the ozonolysis is performed in methanol; in the latter case, however, acid treatment must last longer and yields are lower ([Scheme 44](#)) <1999JOC2830>.



Scheme 44

The same procedure was applied to several unsaturated nitriles **125**, prepared from various acyclic carboxylic esters with a terminal double bond **124**. The intermediate carbonylic compound **126** cyclized either during silica gel chromatography, or on sequential treatment with calcium hydride followed by aqueous ammonium chloride. The result was a five- or six-membered cyanocycloalkenone **127** ([Scheme 45](#) and [Table 17](#)) <1999JOC2830>.



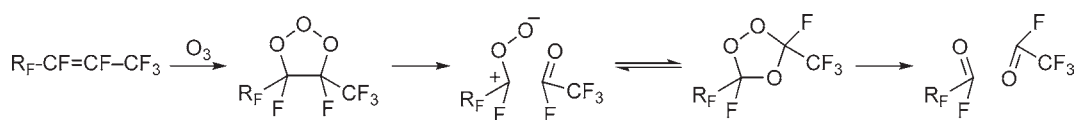
Scheme 45

Table 17 Syntheses of 2-cyanocycloalk-2-ene-1-ones

R^1	R^2	R^3	R^4	n	Yield (i) (%)	Yield (ii+iii) (%)
Me	H	H	H	0	81	83
H	Me	Me	H	0	73	91
H	H	H	Me	0	71	91
H	OH	Me	H	1	70	53
H	OSiMe_3	Me	H	1	58	57

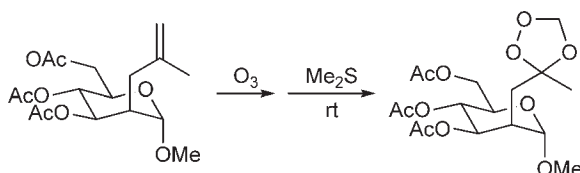
6.06.8.2.7 Cryo-ozonolysis

Low-temperature (77–280 K) ozonolysis of tetrafluoroethylene, hexafluoropropene, and perfluoro-4-methyl-2-pentene was studied in the absence of oxygen and solvents [<2001RJA704>](#). The latter perfluoroalkene is the dimer of perfluoropropene. The ozonide of tetrafluoroethylene is more stable than the ozonide of hexafluoropropene. Ozone was freed from oxygen by vacuum distillation at 77 K, and the crystalline ozone was purified by sublimation. After known (equimolar) amounts of alkene and ozone were condensed together at 77 K in a calorimetric cell, the temperature was raised gradually and the reaction course was monitored by the heat release and by IR spectrometry. It appears that the three-step Criegee reaction mechanism operates also in such cases. The primary ozonide is formed rapidly releasing $240 \text{ kcal mol}^{-1}$, its dissociation releases 32 kcal mol^{-1} , and the recombination to form the 1,2,4-trioxolane (secondary ozonide) releases another $214 \text{ kcal mol}^{-1}$, totaling $486 \text{ kcal mol}^{-1}$ (all these values are calculated for the perfluoropropene dimer), in fair agreement with the experimental value of $505 \pm 5 \text{ kcal mol}^{-1}$. At temperatures around 333 K (60°C) the secondary ozonide decomposes irreversibly into oxygen and two perfluoroacyl fluorides ([Scheme 46](#)). The secondary ozonides can initiate polymerizations at temperatures in the range 240–300 K [<2000MI1>](#). No low-temperature ozonation of perfluoro-2,4-dimethyl-3-ethyl-2-pentene (the trimer of perfluoropropene) could be achieved, probably owing to steric hindrance ([Scheme 46](#)).



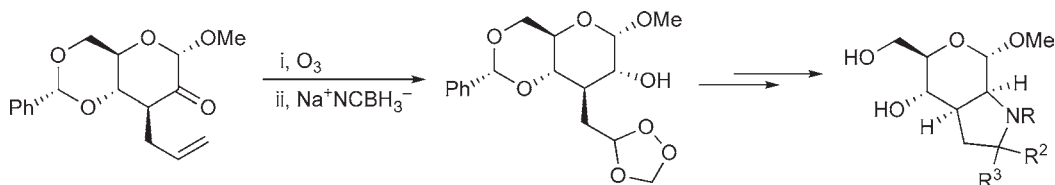
Scheme 46

From a glucose epoxide, a pyranose with a 2-methylpropenyl group was obtained. Its ozonolysis at -70°C followed by reduction with dimethyl sulfide at room temperature left the ozonide ring intact ([Scheme 47](#)). The mixture of the two diastereomeric ozonides was surprisingly stable for months at room temperature [<2002JOC7561>](#).



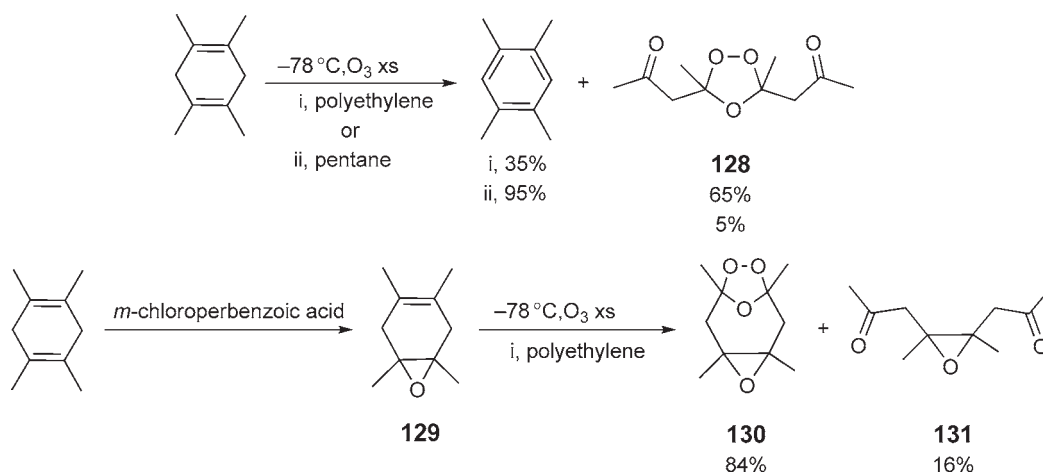
Scheme 47

Ozonolysis of a known chiral allyl phenylacetal proved to be a simple way to introduce a hydroxyethyl group with a precise stereochemistry. The ozonolysis was carried out in CH_2Cl_2 at -78°C , and the resulting keto-ozonide was treated with cyanoborohydride at room temperature, when the carbonyl group was reduced to a secondary alcohol but the 1,2,4-trioxolane ring was not affected. Reduction of the ozonide with Me_2S or $\text{Zn} + \text{AcOH}$ gave complex mixtures, but polymer-bound Ph_3P was the most satisfactory method. After several steps, the target aza-heteroannulated pyranoside was obtained as shown in [Scheme 48](#) [<2005TL307>](#).



Scheme 48

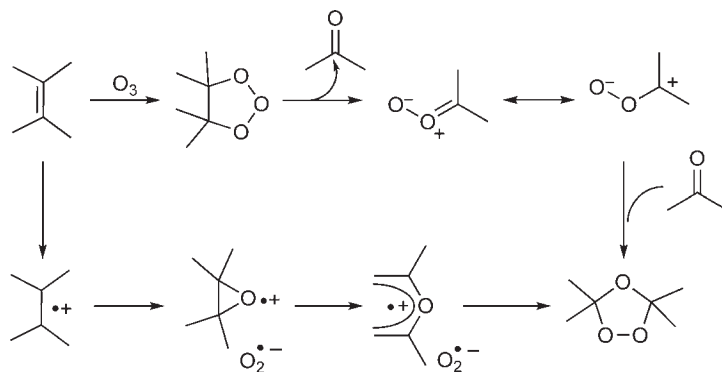
The Criegee mechanism is known to operate when conjugated dienes such as substituted or unsubstituted 1,3-cyclohexadiene and naphthalene are ozonolyzed. In an investigation with nonconjugated related systems, 1,2,4,5-tetramethylcyclohexadiene was ozonolyzed either on polyethylene or in pentane. In the latter case, durene was the main product, but on polyethylene where the fragments of the molozonide are held in place an ozonide **128** is the main product. Its structure, however, was abnormal, and it was checked that no 'normal diozonide' or its ozonide-epoxide decomposition product **130** was present, by synthesizing this ozonide-epoxide from the monoepoxide of the 1,2,4,5-tetramethylcyclohexadiene **129** (Scheme 49) <2001EJO1899>.



Scheme 49

In an argon matrix, ethylene and ozone that were co-deposited around 20 K did not react till the matrix softened. However, in an amorphous carbon dioxide matrix the primary and secondary ozonides appeared already at 25 K and were identified by infrared absorption spectra but in a crystalline CO₂ matrix no reaction took place below 77 K <1996JA3687>. Theoretical studies took into account the lattice constants relative to the size of the van der Waals complexes between ozone and ethylene.

The ozonolysis of 2,3,3-trimethyl-1-butene (tryptene) was studied at -18°C in CCl₄, in CH₂Cl₂ at -50 and -78°C , and in CFCl₃ in a wider range of temperatures. The yield of 3-*tert*-butyl-3-methyl-1,2,4-trioxolane was around 30%, and other products predominated. On the basis of these findings, it was assumed that there may exist cases that the clear-cut Criegee mechanism does not cover, namely cases when dioxygen molecules participate in the reaction, or cases when single electron-transfer steps operate (Scheme 50) <2000HCA3312, 2004HCA2025>.

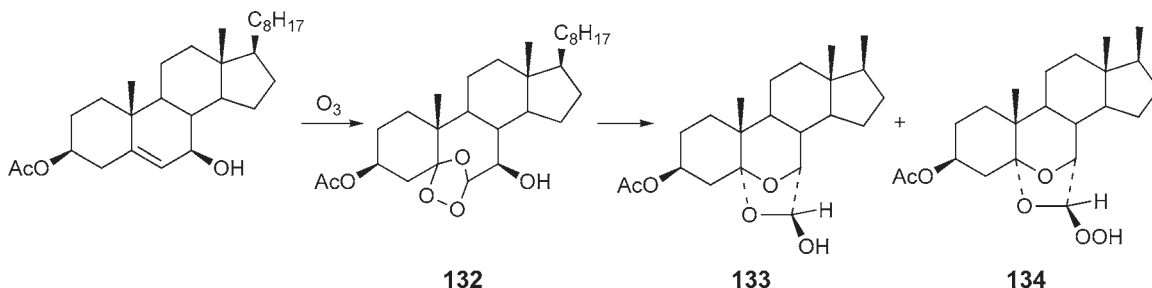


Scheme 50

Alkenyl stannanes afford stable primary ozonides at -78°C in methanol, and their reduction at this temperature with BH₃·SMe₂ converts alkenes into 1,2-diols in good yields. Higher temperatures, longer reaction times, and solvents such as AcOEt or CH₂Cl₂ yield predominantly alcohols by splitting of the C=C bond <2002OL383>.

Ozonolysis of (*E*)- and (*Z*)-1,2-dimethoxyethene at -41°C in the presence of acetaldehyde produced mixtures of (*E*)- and (*Z*)-3-methyl-5-methoxy-1,2,4-trioxolane, and in the presence of isobutyraldehyde mixtures of (*E*)- and (*Z*)-3-isopropyl-5-methoxy-1,2,4-trioxolane. Ozonolysis of vinyl acetate affords 3-acetoxy-1,2,4-trioxolane and 3-acetoxy-1,2-dioxolane in 34% and 51% yields, respectively, in agreement with Criegee's mechanism <1990JOC1120>.

Intramolecular interception of the Criegee carbonyl/carbonyl oxide intermediate was observed in the ozonolysis of steroidal allylic alcohols at -70°C . In hexane, the 1,2,4-trioxolane **132** (a mixture of C_6 -epimers) was isolated in 26% yield. Reductive workup afforded the hemiacetal of the dioxolane **133** which could be oxidized to the dioxolane-lactone; the hydroperoxide **134** can be isolated in other solvents. When the ozonolysis was carried out in ethyl acetate at -78°C , the yield of the dioxolane-hemiacetal **133** was 95% (Scheme 51) <1990J(P1)1220>.



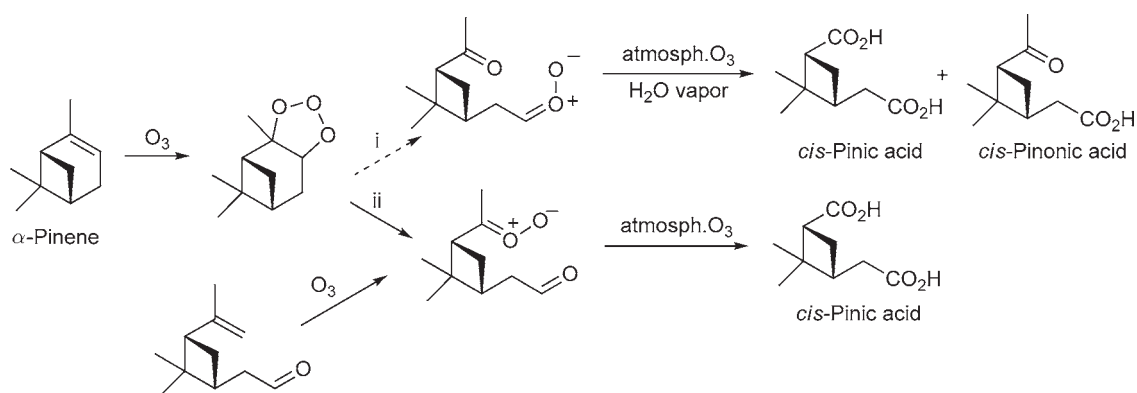
Scheme 51

Cryogenic ozonolysis of trimethylsilyl-ethene co-deposited in an argon matrix and heated gradually to -100°C allowed the identification of a 1,2-trimethylsilyloxy-dioxetane, a 2-trimethylsilyperoxy-acetaldehyde, and an assigned trimethylsilyloxy-methyl formate. On this basis, postulating a migration of the trimethylsilyl group, it was argued that the primary ozonide does decompose in a concerted manner <2001JOC6977>.

6.06.8.2.8 Ozonolysis of terpenes and implications for ecology

Gas-phase ozonolysis has only recently been able to prove the existence of terpenic ozonides by ^{13}C NMR spectroscopy, thanks to characteristic peaks in the 100–120 ppm range.

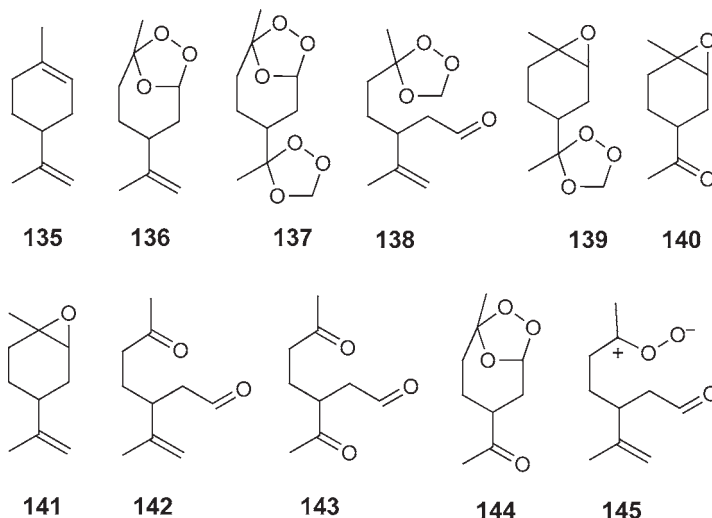
Photochemical smog is composed mainly of secondary aerosol particles, and it contains appreciable amounts of biogenic ozonolysis products. Among the constituents of volatile organic compounds, the monoterpenes are an important constituent, and α -pinene is the most abundant of them. The two final ozonolysis products of α -pinene are *cis*-pinic and *cis*-pinonic acids. The pathway for their formation was investigated by ozonation of a synthetic analog that can form only one of the two possible Criegee intermediates, proving that pinic acid is formed by pathway ii, whereas pinonic acid is formed by both pathways <2007CC1328>. The reaction via pathway i, is strongly dependent on the relative humidity of the atmosphere (Scheme 52).



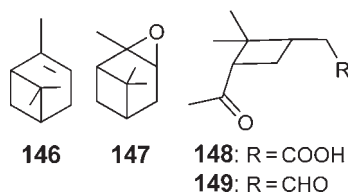
Scheme 52

Similarly, the relative humidity has a strong influence on the chemical composition of the secondary organic aerosol formed in the atmosphere by the reaction of ozone with 1-tetradecene <2000EST2116>: thermal desorption particle beam mass spectrometric determinations found that the main products are α -hydroxytridecyl hydroperoxide and a peroxy-hemiacetal.

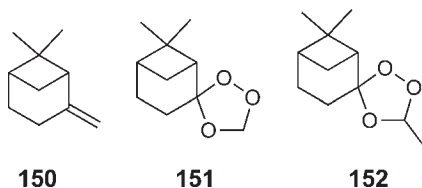
In pentane solution at -45°C , treating (+)-limonene **135** with 1 molar equiv of ozone afforded the mono-ozonide at the ring double bond **136**, two diastereomeric diozonides **137**, and the mono-ozonide with an aldehydic group **138**, whereas with 2 molar equiv of ozone in pentane or on polyethylene only the two diastereomeric diozonides **137** were obtained <1996T14813>. All of them are stable at room temperature and were individually separated and characterized. In the presence of formaldehyde in CH_2Cl_2 the amount of the mono-ozonide with an aldehydic group **138** increased considerably, proving that the more substituted double bond is attacked preferentially in ozonolysis. Reduction with Ph_3P gave the expected products **140** and **141–143**. Like all cyclohexene ozonolyses, the ozonide yields were fairly low and probably involve the intermediate **145**.



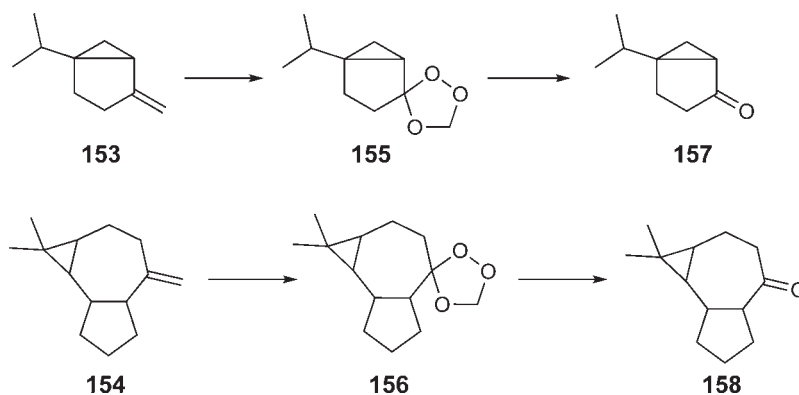
Ozonolysis of (–)- α -pinene **146** in pentane at -35°C or on polyethylene at -70°C affords only epoxide **147** and its degradation products **148** and **149** but no ozonide, perhaps due to steric hindrance caused by the two geminal methyl groups <1996T14813>.



Ozonolysis of (–)- β -pinene **150** in pentane at -40°C affords only one ozonide **151** as reported previously. Using acetaldehyde as solvent for ozonolysis two diastereomeric ozonides **152** were obtained.



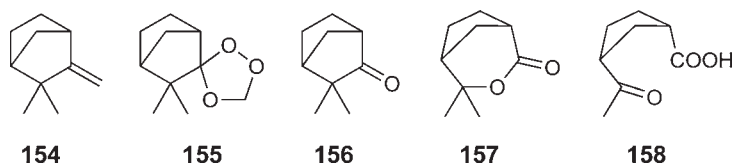
Each of the two terpenes (+)-sabinene **153** and the azulenic (+)-aromadendrene **154** gave two diastereomeric ozonides in pentane in a combined high yield. They were characterized individually by ^1H , ^{13}C , and ^{17}O NMR and by reduction to the corresponding ketones (Scheme 53).



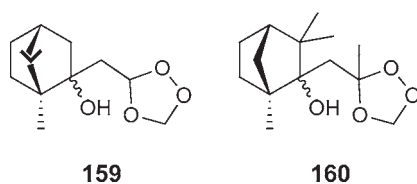
Scheme 53

Gas-phase ozonolysis of (–)- β -pinene **150** and of (+)-sabinene **153** at room temperature afforded the corresponding ozonides as mixtures of two diastereomers each [<1998EST647>](#). The results differ from those reported in solution.

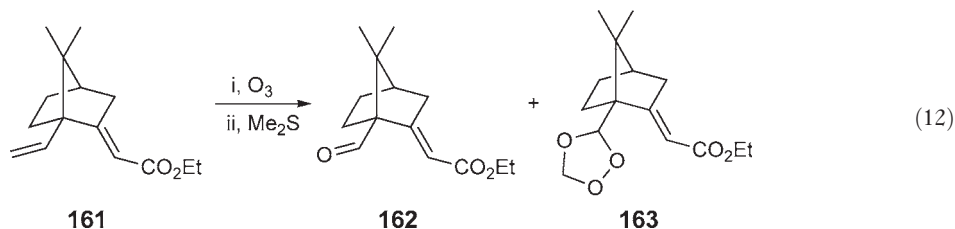
Camphene **154** in pentane at -40°C afforded an ozonide **155** and its presence in the crude reaction mixture was proved by ^1H and ^{13}C NMR and by reduction with Ph_3P to the expected products. However, this ozonide could not be isolated as it decomposes at temperatures above -20°C .



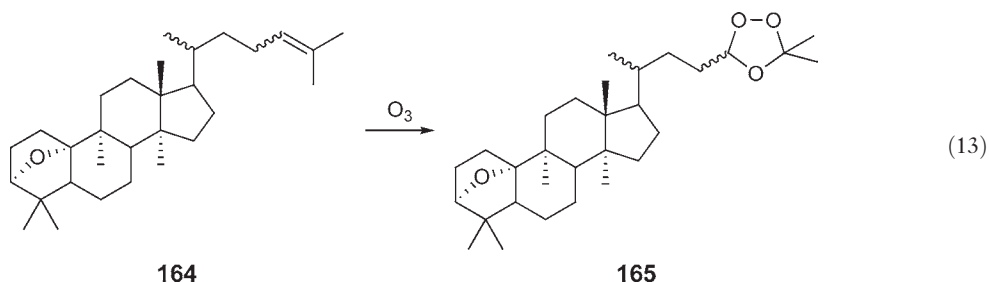
Several allylic and homoallylic alcohols prepared from (+)-camphor and (–)-fenchone were ozonolyzed in Et_2O at -78°C and then treated with Et_3N or LiAlH_4 furnishing chiral hydroxyl carbonyl compounds and diols (the latter with high diastereoselectivity). Several relatively stable 1,2,4-trioxolanes were isolated and characterized by ^1H , ^{13}C , and ^{17}O NMR spectra and by ESI-MS [<1999HCA1385>](#). All stereoisomers of products **159** and **160** were isolated and characterized.



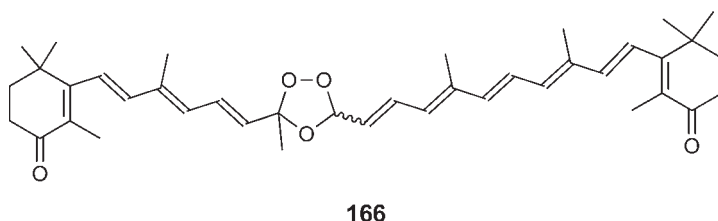
An α,β -unsaturated ester with a bornane skeleton **161** having a vinyl group reacts on ozonolysis in CH_2Cl_2 at -78°C at the more reactive vinylic double bond but not at the conjugated double bond. Subsequent treatment with dimethyl sulfide affords the aldehyde-ester **162** in 84% yield, leaving the ozonide **163** in 8% yield (Equation 12) [<2001RJO1102>](#).



From dried leaves of a Brazilian plant, a triterpene ozonide **165** was isolated. It was also obtained at -78°C in hexane by ozonolysis of its precursor **164** isolated from the same plant. In contrast to natural endoperoxides, such as artemisinin, this 1,2,4-trioxolane does not show antiparasmodial activity (Equation 13) <2003AP205>.



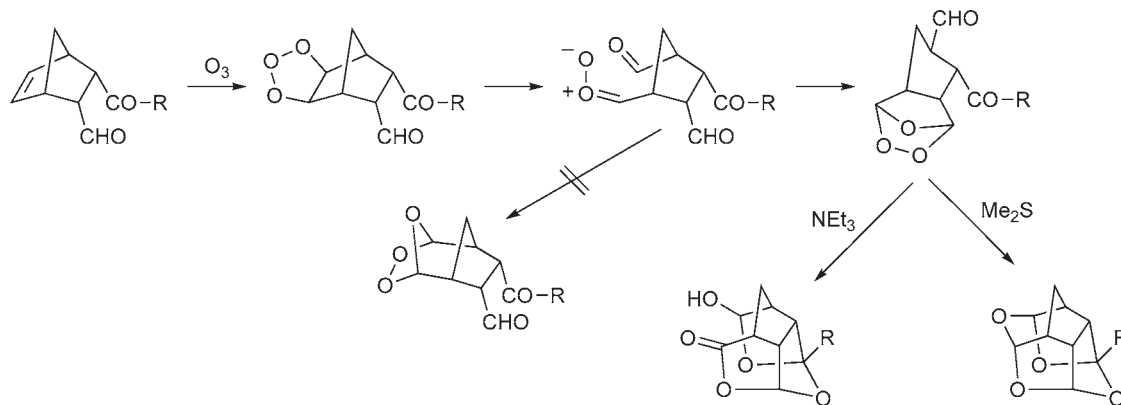
The reaction of canthaxanthin (β,β -carotene-4,4'-dione) with *meta*-chloroperbenzoic acid furnishes dihydrooxepins <1997TL7853>. Two isomeric 1,2,4-trioxolanes **166** have been obtained more recently as products of the same reaction when it was carried out with potassium 6-C-18 crown ether in CH_2Cl_2 : the 13,14-*cis*-isomer is the main product in the presence of oxygen, whereas the 13,14-*trans*-isomer predominates when the solvent was degassed <1999T2307>.



6.06.8.2.9 Regioselective fragmentation of molozonides

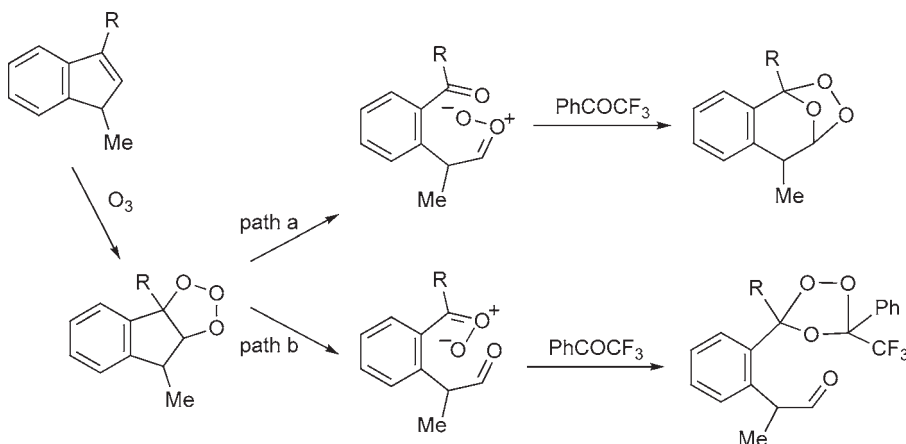
The fragmentation regioselectivity of nonsymmetrical molozonides to afford mainly or exclusively one of the two possible Criegee intermediates was discussed until recently in terms of nearest neighboring groups, and examined experimentally by using protic solvents such as methanol: the preferred path places electron-donating substituents on the CO fragment so that the partial positive charge is better accommodated, while electron-withdrawing substituents are incorporated into the carbonyl product. A refinement involving the control by remote carbonyl groups was possible by studying the ozonolysis of norbornene derivatives and using the reaction of the final ozonides with triethylamine <1996JOC3820>.

The molozonide has two possibilities for ring opening to form Criegee intermediates, and only the selected one is written in Scheme 54. The next step also has two possibilities of closing the 1,2,4-trioxolane ring with one of the two nonequivalent formyl groups, both shown in Scheme 54. The formyl group, rather than the acyl group, determines the regioselectivity of the molozonide fragmentation. The cage compounds obtained by reduction with dimethyl sulfide and triethylamine are different, and the latter, which is less symmetrical, supports the structure.



Scheme 54

1-Alkyl-3-methyl-substituted indenenes with bulky alkyl substituents afford high yields of ozonides, whereas 1,3-dimethylindene gives mainly oligomeric ozonides <1996JOC5953>. In order to better understand the steric effect of such substitutions on the regioselectivity of the cleavage of the primary ozonide, the ozonolysis was carried out in ethyl ether in the presence of trifluoroacetophenone, and the results are presented in **Scheme 55** and **Table 18**. Clearly, only path b where the bulky substituent remains attached to the carbonyl oxide fragment leads to co-ozonolysis while trifluoroacetophenone has no effect in path a.



Scheme 55

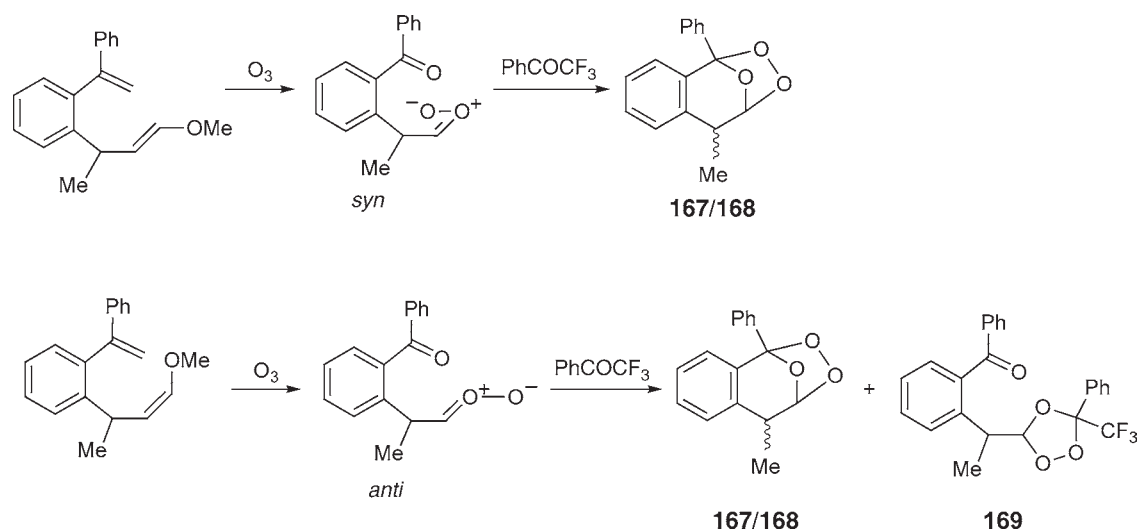
Table 18 Ozonation of 1-alkyl-3-methylindenes

<i>R</i>	<i>Path a</i>		<i>Path b</i>
	<i>Yield (%)</i>	<i>exo/endo</i>	<i>Yield (%)</i>
Me			72
Pr ⁱ			96
Ph	84	80/20	
Bu ^t	86	90/10	

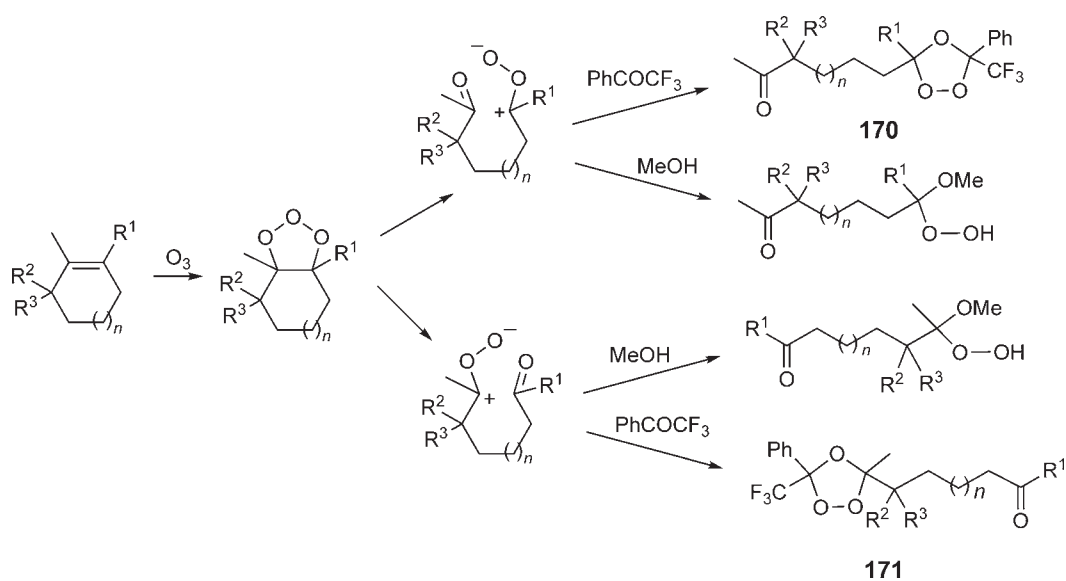
The study was continued with diastereoisomeric vinyl ethers. The (*E*)-isomer afforded on ozonolysis at -70°C in ether a *syn*-carbonyl oxide, and with or without trifluoroacetophenone only the intramolecular ozonide **167**, while the (*Z*)-isomer led to an *anti*-carbonyl oxide and to co-ozonolysis in the presence of trifluoroacetophenone, because the *anti*-carbonyl oxide cannot adopt a suitable conformation for the intramolecular ozonide formation (**Scheme 56**) <1996JOC5953, 1998JOC5617>.

The following three factors play a role in determining the regioselectivity of cleavage of the C–C and C–O bonds in the primary ozonide forming a carbonyl oxide and a carbonyl group that then recombine after rotation into the secondary ozonide: (1) electronic effect of substituents at the C–C bond in the 1,2,3-trioxolane; (2) electronic effect of any heteroatom at allylic positions in the alkene; and (3) steric effects of atoms at these allylic positions. Ozonolysis experiments with substituted five- or six-membered cycloalkenes in ether with trifluoroacetophenone or in methanol provided the following results <1996JOC5953>: 1,2,3,3-tetramethylcyclohexene **b** and 1,5,5-trimethylcyclopentene **f** afforded the cross-ozonide **170** derived from the sterically less-congested carbonyl oxide, due to the steric effect of the gem-dimethyl groups. By contrast, the 6,6-dialkyl-1-methylcyclohexenes **c** and **d** yielded the crossed ozonide **171** derived from the sterically more-congested carbonyl oxide. Therefore, one can conclude that in the last case the directive effect of the electron-donating methyl substituents at C-1 is more important (**Scheme 57** and **Table 19**).

On treating five- or six-membered cycloalkene acetates with ozone in methanol, it was possible to distinguish between the steric and electronic effects of substituents. 4,4-Dimethyl-2-cyclohexen-1-yl acetate gave exclusively the hydroperoxide **173**, which was subsequently converted into a methyl ester, proving the prevalence of the electronic effect of the allylic acetoxy group. On the other hand, from 4,4-dimethyl-2-cyclopenten-1-acetate both products were obtained, with **172** predominating in a ratio of 90:10, indicating that in this case the steric effect prevails (**Scheme 58** and **Table 20**) <1996JOC5953>.



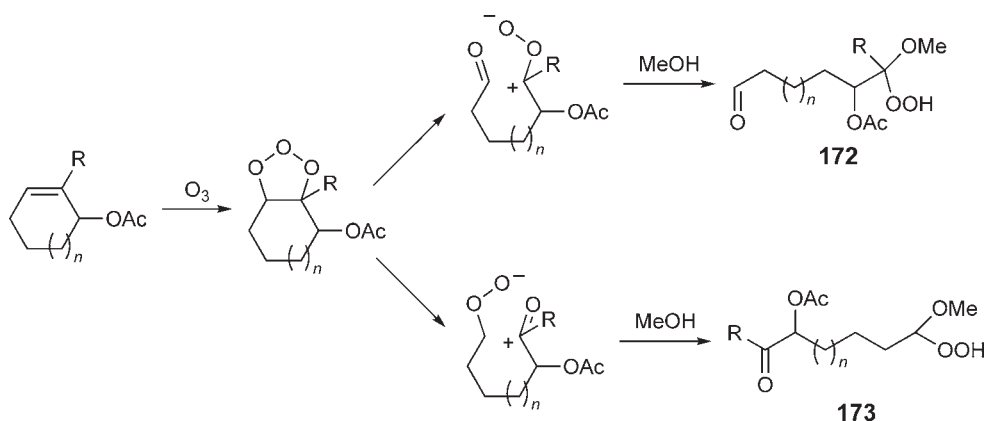
Scheme 56



Scheme 57

Table 19 Ozonations of cycloalkenes

Comp.	R^1	R^2	R^3	n
a	H	H	H	1
b	Me	Me	Me	1
c	H	Me	Me	1
d	H		$-(CH_2)_4-$	1
e	H	H	H	0
f	Me	Me	Me	0



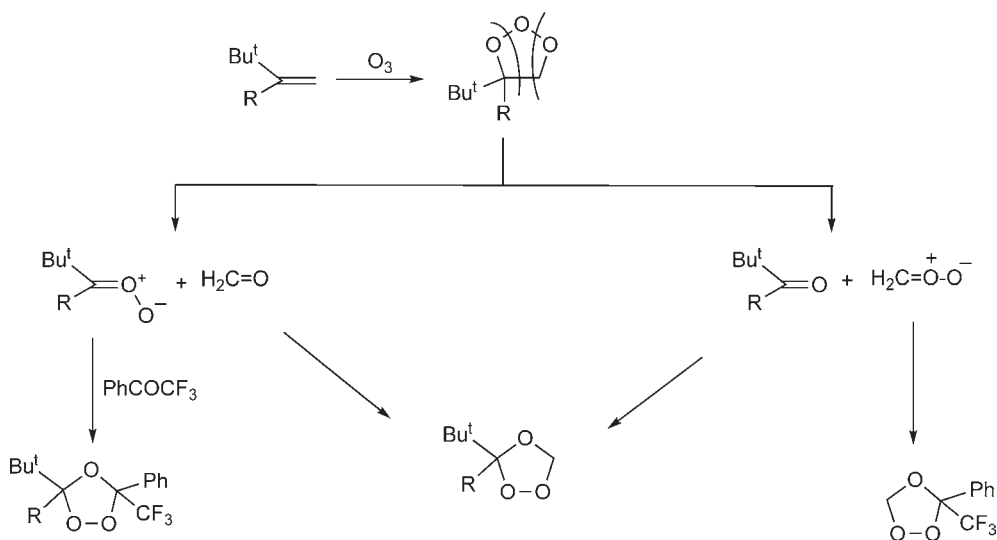
Scheme 58

Table 20 Ozonations of cycloalkene acetates

<i>Comp.</i>	<i>R</i>	<i>n</i>
g	H	1
h	Me	1
i	H	0
j	Me	0

It was established [2002T891](#) that in the presence of trifluoroacetophenone as trapping agent, the ozonolysis of 2,2,6-trimethyl-1-methylenecyclohexane afforded only the cross-ozonide derived from the capture of formaldehyde oxide, whereas the ozonolysis of 2,2,5-trimethyl-1-methylenecyclopentane gave only the alternative cross-ozonide derived from cycloadditions of 2,2,5-trimethylcyclopentanone oxide.

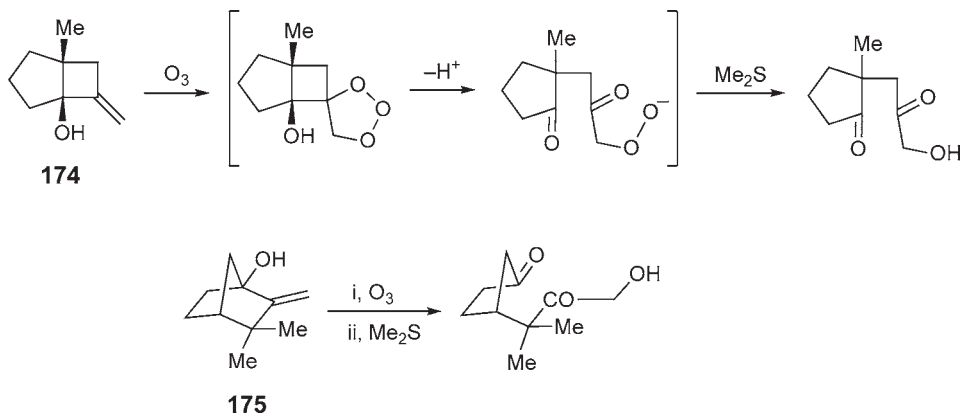
1-Alkyl-1-*tert*-butyl-ethylenes on ozonolysis in the presence of trifluoroacetophenone provide only the ozonide formed by the control of electronic effects of alkyl substituents. However, 1,1-di-*tert*-butylethylene affords the ozonide determined by cleavage controlled by steric effects such that the less-congested formaldehyde oxide is exclusively formed (**Scheme 59**) <2002T891>.



Scheme 59

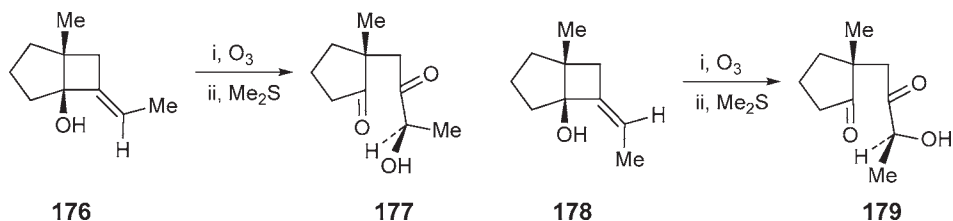
6.06.8.2.10 Grob fragmentation and Baeyer–Villiger rearrangement

An anomalous result of the ozonolysis of an allylic alcohol **174** (an α -hydroxy methylenecyclobutane with two stereogenic centers), followed by reduction by dimethyl sulfide, was interpreted as involving a Grob fragmentation following the trapping of the primary ozonide, without conversion into the secondary ozonide. A similar reaction occurred with the allylic alcohol **175** with a methylene–norbornane skeleton where any allylic rearrangement was precluded by Bredt's rule (**Scheme 60**) <2001OL627>.



Scheme 60

An interesting follow-up was a variation of the first reaction in which the methylene group of compound **174** was replaced by a *cis*- or *trans*-ethylidene group, which led to one or the other of the two diastereomers **177** and **179**, respectively (**Scheme 61**).



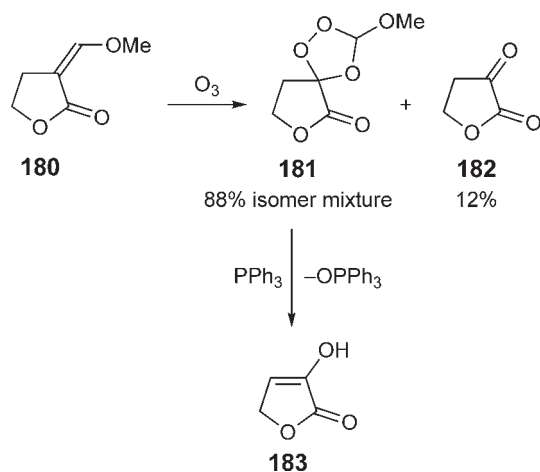
Scheme 61

Enol ethers of 1,2- and 1,3-diketones afford on ozonolysis products that are not in full agreement with the Criegee mechanism, because in some cases products of the Baeyer–Villiger rearrangement are formed. The main product in the ozonolysis of the enol ether **180** is a mixture of spiranic stereoisomers **181** involving a lactone and a 1,2,4-trioxolane ring (**Scheme 62**) <2004HCA2025>.

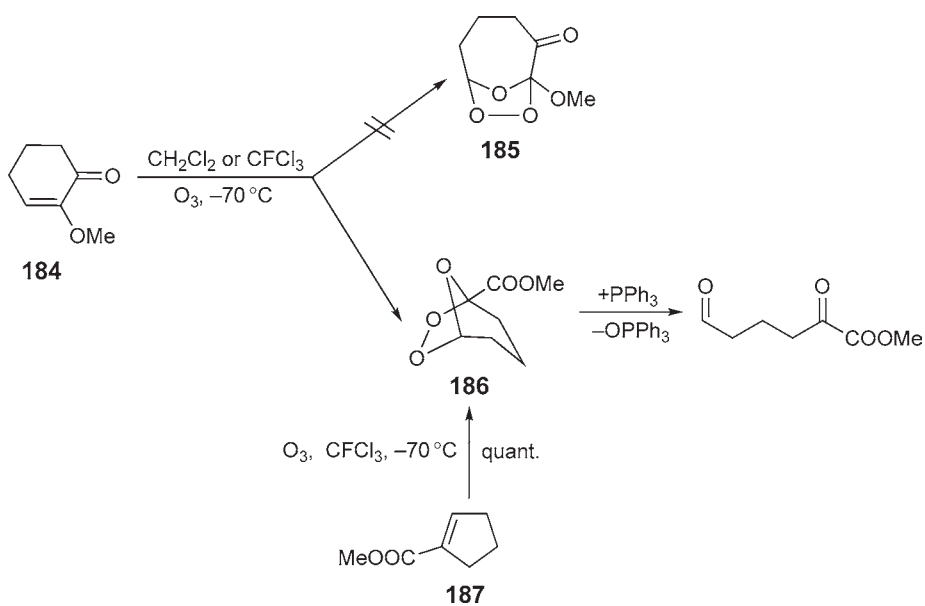
When the enol ether **184** of 1,2-cyclohexanedione is ozonolyzed, instead of the normal ozonide **185** one obtains the product **186** of an intramolecular cross-ozonation which was also synthesized as the normal ozonide from methyl 1-cyclopentenecarboxylate **187** (**Scheme 63**).

6.06.8.2.11 Formation of unsaturated hydroperoxy acetals

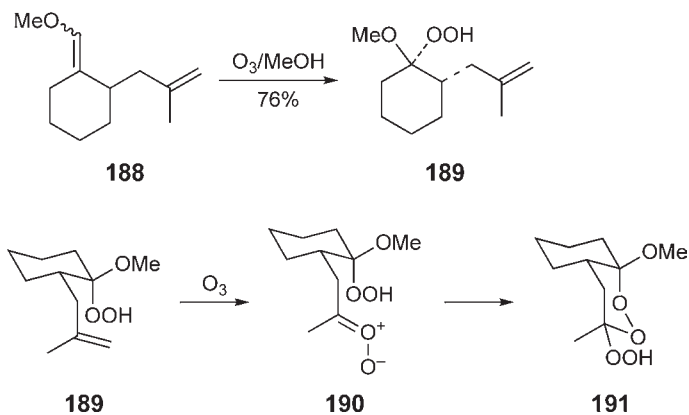
Unsaturated hydroperoxy acetals **189** are formed as the result of normal mono-ozonolysis in methanol of the more reactive double bond in dienes. Their subsequent ozonolysis in ether affords a 1,2-dioxane, resulting from the isopropenyl group (**Scheme 64**).



Scheme 62

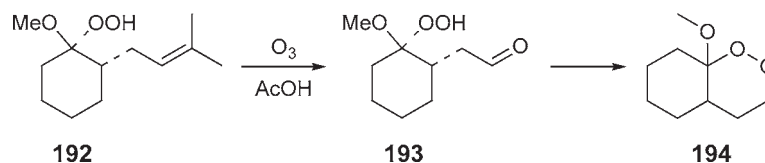


Scheme 63



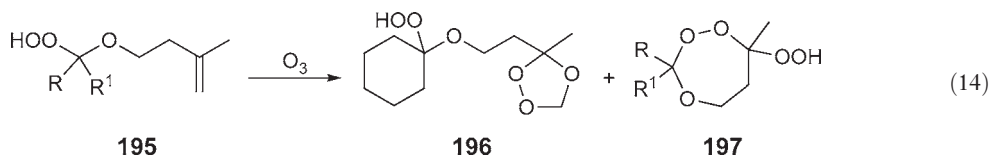
Scheme 64

By contrast, the homolog **192** with a trisubstituted double bond forms a different 1,2-dioxane **194** based on the product of ozonolysis of the isopropylidene group (**Scheme 65**) <2000H(53)1293>.



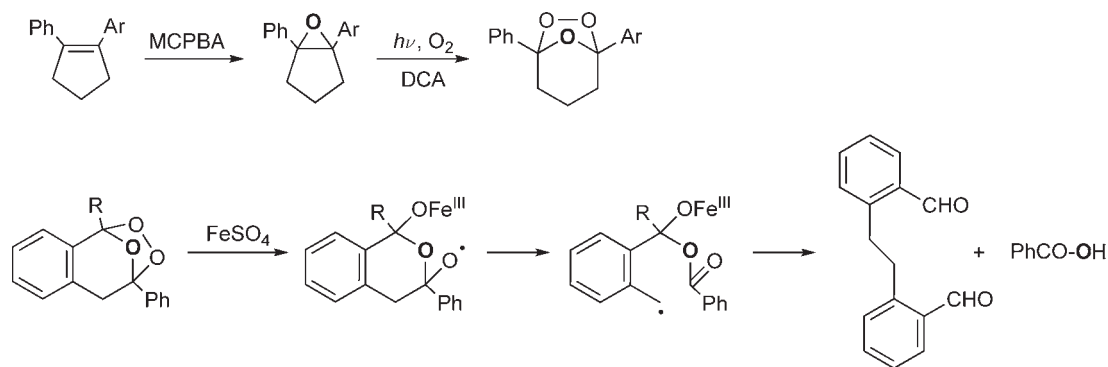
Scheme 65

More complex reaction mixtures containing also trioxolanes **196**, trioxepanes **197**, and (with longer chains) a trioxocane were formed from cyclohexane-based unsaturated hydroperoxy acetals **195** (Equation 14) <1997JOC4949>.



6.06.8.2.12 Fragmentation with Fe(II) compounds

In connection with the Fe(II)-induced decomposition of 1,2,4-trioxolanes, regiospecifically ^{18}O -labeled ozonides <1999JA6556> were synthesized by first preparing labeled epoxides from alkenes (1-aryl cyclopentene, 1,2-diaryl cyclopentene, or substituted 2-phenylindenes) and [^{18}O]meta-chloroperoxybenzoic acid obtained from the acid chloride and $\text{H}_2^{18}\text{O}_2$. Then electron-transfer photooxygenation photosensitized with dicyanoanthracene (DCA) afforded the labeled ozonide (boldface **O** in **Scheme 66** indicates ^{18}O). It was then shown that FeSO_4 causes fragmentation by attacking the less-hindered side of the peroxidic bond (in the case of cyclopentene ozonides with phenyl/mesityl groups, this was the phenyl-substituted side; in the case of indene ozonides it was the side with $\text{R}=\text{H}$). Mass spectrometric analyses of the fragmentation products traced the labels. This investigation is relevant for understanding the mode of action of the 1,2,4-trioxolane antimalarial drugs (see Section 6.06.10.3).



Scheme 66

6.06.9 Syntheses of Particular Classes of Compounds

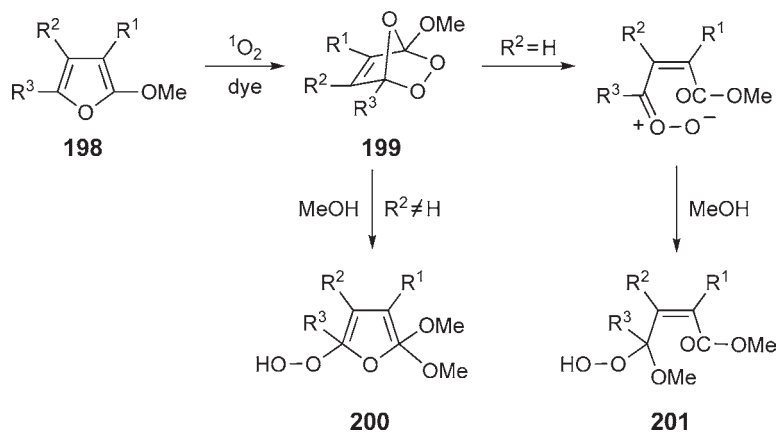
6.06.9.1 Parent Systems Including S-Oxides and S,S-Dioxides

6.06.9.1.1 *endo*-Peroxides

The *endo*-peroxides of aromatic oxygen-containing five-membered heterocycles such as furan and oxazole are actually ozonides (1,2,4-trioxolanes), and by a reverse dipolar [3+2] cycloaddition they can be a source of carbonyl oxides.

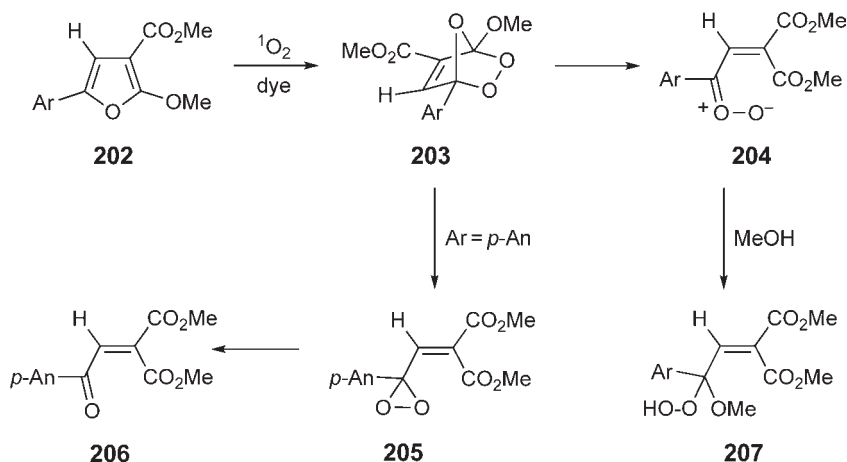
These ozonides can be prepared by photosensitized oxidation of suitably substituted heterocycles with singlet oxygen at low temperatures. The dye sensitizers are usually Methylene Blue, Rose Bengal, tetraphenylporphyrin, or 9,10-dicyanoanthracene.

By using tetraphenylporphyrin as sensitizer at -80°C , the *endo*-peroxide of a 2-methoxyfuran **198** afforded an ozonide **199** which behaved differently depending on the nature of the 4-substituent (R^2), although the products were hydroperoxides in both cases (Scheme 67) <1995JOC5324>.



Scheme 67

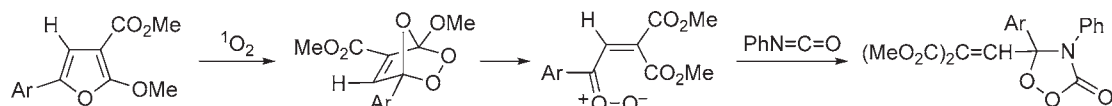
With *endo*-peroxides obtained similarly in the presence of tetraphenylporphyrin from 2-methoxy-3-carbomethoxy-5-arylfurans **202**, when the aryl group is electron donating (*para*-anisyl, *p*-An), the product **206** is derived from a dioxirane **205** formed by the isomerization of the intermediate carbonyl oxide (Scheme 68). With methanol a hydroperoxide **207** is obtained as in the previous case <1994JCS(P1)147>.



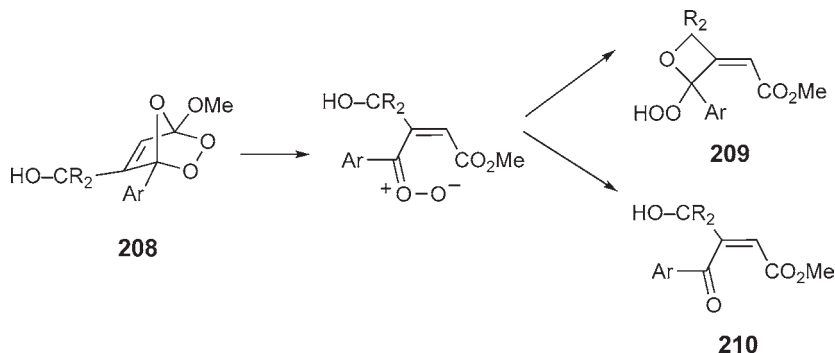
Scheme 68

Convincing evidence about the formation of the carbonyl oxide was obtained by trapping it with phenyl isocyanate as a dipolarophile (Scheme 69) <94JCS(P1)3295>.

An interesting 2-oxetanyl hydroperoxide **209** was obtained by Methylene Blue photosensitized oxidation as the main product from a furanic *endo*-peroxide **208** (Scheme 70) <2001JOC4732>.

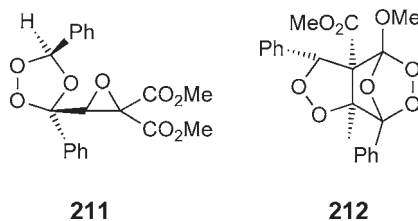


Scheme 69



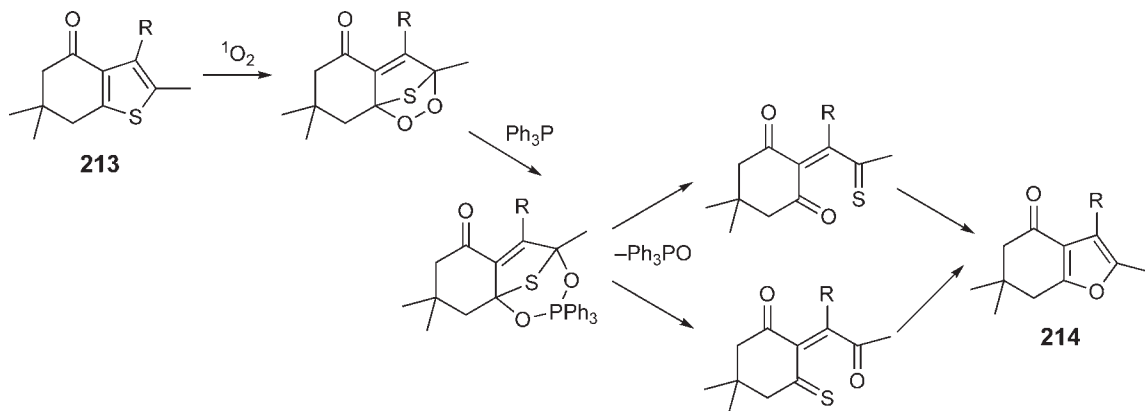
Scheme 70

The structures of products **211** and **212** obtained from furanic *endo*-peroxides with dimethyl malonate residues were confirmed by single crystal X-ray diffraction [<1989CC1608>](#).



6.06.9.1.2 Sulfur compounds

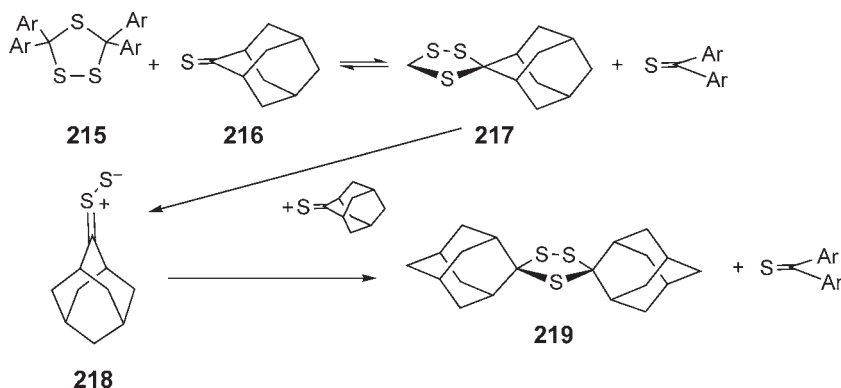
It is known that thiophenes react with singlet oxygen forming endoperoxides, which are thiazonides, and whose thermal reactions have been investigated. A novel reaction of acylthiophene endoperoxides **213** (photosensitized oxidation with tetraphenylporphyrine at -30°C) involves their treatment with triphenylphosphine. The nucleophilic attack finally leads to a furan derivative **214** by elimination of O and S atoms bound to phosphorus (**Scheme 71**) [<1995TL7431, 1998JA8914>](#).



Scheme 71

The endoperoxide transfers a sulfur atom to alkenes forming thiiranes (episulfides); the process is made more efficient in the presence of the tetraphenylporphyrinato cobalt(II) complex <1996CC177>. With cyclic alkynes such as cyclooctyne, an interesting thiirenium ion intermediate could be observed <2002JA8316>.

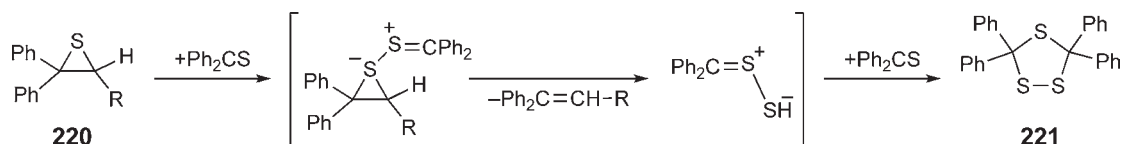
The metathesis equilibration between adamantanethione **216** and trithiolanes **215** is driven to the right (82% yield) via the intermediate thiosulfine **218** on refluxing in CHCl_3 probably by the conjugation energy of the thiobenzophenone. With an excess of adamantanethione the monospiro-trithiolane affords at 130°C a dispiro-trithiolane **219** (Scheme 72) <1997T939>.



Scheme 72

The electron impact mass spectra of 3,3-diphenyl-5-adamantyl-1,2,4-trithiolanes provide strong evidence for cycloreversion, with the base peak for the radical cation of the adamantanecarbonyl fragment and a strong peak corresponding to the radical cation of the second fragment, the radical cation of diaryl ketone. However, when one of the aryl groups is *para*-chlorophenyl, both modes of fragmentation occur. A different fragmentation consists of S_2 elimination, when one observes the remaining fragment as a radical cation <1997T939>.

Tetraphenyl-1,2,4-trithiolane **221** precipitated with a yield of 84% from a solution of 3-methyl-2,2-diphenylthiirane **220** ($\text{R} = \text{Me}$) and thiobenzophenone in a twofold molar excess kept in ether at room temperature during 3 weeks. In the mother liquor, 1,1-diphenylpropene was present in 90% yield. It was concluded that the 1,2,4-trithiolane has a remarkable formation tendency (Scheme 73) <1997T939>.

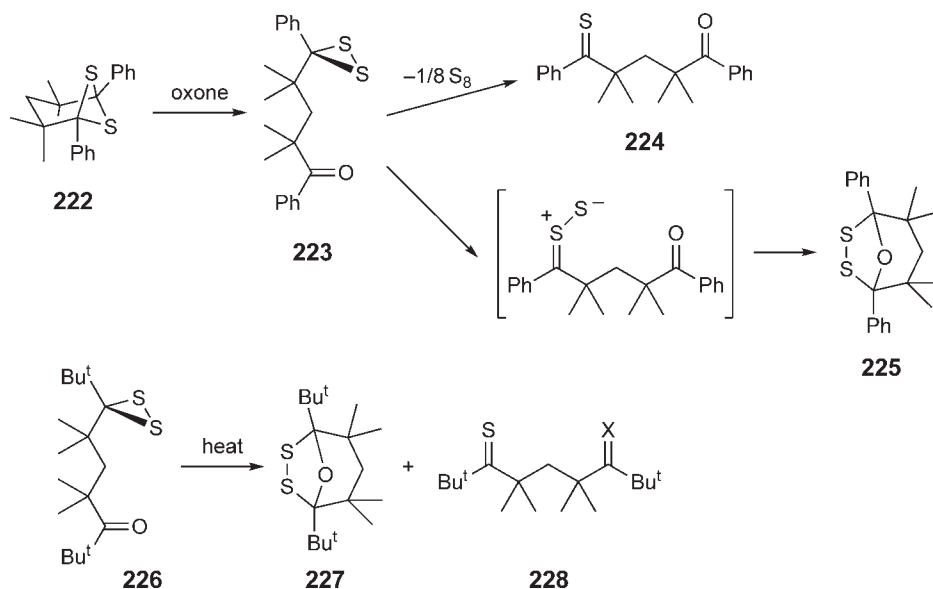


Scheme 73

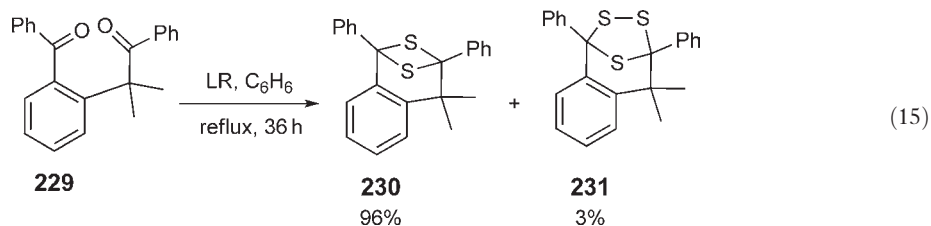
A stable dithiirane **223** was obtained from the oxidation of 6,7-dithiabicyclo[3.1.1]heptane **222** with oxone ($2\text{KHSO}_5 \cdot \text{KHSO}_4 \cdot \text{K}_2\text{SO}_4$). Heating in solution afforded a thioketone **224** and 8-oxa-6,7-dithiabicyclo[3.2.1]octane **225** (resulted from an intramolecular [3+2] cycloaddition of the δ -thioketone S -sulfide intermediate) (Scheme 74) <1997TL1431, 1997BCJ509>.

In a similar reaction, heating the di-*tert*-butyl-tetramethyl-keto-thiirane **226** affords an analogous 8-oxa-6,7-dithiabicyclo[3.2.1]octane **227**, in competition with desulfurizing reactions yielding a thioketone **228** ($\text{X} = \text{S}$) and a diketone **228** ($\text{X} = \text{O}$) (Scheme 74) <1997TL1431, 1997BCJ509>.

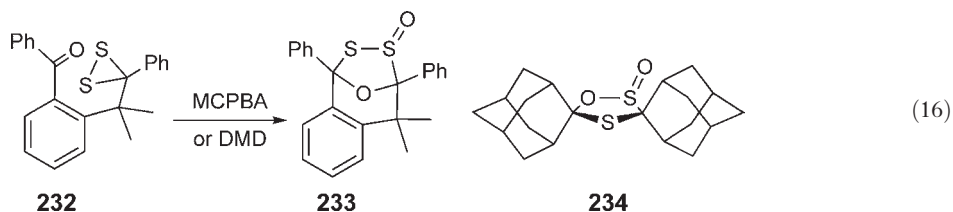
During the study of dithiiranes, thionations with Lawesson's reagent (LR) in refluxing 1,4-dioxane converted the aromatic diketone **229** into a 1,3-dithietane **230** (main product) and a 1,2,4-trithiolane **231** (Equation 15) <1997BCJ509>.



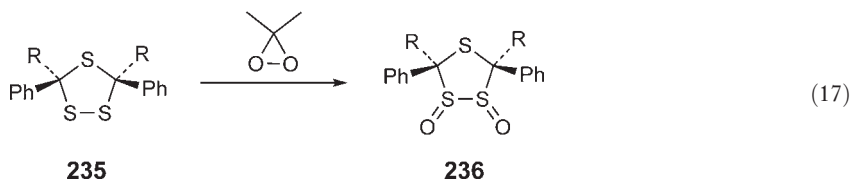
Scheme 74



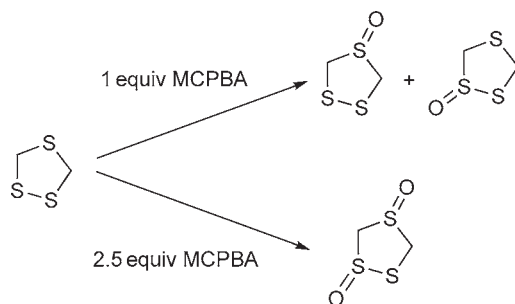
Oxidation of compound **232** with *meta*-chloroperbenzoic acid (MCPBA) or dimethyldioxirane (DMD) afforded an aromatic 1,3,4-oxadithiolane-3-oxide **233**, whose structure was confirmed by X-ray crystallography (Equation 16). An aliphatic bis-spiranic 1,2,4-oxadithiolane-2-oxide **234** derived from two adamantanonone groups was also prepared <1997BCJ509>.



Oxidation of stereoisomeric 3,3,5,5-tetrasubstituted trithiolene **235** with 4 molar equiv of DMD in CH_2Cl_2 at $-20^\circ C$ converted both 1,2-disulfide atoms into sulfoxidic groups. Yields were 42% for $R = Bu^t$ and 60% for 1-adamantyl. Equation (17) shows only one of the stereoisomers. With a limited amount of DMD, two stereoisomeric monoxides were obtained and they reacted with different rates to form the 1,2-dioxide and the 1-thiosulfonate with an SO_2 (sulfone) group. Longer heating (reflux in $CDCl_3$ or xylene) led to the formation of stereoisomeric episulfides. X-Ray crystallography confirmed the structures <2002TL5033, 2004JOC1695>.



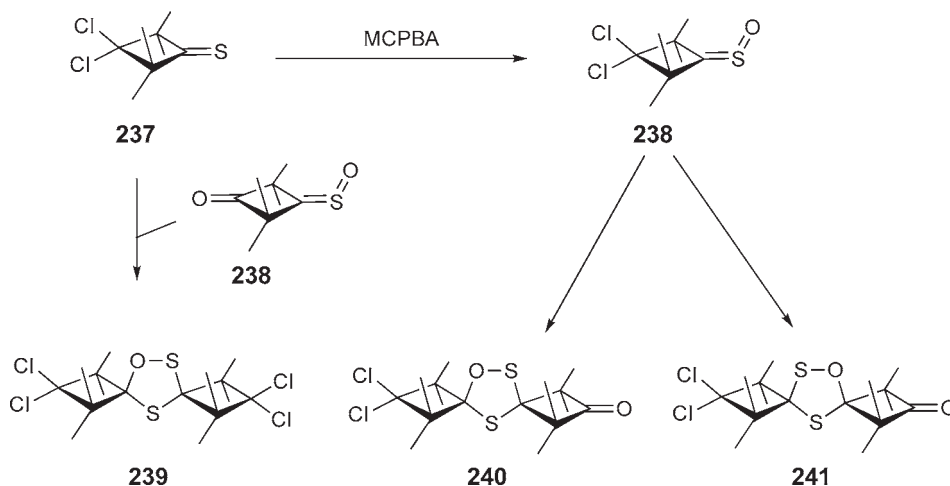
The investigation of how sulfur atoms in 1,2,4-trithiolane become oxidized to sulfoxide groups showed that 1 molar equiv of MCPBA in CH_2Cl_2 yields both isomers in comparable amounts, but only the compound with the thioether $\text{S}=\text{O}$ group could be isolated pure <2004ICA(357)1897>. With an excess of MCPBA, the dioxide that was obtained had a *trans*-structure, as shown by X-ray analysis (Scheme 75). *Ab initio* calculations were performed for the geometry and vibrational modes of the new compounds <2004ICA(357)1897>.



Scheme 75

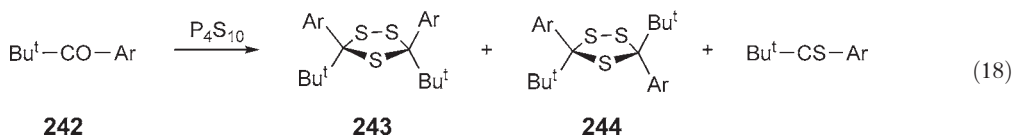
Oxidation of 3,3,5,5-tetramethyl-1,2,4-trithiolane with peracetic acid, however, proceeded regioselectively affording the 4-oxide, whereas with an excess (3 molar equiv) of peracetic acid, both the *cis*- and *trans*-stereoisomers of the 1,4-dioxide were obtained; surprisingly, with 6 equiv of peracetic acid, the stable 1,1,4,4-tetraoxide was formed <2004ICA(357)1857> (see also <2000ZNB453, 2002TL5033>).

Thiocarbonyl compounds (e.g., compound **237**) can be oxidized by *m*-Cl-C₆H₄-CO₃H to *S*-oxides (sulfoxes, e.g., compound **238**) which as 1,3-dipoles react with thioketones yielding 1,2,4-oxadithioles **239–241**. The structure of the cross-product **241** was confirmed by X-ray crystallography (Scheme 76) <2005HCA2624>.

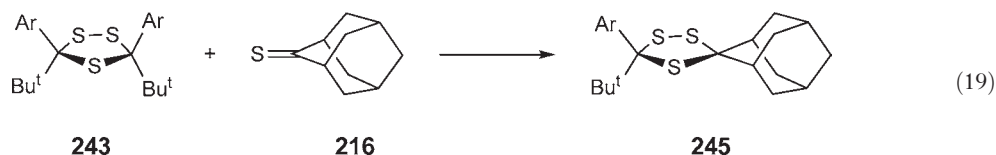


Scheme 76

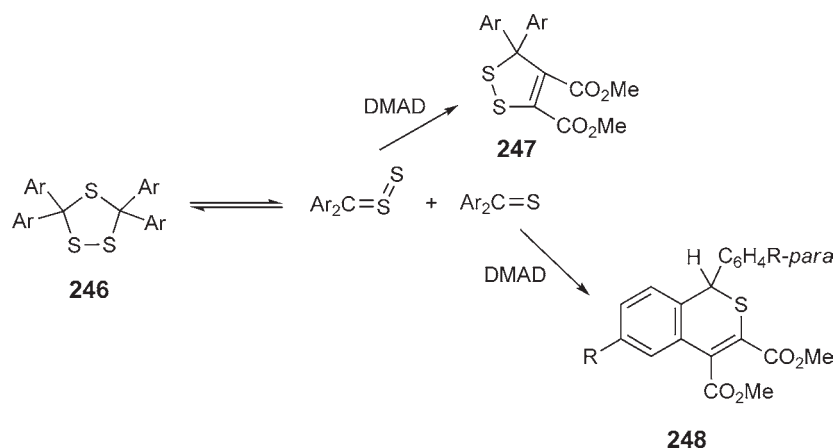
Pivalophenones **242** (Ar = *para*-tolyl) afford with tetraphosphorus decasulfide, on heating in refluxing pyridine, *cis*- and *trans*-3,5-di-*tert*-butyl-3,5-diaryl-1,24-trithiolanes **243** and **244** (Equation 18) <2000CC1535>. Structures were confirmed by X-ray crystal analysis. On refluxing in toluene the *cis*-isomer rearranges slowly into the more stable *trans*-diastereomer, along with degradation leading to Ar-CS-Bu^t.



Assuming that the mechanism of this isomerization involves fragmentation and formation of a thiocarbonyl *S*-sulfide, refluxing in toluene in the presence of adamantane-2-thione **216** led to a mixed trithiolane **245** (Equation 19) <2000CC1535>.

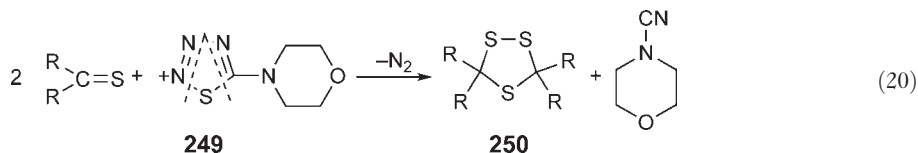


Dimethyl acetylenedicarboxylate (DMAD) is able to trap both products of the reversible thermal 1,3-dipolar cycloreversion. With an excess of DMAD at 60 °C without solvent, the product **247** (Ar = Ph) arising from thiosulfine was formed in 83% yield, and the benzothiopyran **248** arising from the thiobenzophenone in 68% yield. With R = Cl, yields were slightly lower (Scheme 77) <1997T939>.



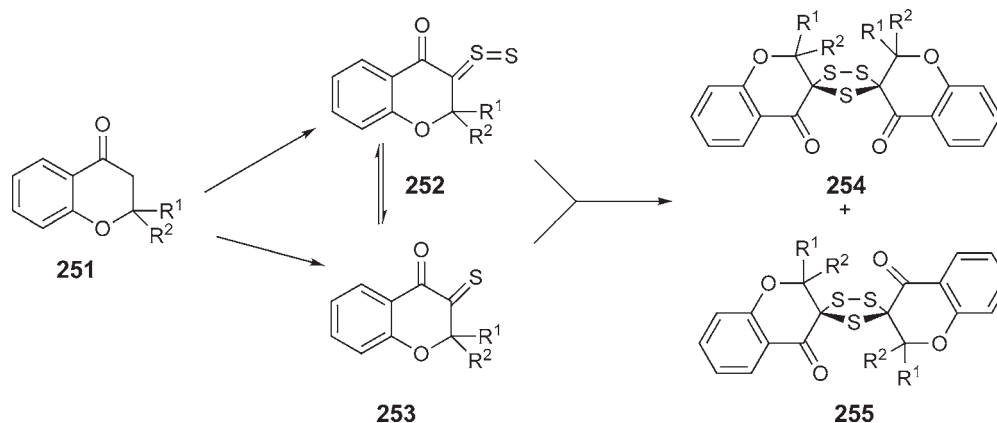
Scheme 77

It was discovered recently that 5-morpholino-1,2,3,4-thiadiazole **249** on refluxing in toluene decomposes into dinitrogen, morpholino-cyanamide, and an active form of sulfur that is able to react with thioketones converting them into elusive thiocarbonyl-*S*-sulfides. With a second mole of thioketone, these reactive thiosulfines combine forming 1,2,4-trithiolanes **250** <2007HCA594>; the R₂C groups are parts of rings (adamantanethione, or 2,2,4,4-tetramethyl-3-thioxocyclobutanone). When a mixture of equimolar amounts of the above two thiones was heated with the morpholino-thiadiazole, the three products were in 1:2:1 ratio, with the mixed one predominating. With R = Ph, the morpholino-thiadiazole, and 2,2,4,4-tetramethyl-3-thioxocyclobutanone also led to the mixed tetrasubstituted 1,2,4-trithiolane **250** (Equation 20).



From the sequential reaction of 4-chromanones **251** with thionyl chloride, thioacetic acid, and morpholine, a mixture of thioxochroman-4-one **252** and its *S*-sulfide **253** can be obtained (actually they can disproportionate). By cycloaddition, stereoisomeric 1,2,4-trithiolane derivatives **254** and **255** have been obtained; the R¹, R² groups in Scheme 78 can actually be derived from cyclanones <1998JOC9480>.

It was mentioned earlier that thiocarbonyl thiolates reacted with thioketones forming 1,2,4-trithiolates <1987JA902>. Aromatic thioketones (e.g., thiobenzophenone) are super-dipolarophiles and at 80 °C in a three-reagent mixture with phenyl azide and cyclobutanethiones they form spiranic compounds with X = CO, CS, or CH₂ (Equation 21) <1995HCA1298>. An X-ray study of the compound with Ar = 4-MeOC₆H₄ confirmed the molecular structure.



Scheme 78



6.06.9.2 C-Linked Substituents

No significant developments have been reported since the publication of CHEC-II(1996) <1996CHEC-II(4)581>.

6.06.9.3 N-Linked Substituents

No significant developments have been reported since the publication of CHEC-II(1996) <1996CHEC-II(4)581>.

6.06.9.4 O-Linked Substituents

No significant developments have been reported since the publication of CHEC-II(1996) <1996CHEC-II(4)581>.

6.06.9.5 Halogens Attached to the Ring

No significant developments have been reported since the publication of CHEC-II(1996) <1996CHEC-II(4)581>.

6.06.10 Important Compounds and Applications

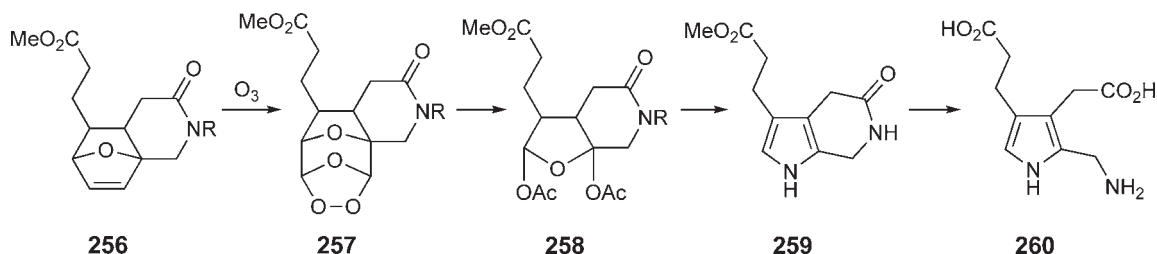
6.06.10.1 Applications in Research and Industry

6.06.10.1.1 Synthesis of porphyrinobilinogen

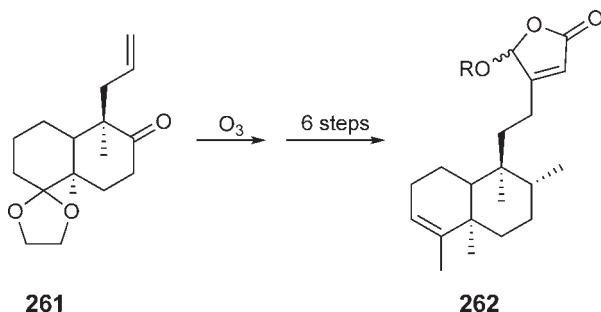
An interesting application of ozonolysis was the synthesis of porphyrinobilinogen **260** starting from *N*-benzylfurfurylamine which was converted in several steps into a tricyclic 7-oxanorbornene **256**. This was ozonolyzed, converted into a tetrahydrofuranic derivative **258** and then into a pyrrolic lactam methyl ester **259**. The last step involved the hydrolysis of the porphyrinobilinogen lactam methyl ester to furnish porphyrinobilinogen **260** <2001JA9307>, which is the precursor of the biologically important tetrapyrroles, also used in photodynamic therapy and in treating acute lead poisoning (Scheme 79).

6.06.10.1.2 Synthesis of clerodane and 4-alkyl-4-ketoglutaric acids

For the synthesis of an antibacterial clerodane **262**, ozonolysis of a substituted optically pure (–)-2-decalone **261** with (5*R*,9*R*,10*R*)-configuration was the starting step (Scheme 80) <1995J(P1)757>.

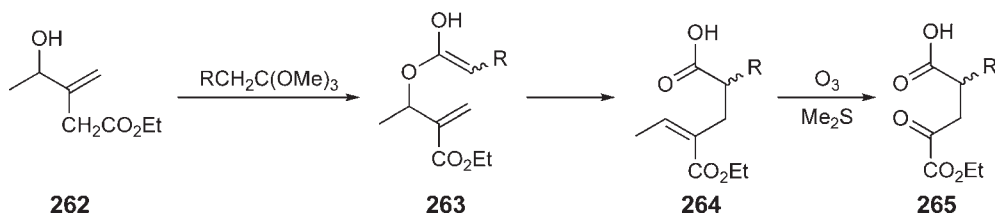


Scheme 79



Scheme 80

4-Alkyl-4-ketoglutaric acids **265**, potential substrates of transaminases that are important for the nervous system, can be synthesized (from an enol ether **263** that was not isolated) by a Claisen–Johnson rearrangement affording a 2-ethylidene-4-methylglutarate **264** whose ozonolysis in CH_2Cl_2 at -78°C followed by reduction with dimethyl sulfide provided the final product (Scheme 81) <1999TL6577>.



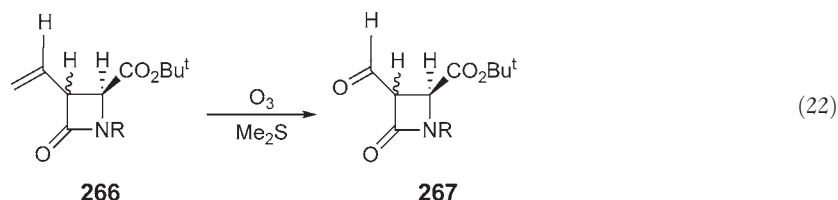
Scheme 81

6.06.10.1.3 Analysis of LDL by mass spectrometry after ozonolysis

Low-density lipids in the blood cause cholesterol deposits. Their presence and nature, including the position and number of double bonds, can be analyzed by means of ESI-MS techniques <2000JMP224>. Reverse-phase HPLC microsamples containing phospholipids were treated with bis(trimethylsilyl) trifluoroacetamide, then with methoxyamine, and then exposed for 8 min to ozone gas at room temperature; ESI-MS followed and showed the fragments corresponding to ozonides.

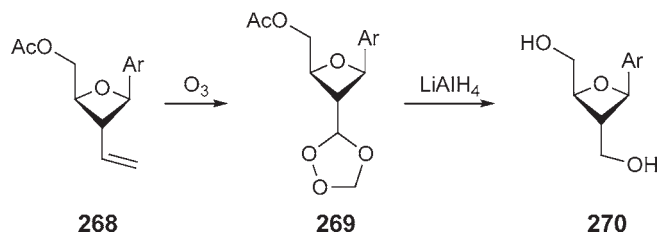
6.06.10.1.4 Synthesis of β -lactams

A convenient synthesis was developed for ibotenic β -lactams **267** (glutamate receptor analogues) using a ‘ring-switching’ technique, wherein ozonolysis of BOC-protected **266** ($\text{R} = \text{Bu}^t\text{-O-CO-}$) followed by reduction with dimethyl sulfide provided a key aldehyde. Irrespective of the *cis/trans* ratio of the initial vinyl- β -lactam, the same mixture of diastereoisomers resulted, and they were further used without purification because of the instability of the aldehydes (Equation 22) <2003OBC2670>.



6.06.10.1.5 Synthesis of oxetanocin analogues

The stereoselective synthesis of oxetanocin analogues **270** (antiviral nucleosides used against HIV and cytomegalovirus) with Ar = phenyl, *m*-tolyl, or *p*-anisyl involved ozonolysis of alkene **268** in CH₂Cl₂ at –78 °C followed by reduction (**Scheme 82**). Using NaBH₄, the intermediate ozonide **269** could be isolated, but LiAlH₄ gave directly the diol **270** <1996TL7667>. In oxetanocin, Ar is an adenyl group.



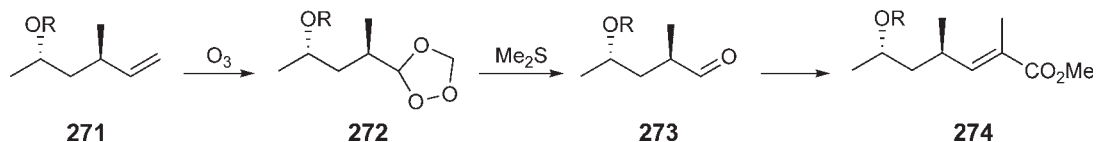
Scheme 82

6.06.10.1.6 Toxicities of ozonides

A comparison between the lung toxicity of methyl linoleate 9,10-ozonide and cumene hydroperoxide on rats showed that the former is 3 times more toxic than the latter <1994MI243>. It was also found that the ozonide did not enhance lipid peroxidation. Glutathione and vitamin E protected rats against the effect of the ozonide.

6.06.10.1.7 Synthesis of jasplakinolide

One of the key steps in the synthesis of the depsipeptide jasplakinolide involved the preparation of an aldehyde **273** by ozonolysis of an alkene **271** with the correct stereochemistry of the substituents (**Scheme 83**). The hydroxyl group was protected with R = *tert*-butyl(dimethyl)silyl <2004ASC855>.



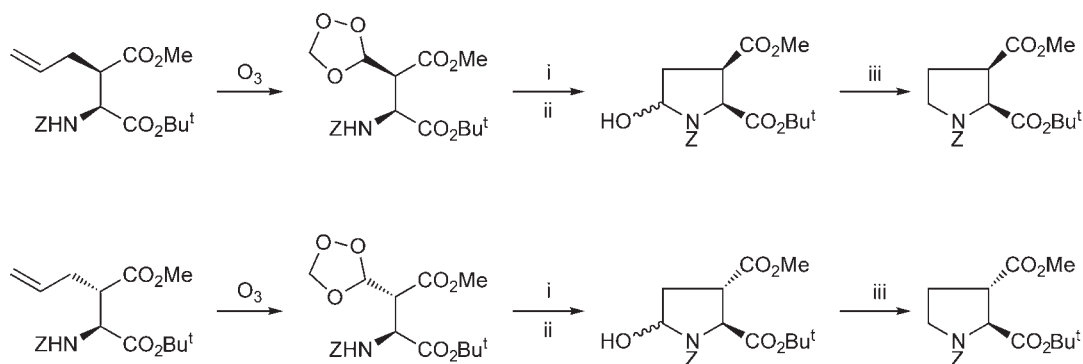
Scheme 83

6.06.10.1.8 Ozonolysis in asymmetric synthesis

An asymmetric synthesis of both diastereomers of 3-carboxyproline derivatives was based on the regiospecific deprotonation of aspartate esters, which allowed the synthesis of diastereomeric allyl aspartates. Their ozonolysis in methanol at –70 °C in the presence of 1 molar equiv of acetic acid (i), followed by reduction with Me₂S (ii) and catalytic hydrogenation with Pd/C (iii), led to the two diastereomers <1994TL8859>. Treatment with trifluoroacetic acid (TFA) removed isobutene and the (*Z*) protecting group, but did not affect the carbomethoxy group. This was the starting point for several other stereospecific reactions (**Scheme 84**) <1995T8525>.

6.06.10.2 Natural Occurrence

Among the numerous papers published during the last decade about the smell of 1,2,4-sulfur/oxygen-containing saturated compounds, only a small part will be mentioned. Although most sulfur compounds are generally malodorous



Scheme 84

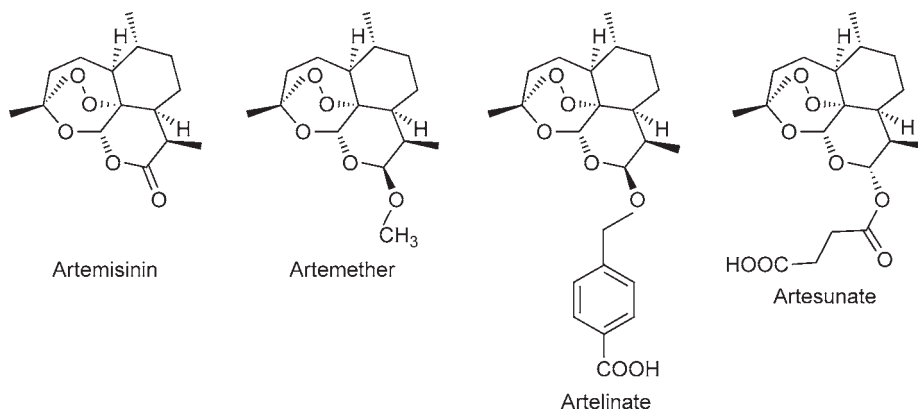
substances, a few have gained acceptance as desired aromas. It is common knowledge that the smell of garlic and onion is connected with sulfur compounds. The odorous components of dried shiitake mushrooms (*Lentinula endodes*) continue to draw attention because this is the biggest mushroom business in Japan <2004BBB66, 2004JWS358>. An important constituent is 3,5-dimethyl-1,2,4-trithiolane. The formation of such compounds takes place during cooking meat products via the Maillard reaction/Strecker degradation of cysteine and/or methionine <1997JFA894>. In Southeast Asian countries, a fruit called durian (*Durio zibethinus* Murr) is much appreciated and extracts are sold also on the West American coast (its smell is described as a mixture of old cheese and onions flavored with turpentine) <2005JFE66>. Many of the papers describe dozens of constituents determined by refined analytical techniques.

6.06.10.3 Biological Activity

6.06.10.3.1 Ozonides with antimalarial activity

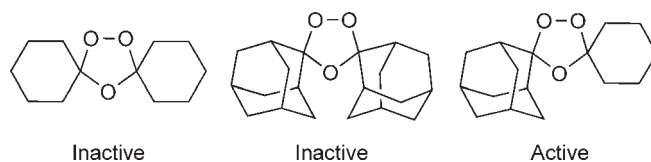
One of the most serious diseases in the world at present is malaria. One million people (out of 2.4 billion people at risk) die every year, mostly children under the age of 5 and pregnant women in 90 developing countries, due to this disease <2002NAT686>. The deadly parasites *Plasmodium falciparum* (blood sporozoa) are transmitted via *Anopheles* mosquitoes, and they have become resistant to quinine and most of the traditional synthetic drugs such as chloroquine. This disease has been around since the evolution of *Homo sapiens* and has given rise to genetic adaptations of African (sickle cell anemia) and Southeast Asian populations (thalassemia), whereby resistance to parasites is conferred in exchange for altered erythrocytes when one of the parents carries the corresponding gene (however, when both parents are carriers, the anemia may be fatal). Endemic malaria is not confined, however, to tropical and equatorial countries, but is encountered also at high latitudes where there are many mosquitoes, but there the population density is much lower.

In 1972, artemisinin, which has a 1,2,4-trioxane ring, was isolated from the Chinese plant Qinghao (*Artemisia anna* L.) that had been known for a long time among medicinal herbs. Its structure was elucidated by X-ray crystallography in 1979. It was then discovered that it can kill chloroquine-resistant strains of *Plasmodium*. With semisynthetic analogues (artemether, artelinate, and artesunate), this was the first recent breakthrough against malaria <1985SCI1049, 1992J(P1)3251, 1996J(P1)1101, 2002ACR255>. At present an international effort is under way for cultivating Qinghao, but the better hopes are for a fully synthetic and cheaper product.

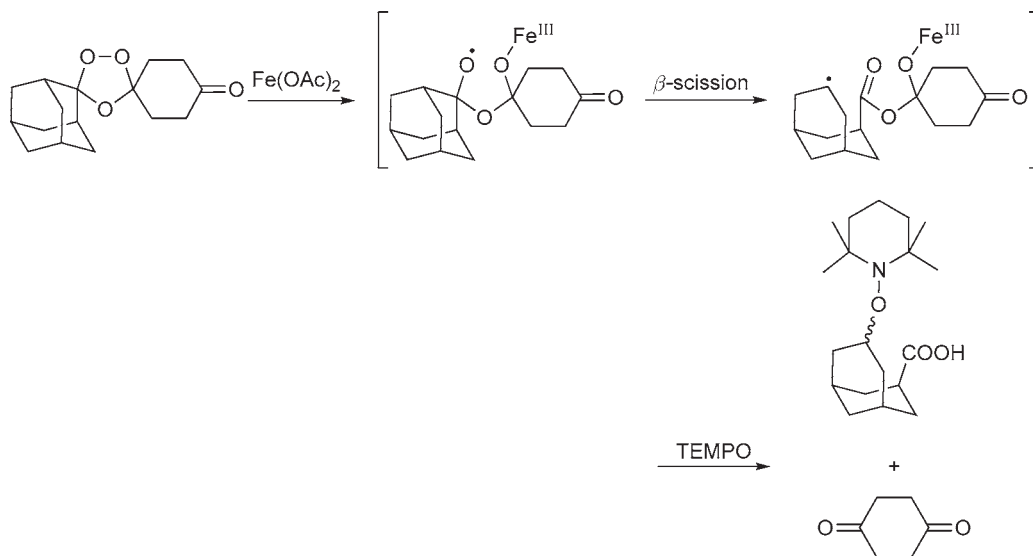


The mechanism of action for such peroxidic compounds involves a reductive activation by iron in haem, released as a result of hemoglobin digestion by *Plasmodium*. This irreversible redox reaction affords carbon-centered free radicals causing the alkylation of haem and of proteins. One such protein (the sarcoplasmic-endoplasmic reticulum ATPase PfATP6) appears to be critical for parasite survival, and there is no indication for resistance by the parasite. However, treatment is expensive and recrudescence of malaria occurs often. Moreover, it was found that at high doses such compounds are neurotoxic.

Starting from the finding that sterically hindered secondary ozonides derived from tetra-substituted alkenes are stable and can be readily synthesized by the cross-ozonation reaction, a drug design process was initiated taking into account the finding that asymmetrically substituted 1,2,4-trioxolanes show antimalarial activity. In order to obtain stable tetrasubstituted trioxolanes, the first attempts involved co-ozonolysis reactions of *O*-methyl-2-adamantanone oxime or *O*-methyl-cyclohexanone oxime (to provide the reactive carbonyl oxide along with methyl nitrite) and a carbonyl derivative. It was found that the symmetrically tetrasubstituted trioxolanes were inactive (the peroxide bond in the first one was too exposed, and in the second one was sterically hindered), but the nonsymmetrical one showed the expected biological activity, and this was the lead compound <2004NAT900>. Then the difficult task of optimizing this lead structure started.

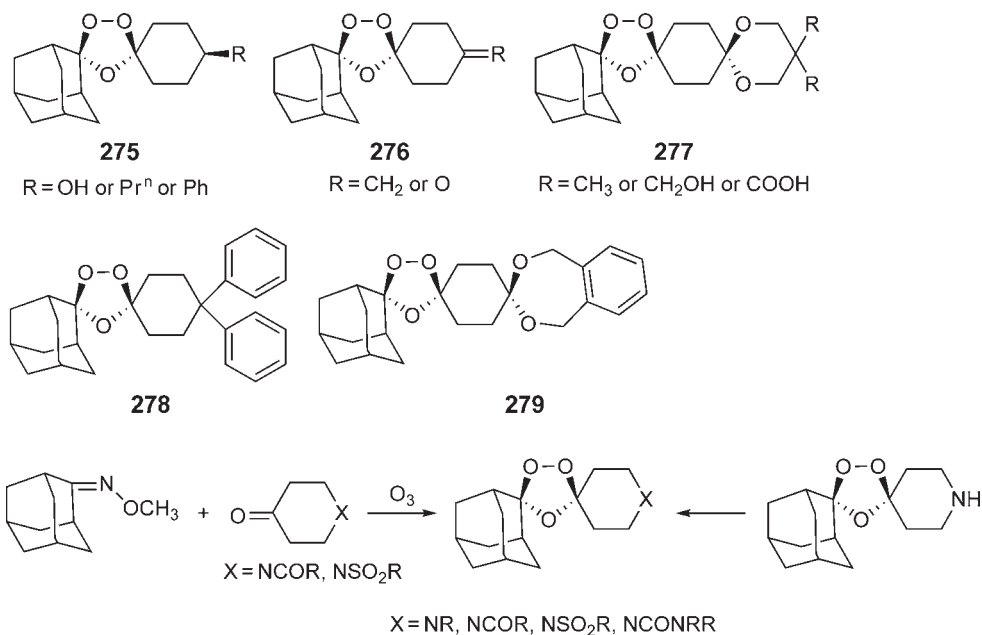


First, one had to check that the mechanism of action was correct. The product of co-ozonolysis of *O*-methyl-2-adamantanone oxime with 1,4-cyclohexanedione afforded on treatment with ferrous acetate a secondary carbon-centered free radical that was trapped with the usual spin trap, 2,2,6,6-tetramethylpiperidine-*N*-oxide (TEMPO), and involved a β -scission of the adamantane fragment, thus proving that the attack of the Fe(II) species occurred on the less-hindered peroxide bond oxygen atom (Scheme 85) <2004NAT900, 2005JOC513>.



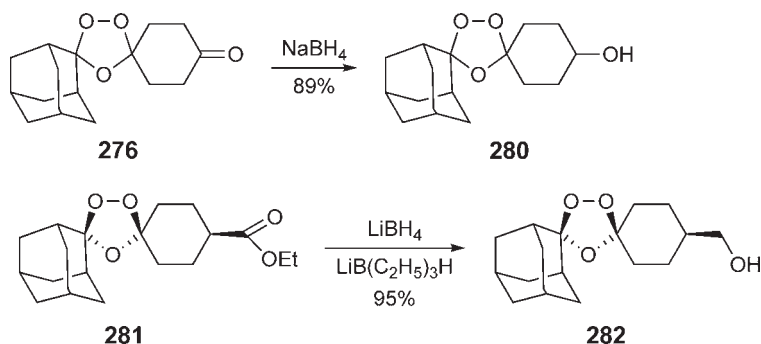
Scheme 85

Among the possible cyclohexanone derivatives, the choice fell on 4-substituted ones (which would not lead to enantiometric mixtures) and to substituents that would yield convenient lipophilicities <2006BMC6368, 2006BML5542, 2007BML1260>. A few such compounds are shown below, and they are derived from 4-substituted cyclohexanones or from 4-pyridone derivatives (Scheme 86).



Scheme 86

It was found that the 1,2,4-trioxolane ring is not affected by borohydrides which can reduce keto or ester groups as shown in [Scheme 87](#).



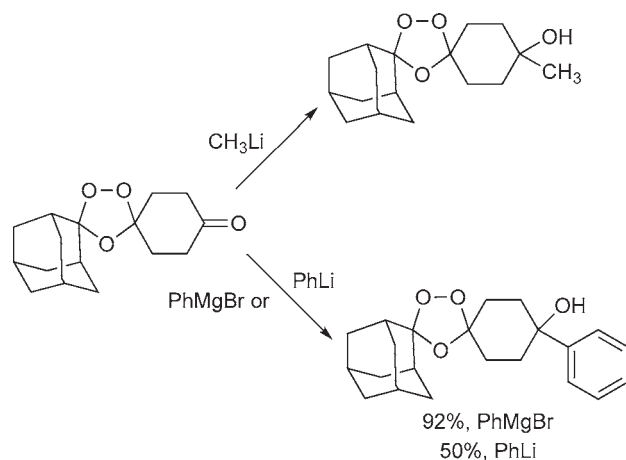
Scheme 87

Carbon nucleophiles (Grignard or lithium reagents) react normally as shown in [Scheme 88](#).

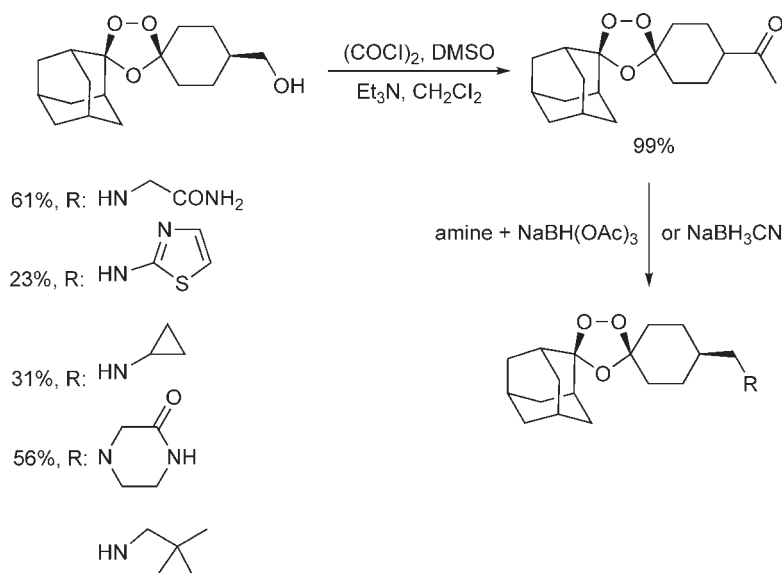
Amination reactions can be carried out in convenient yields ([Scheme 89](#)).

Lead optimization led to the selection of several totally synthetic active compounds, among which the last one, compound **285** ([Scheme 90](#)), has already passed phase-I and -IIa clinical trials.

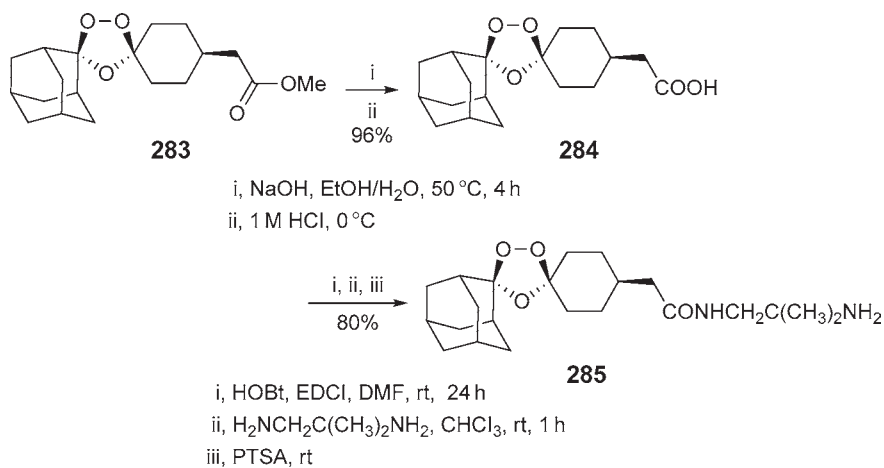
It is a short- and rapidly acting compound, which has to be combined with a long-acting drug, piperazine phosphate. This will be the first synthetic peroxide antimalarial, inexpensive, and extremely active. The adamantane building block may be synthesized by Schleyer's catalytic isomerization of perhydro-dicyclopentadiene; recent findings of adamantane and other diamond hydrocarbons in oil deposits make it likely that this rich source of such hydrocarbons will lower even more the cost of starting materials for this promising antimalarial drug. Other tropical diseases such as schistosomiasis may also be cured.



Scheme 88



Scheme 89



Scheme 90

6.06.11 Further Developments

Because nowadays the ozonation reaction has reached industrial development maturity, being no longer only a laboratory curiosity, and because it rests on a sound mechanistic background, future applications are very likely to emerge. The stability of adequately-substituted secondary ozonides may lead to their use in medicine, although bioavailability problems may arise as in the case of compound **285**; however, other cyclic peroxidic antimalarial compounds may be found <2007JMC2516>.

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Biographical Sketch



Teodor Silviu Balaban was born in Bucharest, Romania in 1958 and studied chemistry at the University 'Politehnica' in Bucharest (UPB). He started his career at the 'C.D. Nenitzescu' Centre for Organic Chemistry of the Romanian Academy of Sciences in 1983 in Bucharest and obtained his PhD degree in 1990 at the UPB under the supervision of Ecaterina Ciorănescu-Nenitzescu. Postdoctoral studies in Germany were due to an Alexander-von-Humboldt fellowship with Günther Snatzke in Bochum and with Klaus Hafner in Darmstadt. In 1993 he moved to the Max-Planck Institute for Radiation Chemistry in Mülheim an der Ruhr where he worked with Kurt Schaffner and Alfred Holzwarth on the structural elucidation of the chlorosome architecture, a light-harvesting organelle of photosynthetic bacteria. He was appointed temporary positions in Mülheim and in 1997 in Strasbourg (France) with the CNRS at the Laboratoire de Chimie Bioorganique where he worked on a vaccine against the Alzheimer disease. In Strasbourg he met Jean-Marie Lehn who allowed him to enjoy the facilities and work atmosphere of his laboratories. Silviu has remained associated with Professor Lehn, first as Maître de Conférences at the Collège de France and since 1999 at the Research Centre in Karlsruhe where he has initiated and directed a laboratory in the Department of Supramolecular Chemistry at the Institute for Nanotechnology. He has obtained in 2000 his habilitation from the Université Louis Pasteur in Strasbourg under the guidance of Professor Lehn. Silviu's main research interests are natural and artificial light-harvesting systems, nanochemistry, self-assembling systems including chromophores, high-energy materials (explaining his interest in peroxides and ozonides related to the present chapter), odorants, and last, but not least, chemical applications of graph theory. He is author or co-author of over one hundred journal articles and five book chapters. Since 2007 he has been appointed full professor for organic supramolecular assemblies at the Université Paul Cezanne in Marseille, France.



Alexandru T. Balaban was born in Timișoara, Romania in 1931 and studied mathematics, chemistry, and radiochemistry in Bucharest. He obtained a PhD in organic chemistry under the guidance of Costin D. Nenitzescu in 1959, shortly after discovering a novel synthesis of pyrylium salts and the birth of his son Silviu. He was head of the Laboratory for Labeled Organic Compounds at the Institute of Atomic Physics in Bucharest between 1961 and 1975 and during

1967–70 he served as senior research officer at the International Atomic Energy Agency in Vienna, Austria. He has taught general chemistry and organic chemistry at the University ‘Polytechnica’ in Bucharest from 1956 until 1999 having supervised more than 40 PhD theses. Because of his opposition of the communist doctrine, regime, and leaders he was never allowed to operate a large research group or to have leading positions after 1975 until the fall of the Iron Curtain in late 1989. As reparation, afterwards, he was elected as vice president of the Romanian Academy. Since 2000 he has been a tenured professor of chemistry at the Texas A&M University at Galveston and continues to enjoy teaching and research in a magnificent environment. Sandy has authored more than 650 research papers, over 50 book chapters in books edited by other authors, has edited seven books and has authored nine books. Additionally, 26 patents have been issued with him as an inventor. He is recipient of numerous awards of which we mention only the Herman Skolnik Award of the Division of Chemical Information of the American Chemical Society in 1994. He has been elected to the Romanian Academy in 1963 and is since 2001 an honorary member of the Hungarian Academy of Sciences. Since 2005 he acts as president of the International Academy of Mathematical Chemistry in Dubrovnik, Croatia. Main research interests are divided into two groups (1) experimental organic and bio-organic areas and (2) theoretical chemistry areas and drug design. Among other experimental contributions, which are more related to the present chapter than the theoretical works, he is well known for syntheses of heterocyclic compounds, stable nitrogen free radicals, nitric oxide donors, catalytic isomerizations of polycyclic aromatic hydrocarbons, homogeneous catalysis and isotopically labeled compounds.

6.07

Tetrazoles

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6.07.1	Introduction	259
6.07.1.1	Historical	259
6.07.1.2	General Survey of Literature	260
6.07.1.3	Structural Types and Nomenclature	261
6.07.2	Theoretical Methods	262
6.07.2.1	Electronic Structure and Geometry	263
6.07.2.2	Energetic Aspects	264
6.07.3	Experimental Structural Methods	265
6.07.3.1	X-Ray Crystal Structures	265
6.07.3.1.1	NH-Unsubstituted tetrazoles	265
6.07.3.1.2	1-Substituted tetrazoles	267
6.07.3.1.3	2-Substituted tetrazoles	269
6.07.3.1.4	Nonconjugated tetrazoles	270
6.07.3.1.5	Tetrazolate anions	271
6.07.3.1.6	Tetrazolium ions	271
6.07.3.2	Microwave Spectroscopy	272
6.07.3.3	NMR Spectroscopy	272
6.07.3.3.1	Proton NMR spectra	274
6.07.3.3.2	Carbon-13 NMR spectra	275
6.07.3.3.3	Nitrogen NMR spectra	277
6.07.3.4	Mass Spectrometry	279
6.07.3.5	IR/Raman Spectroscopy	280
6.07.3.6	UV/Fluorescence Spectroscopy	281
6.07.3.7	Photoelectron Spectroscopy	282
6.07.3.8	Dipole Moments	283
6.07.3.9	Other Methods	283
6.07.4	Thermodynamic Aspects	284
6.07.4.1	Aromaticity	284
6.07.4.2	Intermolecular Forces	285
6.07.4.2.1	Melting and boiling points	285
6.07.4.2.2	Solubility, density	286
6.07.4.2.3	Chromatographic behavior	287
6.07.4.3	Thermochemical Properties	287
6.07.4.3.1	Enthalpies of formation and related parameters	288
6.07.4.3.2	Explosive and combustion parameters	290
6.07.4.4	Tautomerism	291
6.07.4.4.1	Annular tautomerism	291
6.07.4.4.2	Ring substituent	296
6.07.4.4.3	Ring-chain tautomerism	298
6.07.4.5	Acid–Base Equilibrium	300
6.07.4.5.1	Acidity	300

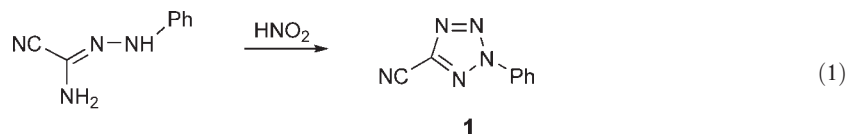
6.07.4.5.2	Basicity	303
6.07.4.5.3	Hydrogen bonding	304
6.07.5	Reactivity of Fully Conjugated Ring	305
6.07.5.1	General Survey	305
6.07.5.2	Unimolecular Thermal and Photochemical Reactions	305
6.07.5.2.1	Fragmentation of N-unsubstituted and 1-substituted tetrazoles	305
6.07.5.2.2	Fragmentations of 2-substituted tetrazoles	310
6.07.5.2.3	Rearrangements	313
6.07.5.3	Electrophilic Attack at Endocyclic Nitrogen Atoms	315
6.07.5.3.1	Reactivity of neutral tetrazoles	316
6.07.5.3.2	Reactivity of tetrazolate anions	319
6.07.5.3.3	Reactivity of tetrazolium cations	327
6.07.5.3.4	Complex formation with metal ions	330
6.07.5.4	Electrophilic Attack at Endocyclic Carbon	336
6.07.5.5	Nucleophilic Attack at Endocyclic Carbon	337
6.07.5.6	Nucleophilic Attack at Hydrogen Attached to Endocyclic Carbon	338
6.07.5.7	Reactions with Radicals and Electron-Deficient Species, Reaction at Surfaces, and Reduction	339
6.07.6	Reactivity of Nonconjugated Rings	339
6.07.7	Reactivity of Substituents Attached to Ring Carbon Atom	342
6.07.7.1	General Survey	342
6.07.7.2	C-Linked Substituents	342
6.07.7.2.1	Fused ring	342
6.07.7.2.2	Aryl and hetaryl groups	344
6.07.7.2.3	Alkyl group	347
6.07.7.2.4	Aldehydes and ketones	349
6.07.7.2.5	Carboxylic acids and their derivatives	350
6.07.7.2.6	Other substituted alkyl groups	352
6.07.7.2.7	Vinyl group	352
6.07.7.3	N-Linked Substituents	355
6.07.7.3.1	5-Aminotetrazole and its derivatives	355
6.07.7.3.2	5-Nitrotetrazole	358
6.07.7.3.3	5-Azidotetrazole	359
6.07.7.3.4	Other N-linked substituents	360
6.07.7.4	O-Linked Substituents	360
6.07.7.5	S-Linked Substituents	361
6.07.7.6	5-Halotetrazoles	363
6.07.8	Reactivity of Substituents at Ring Nitrogens	364
6.07.8.1	General Survey	364
6.07.8.2	C-Linked Substituents	364
6.07.8.2.1	Aryl and hetaryl groups	364
6.07.8.2.2	Alkyl group	365
6.07.8.2.3	Aldehydes and ketones	367
6.07.8.2.4	Carboxylic acids and their derivatives	367
6.07.8.2.5	Other substituted alkyl groups	368
6.07.8.2.6	Vinyl group	369
6.07.8.3	N-Linked Substituents	369
6.07.8.3.1	1,5-Diaminotetrazole and 1-amino-5-methyltetrazole	369
6.07.8.3.2	Tetrazolium N-aminides	370
6.07.8.4	O- and S-Linked Substituents	370

6.07.9 Ring Synthesis From Acyclic Compounds	371
6.07.9.1 Formation of One Bond in a Five-atom Component	371
6.07.9.1.1 Tetrazoles from imidoyl azides and related substrates	371
6.07.9.1.2 Tetrazole from geminal diazides	378
6.07.9.1.3 Cyclization of triazenes, tetrazenes, and formazans	382
6.07.9.2 Formation of Two Bonds from [3+2] Atom Components	383
6.07.9.2.1 1H-Unsubstituted tetrazoles from nitriles	383
6.07.9.2.2 Cycloaddition of organic azides to nitriles and nitrilium ions	386
6.07.10 Tetrazoles from Transformations of Other Heterocyclic Rings	392
6.07.11 Preferred Routes to Tetrazole Classes	392
6.07.12 Important Compounds and Applications	393
6.07.12.1 Biologically Active Derivatives	393
6.07.12.1.1 Tetrazoles as isosteres of pharmacophores of natural molecules	394
6.07.12.1.2 Drug application	401
6.07.12.2 Energetic Tetrazoles	402
6.07.12.3 Tetrazoles in Supramolecular Chemistry and Nanotechnology	404
6.07.12.4 Tetrazoles as Activators of Chemical and Biochemical Reactions	405
6.07.12.4.1 Oligonucleotide synthesis and related processes	405
6.07.12.4.2 Julia–Kocienski olefination	406
6.07.12.4.3 Catalytic asymmetric synthesis	406
6.07.12.4.4 Other examples of catalytic activity	406
6.07.12.5 Corrosion Inhibitors	407
6.07.12.6 Analytical Uses	407
6.07.13 Further Developments	407
References	408

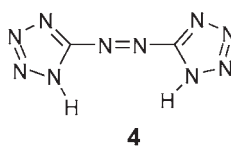
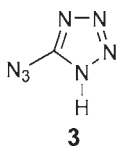
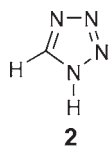
6.07.1 Introduction

6.07.1.1 Historical

Compounds containing a tetrazole ring were synthesized for the first time in 1885 by J. A. Bladin at Uppsala University (Sweden). On treating dicyanophenylhydrazine with nitrous acid, Bladin obtained a substance that he believed to be 1-phenyl-5-cyanotetrazole <1885CB1544>. Later, when the structure of the dicyanophenylhydrazine was completely established, it turned out that Bladin in his first works dealt not with a 1-phenyl-5-cyanotetrazole but with its isomer, 2-phenyl-5-tetrazole **1** (Equation 1).



It should be mentioned that the same reaction was carried out 7 years earlier by Emil Fischer, but he failed to identify the compound obtained. Bladin proved to be more persistent, and the honor of tetrazoles discovery belongs to him. Interestingly, Bladin had published the first data on five-membered heterocycles containing many nitrogen atoms (1,2,4-triazoles and tetrazoles) 5 years earlier than hydrazoic acid (HN₃), its salts, and organic azides were discovered (T. Kurtzius). The latter compounds were widely used later in tetrazole synthesis. In extension of his investigations, Bladin prepared from compound **1** 2-(4-aminophenyl)-5-carboxytetrazole whose oxidation with potassium permanganate afforded unsubstituted tetrazole **2**. In 1892, J. Thiele also became enthusiastic about tetrazole synthesis. He succeeded in preparation compounds of this series with an abnormally high nitrogen content: 5-azidotetrazole **3** (ca. 1893) and azoditetrazole **4** (ca. 1898), whose molecules contained 88.3 and 83.4% of nitrogen, respectively.



The tetrazoles were regarded then only as exotic compounds. Even Bladin himself hardly thought that these compounds would sometimes find any practical application. Actually, till 40 years after tetrazoles' discovery, only a few studies dealt with them but the situation gradually changed. Interest in tetrazoles grew, especially in the middle of the 1950s when the main approaches to the synthesis of these compounds were developed and the possibility of application was demonstrated of the great stock of the chemical energy accumulated in the tetrazole ring. A strong impact on the development of preparation procedures for versatile tetrazole derivatives was given by the discovery of the high biological activity in some compounds of this series. Important contributions to the advancement of the tetrazole chemistry in the years preceding World War II were made by O. Dimroth, E. Oliveri-Mandala, E. von Herz, R. Stolle, J. Thiele, J. Lifschitz, and in further decades, by W. Finnegan, R. Henry, R. Herbst, E. Lippmann, A. Könnecke, B. Stanovnik, M. Tisler, R. Butler, R. Huisgen, P. Gaponik, I. Postovsky, K. Sharpless, and many others.

Nowadays interest in tetrazoles continues to grow as shown by the dynamic increase in the number of publications concerning the development of efficient and relatively safe methods of their preparation. Much attention has been paid to the study of the physicochemical characteristics of tetrazoles, in particular their reactivity. The introduction of a tetrazole fragment into a molecular structure of various organic substrates as a stable-to-metabolism analog of carboxy or *cis*-amido groups was regarded as a new approach to the strategy for drugs synthesis and design <B-1998MI1>. This approach proved to be efficient for the synthesis of the newest drugs, among them some occupying a significant part in the worldwide pharmaceutical market. Progress in the coordination chemistry of tetrazoles also cannot be underestimated. Tetrazoles as ligands in complex formation have become attractive research objects, and some coordination and organometallic tetrazole compounds are used in science and technology.

The tetrazole fragment is virtually unknown in naturally occurring compounds, although the presence of tetrazoles in the metabolism products of some protozoa has been mentioned <1996CHEC-II(4)621>. This is evidently explained by the absence in nature of conditions and sources required for the formation of the tetrazole ring. The imagination may suggest that tetrazoles may be formed under conditions of other planets of the solar system or their satellites containing in the atmosphere or on the surface hydrocarbons and nitrogen. In this event, the tetrazoles would no longer be a rarity in nature.

6.07.1.2 General Survey of Literature

The first review on the preparative methods and some physicochemical properties of tetrazoles was published by Benson in 1947 <1947CRV411>. This review treated the results of research carried out between 1885 and 1943, and contained 147 references. Strategically this publication was of fundamental importance, because Benson systematized for the first time the then existing knowledge on the physical properties and preparation methods of tetrazoles. In 1967, 20 years later, Benson published a second review <B-1967MI(8)8>, where alongside with the description of the preparation methods and the chemical behavior of tetrazoles much attention was paid to the physicochemical aspects: ultraviolet (UV) and infrared (IR) spectra, dipole moments, thermochemical constants, and acid-base properties. About 400 publications were cited in this survey <B-1967MI(8)8> and, although 40 years have passed, it is still the reference manual for all chemists studying tetrazole chemistry.

Within the last three decades, a number of exhaustive reviews were published on synthetic methods, chemical properties, reactivity, and applications of tetrazoles. The classical comprehensive reviews of Butler on synthesis and chemical characteristics of tetrazoles <1977AHC(21)323, 1984CHEC(4)791, 1996CHEC-II(4)621> and of Benson <B-1984MI149> are well known. A review on synthetic procedures and properties of 2-aryltetrazoles by Lippmann and Könnecke is of considerable interest <1976ZC90>. In a series of reviews by Koldobskii, Ostrovskii, and co-workers, publications on a wide range of problems regarding tetrazole chemistry were collected and systematized. Among them are: publications on advances in tetrazole chemistry attained up to the beginning of the 1980s <1981KGS1299> and to the middle of the 1990s <1994RCR797>; reviews summarizing the application of the Schmidt reaction to tetrazoles synthesis <1975KGS723>; and the use of phase-transfer catalysis (PTC) techniques in tetrazole chemistry <1992ZOB3>.

Advances in the chemistry and technology of tetrazole production achieved by the Russian scientific schools have been presented <B-1998MI536>. The principal lines of development in the medicinal chemistry of tetrazoles up to the 1980s are considered in a review <1980MI151>. The material accumulated in this important field up to the

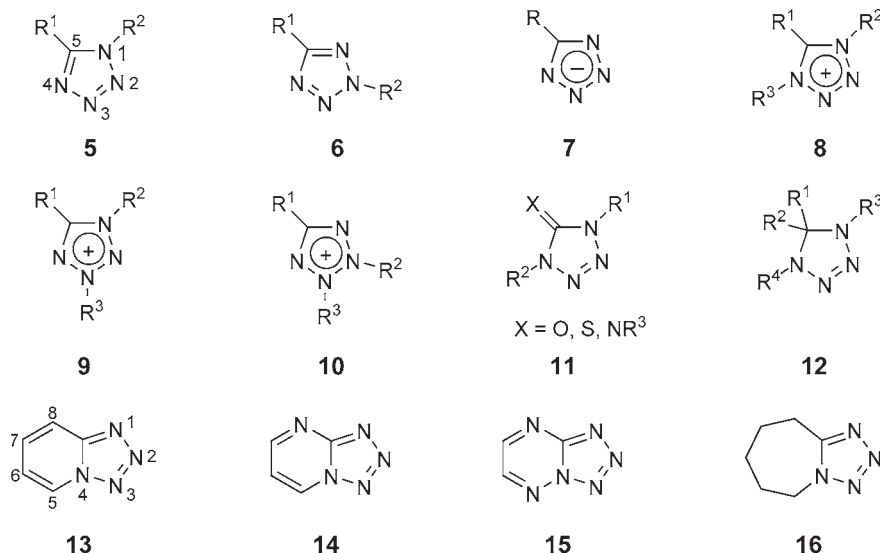
middle of the 1990s was summarized by Wittenberger <1994OPP499>. The problems of tetrazoles' formation from other heterocyclic systems and tetrazole transformation into other heterocycles were treated in a review by Moderhack <1998JPR687>. The methods of synthesis, properties, and the ways of application of the chemical energy accumulated in the molecules of the energetic tetrazoles have been considered <1999THS(3)467>, as well as the thermal decomposition of tetrazoles <1992THE427>. A gap in reviews on the coordination chemistry of tetrazoles formed after the appearance of the review of Popov in 1969 <1969CCR463> was partially filled in 1988 by Moore and Robinson <1988AIC(32)71>.

The period 2000–06 was marked by the publication of a review by Brigas <2004SOS(13)861>, containing comprehensive information on the methods and technique of tetrazole preparation. Information on tetrazole chemistry published in the annual short reviews <1996PHC(8)156, 1997PHC(9)163, 1998PHC(10)165, 1999PHC(11)176, 2000PHC(11)176, 2001PHC(13)182, 2002PHC(14)195, 2004PHC(16)223> is also worth consideration, for it is dedicated to the most significant events in the chemistry of heterocyclic compounds. Since 2000, fundamental articles have been published on the most important lines in the chemistry and application of tetrazoles. To this series belong reviews on electrophilic substitution at endocyclic nitrogens <2000H(53)1421>, preparation methods for mono- and polycyclic NH-tetrazoles <2000CHE759>, the synthesis and properties of 1,3- and 1,4-tetrazolium salts <2002RCR721>, vinyltetrazoles <2003RCR143>, 2-substituted and 2,5-disubstituted tetrazoles <2003RJO453>, 1-substituted 5-alkyl(aryl)sulfanyltetrazoles <2004RJO447>, organometallic tetrazole derivatives <2005RJO1565>, the complexes of 1-alkyltetrazoles with Fe(II) <2004TCC129>, functionalization procedures <2006RJO494> and protolytic equilibria of tetrazoles <2006RJO1585>, and also various aspects of the medicinal chemistry of 5-substituted-1*H*-tetrazoles <2002BMC3379> and 1,5-disubstituted tetrazoles <1999MI417>. Data on the analysis of quantitative structure–activity relationships (QSARs) for tetrazole-containing angiotensin II (AII) antagonists were summarized in a review <2001CRV2727>. Quantum-chemical studies of [2+3] cycloaddition mechanisms important for tetrazole chemistry are treated in a survey <2004CRV459>. A selection of studies on the synthetic methods, thermodynamical, chemical properties, and reactivity of tetrazoles published between 1963 and 1998 was considered in the book by Katritzky and Pozharskii <B-2000MI1>.

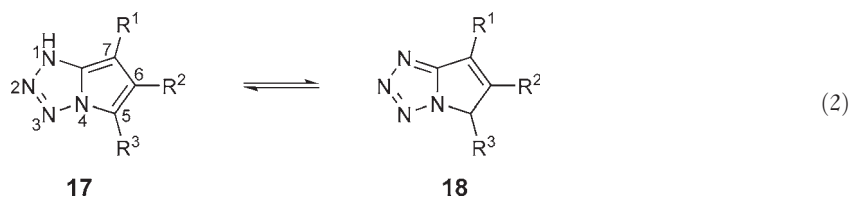
This chapter includes the investigations published since 1996; earlier studies are cited only when it is necessary for completeness. Note that within this period the rate of annual growth of number of publications was steadily greater for tetrazoles compared to the other azoles. Within this period, the overall number of publications was over 10 000, and over 6000 patents were granted on the structure, properties, and application of tetrazoles.

6.07.1.3 Structural Types and Nomenclature

Neutral tetrazoles with a fully conjugated ring can exist as 1-substituted 1*H*- and 2-substituted 2*H*-isomers ($R^2 \neq H$) or 1*H*- and 2*H*-tautomers ($R^2 = H$) **5** and **6**. Isomers **5** and **6** are essentially different in their chemical and physicochemical characteristics (cf. Sections 6.07.3 and 6.07.4). NH-unsubstituted 5-*R*-tetrazoles readily lose a proton when treated with a base providing the corresponding tetrazolate anions **7** that are key intermediates in the synthesis of many practically important compounds <2000H(53)1421>. Tetrazolides of alkali and alkaline earth metals are fairly stable against hydrolysis and exist in water solutions predominantly in an ionic form (cf. Section 6.07.4.5). Three stable isomers of the quaternized tetrazoles (tetrazolium ions) are distinguished by the position of substituents at the nitrogens of the heterocycle **8–10**. It was demonstrated that these compounds are efficient phase-transfer catalysts <1992ZOB3, 2002RCR721>. Note that the protonation of tetrazoles **5** and **6** results in the formation only of tetrazolium ions ($R^2 = H$) **8** and **9** (cf. Section 6.07.4.5). Among the nonconjugated tetrazoles, 1,4-dihydropyrazoles **11** are the most important. These compounds form from the corresponding 5-hydroxy, 5-mercapto, or 5-aminotetrazoles through a tautomeric rearrangement followed by hydrogen substitution. To a lesser extent, Δ^2 -tetrazolines **12** are known that formally cannot be obtained from the corresponding tetrazoles **5** by passing the reduction stage and that are less stable species than aromatic tetrazoles **5** and **6**. Only very limited information is available on tetrahydropyrazoles <1996CHEC-II(4)621>. Fused tetrazoloazines are completely aromatic heterocycles. These compounds always contain in their structure a nitrogen of the 'pyrrole' type belonging simultaneously to both heterocyclic systems. Well-known structures are formed by fusion of the tetrazole ring with pyridine, with isomeric diazines, and also with triazines. Some of them, namely tetrazolo[1,5-*a*]pyridine **13**, tetrazolo[1,5-*a*]pyrimidine **14**, and tetrazolo[1,5-*b*][1,2,4]triazine **15**, are shown below. Although the majority of tetrazoloazines is sufficiently stable, some of them under special conditions are capable of ring opening affording the corresponding azidoazines (cf. Section 6.07.4.4.3). A large number of structures are described where the tetrazole ring is included in a nonaromatic heterocyclic system, for example, cyclopentamethylenetetrazole **16**. In these compounds, the tetrazole ring behaves as 1,5-disubstituted tetrazole **5**.



Azoloazoles represent interesting objects for study. Most of these structures are very unstable and can be regarded only as intermediates [\[1998JPR687\]](#). Nonetheless, some, for instance pyrrolotetrazole and its derivatives, are relatively stable and can exist as the tautomeric forms **17** and **18** (Equation 2). In these structures only one of the heterocycles remains aromatic, for example, it is the tetrazole ring in the 5*H*-tautomer **18** and the pyrrole ring in the 1*H*-tautomer **17**.



6.07.2 Theoretical Methods

Within the last decade, *ab initio* and hybrid quantum-chemical methods were in considerable use in tetrazole chemistry, and the level of calculations significantly improved with extended basis sets used for quite complex polyatomic molecules. During this time, theoretical methods were exploited in the study of several fundamental properties of the tetrazole ring, such as aromaticity and capability to be involved in various kinds of tautomerism, including the effects of substituents and media on these parameters. It was demonstrated that many physical and physicochemical characteristics of tetrazoles could be successfully estimated by these methods not only for the gas phase but also for the condensed state (solvents, crystals).

Theoretical methods were employed in studies on the mechanism of formation of the tetrazole ring and some of its chemical reactions. The investigation of these problems is partly covered by reviews [\[2001AHC\(81\)1, 2004CRV459\]](#). Calculations by the CBS-QB3 procedure for the reaction of hydrazoic acid with HCN affording unsubstituted tetrazole give a value of 25.2 kcal mol⁻¹ for the activation energy and -23.0 kcal mol⁻¹ for the enthalpy of this reaction [\[2005HCA1702\]](#). Density functional theory (DFT) calculations using hybrid B3LYP functions were applied to tetrazole ring formation by dipolar cycloaddition of nitriles and organic azides or azide anion [\[2000IJQ27, 2002JA12210, 2003JA9983, 2003JOC9076\]](#). Coordination of organic nitriles with zinc(II) ion substantially lowers the energy barrier for nucleophilic attack by azide anion [\[2003JA9983\]](#). The mechanism of reaction of isothiocyanates with metal-azido complexes of Pt(II), Pd(II), and Sn and with hydrazoic acid has been studied using DFT [\[2005JOM\(690\)4319\]](#). The mechanism includes three reaction steps: (1) concerted nucleophilic attack of the coordinated azide on the C-atom of the isothiocyanate yielding the corresponding imidoyl azide; (2) cyclization of the latter forming S-coordinated thiolato-tetrazole; (3) isomerization of the S-coordinated structure to the

N-coordinated tetrazolate. Investigation by means of *ab initio* calculations of cyclization of some five- and six-membered azidoheterocycles into the corresponding fused tetrazoles was the subject of a series of publications <2001AHC(81)1, 1999JST(510)165, 2001IC1102, 2004PCA840, 2005JST(751)65>. The energy and geometry of isomeric tetrazolylcarbenes, important intermediates in some chemical reactions, were optimized by the DFT method <2001JST(567)59>. Aldol reactions catalyzed by 5-pyrrolidin-2-yltetrazole have been studied at the B3LYP/6-31G** level in the gas phase and dimethyl sulfoxide (DMSO) solutions <2005EJO4287, 2005TA2764>. Hartikka and Arvidsson suggested a higher stereoselectivity and reactivity of the process compared with the L-proline-catalyzed reaction as was also experimentally confirmed <2005EJO4287>.

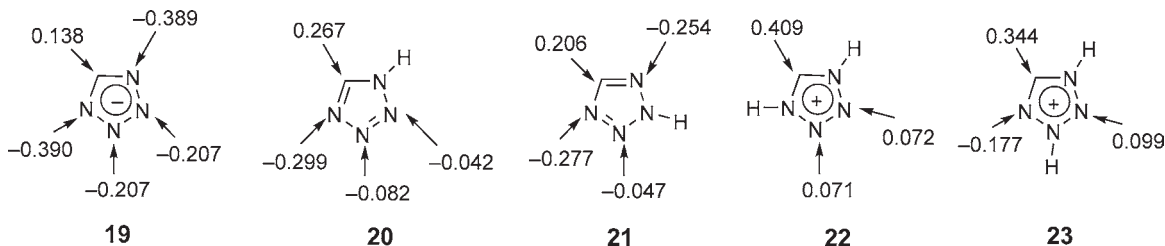
Theoretical methods have been used in the study of spectral characteristics of tetrazoles. Thus, electronic transition energies of some 5-aryltetrazoles were calculated by time-dependent DFT methods <2003CPH65>. Calculated UV absorption bands were compared with the experimental data. The coupled Hartree–Fock gauge-independent atomic orbital (CHF-GIAO) procedure was employed in calculations of nuclear magnetic resonance (NMR) absolute shieldings in tetrazolo[1,5-*a*]pyridine **13** and some its derivatives <1999JST(510)165, 1999JST(477)119>. Other results of calculations of NMR shieldings are given in a review <2001AHC(81)1> and are discussed in more detail in Section 6.07.3.3. Vibration spectra of a series of tetrazole derivatives predicted theoretically (B3LYP functional at 6-31G* and 6-311++G** basis sets) agree with the experimental spectra obtained in an argon matrix at low temperature <2002PCP1725, 2006JPH175, 2006JPH243, 2006JST(786)182>. The vibration spectrum of cesium 5-cyanotetrazolate calculated by the DFT method is also consistent with the observed Fourier transform infrared (FTIR) and FT-Raman spectra <2000IC1840>.

Theoretical approaches are now often used to predict the characteristics of tetrazoles important for their practical application. For instance, tetrazoles ability to complex with metal ions and the structure of the corresponding complexes have been widely studied using quantum-chemical calculations <2001IC6451, 2002RJC1457, 2005IC4894>. Theoretically calculated activation energies of thermal decomposition of a series of energetic tetrazole derivatives and their metal salts can be used to predict their impact sensitivity <1999MI319, 1999CPH243, 2000IJQ350>. Theoretical methods can also bring success in predicting the biological activity of certain tetrazoles <1999FA64, 2004JME5972, 2005JGM51>.

The majority of results obtained by theoretical methods are treated in more detail in appropriate sections of this chapter. We will dwell here briefly on the applicability of various quantum-chemical methods to the description of the tetrazole ring structure and its energetic characteristics.

6.07.2.1 Electronic Structure and Geometry

Charges on the ring atoms of the most stable forms of unsubstituted tetrazole calculated at B3LYP/6-31G* level are shown in formulas **19–23** <2004JMT(668)123>. These data demonstrate that the electronic structure of different tetrazole forms is essentially dissimilar: tetrazolate anion **19** is a highly symmetric structure with the negative charge well delocalized throughout the ring; in the neutral molecules **20** and **21** the highest negative charge is located on the nitrogen in position 4, and the atom will most effectively interact with electrophiles. Note that the nitrogen in position 1 in the 2*H*-tetrazole **21** is also considerably negatively charged and can react with electrophiles, as is confirmed by some experimental findings. For instance, this atom effectively forms coordination bonds with metal ions (cf. Section 6.07.5.3.4).



It was reported that effect of the substituent at endocyclic carbon on the value of the charges of nitrogen atoms is not regular <2004JMT(668)123>. It may be noted only that electron-withdrawing substituents diminish the absolute values of charges, and electron-donating ones increase them relative to the parent heterocycle. In any case, the tetrazole ring behaves as a strong electron-withdrawing fragment.

Natural bond orbital (NBO) analysis can be successfully used in considering various properties of tetrazoles. For instance, by this approach with the use of Hartree–Fock (HF) and DFT procedures, the nucleophilicity of tetrazole and some its derivatives have been quantitatively estimated in the gas phase and water <2005JOC9677>. The NBO analysis performed by *ab initio* and hybrid methods was also applied to estimate the aromaticity of a series of 1*H*- and 2*H*-tetrazoles with different substituents at C-5 <1998JOC2497, 2001JOC8737>. Analysis of molecular orbital (MO), NBO, and electrostatic potentials, calculated by the DFT method, proved to be useful in considering structures, stability, and certain practical properties of some new highly energetic tetrazoles, such as tetrazolylpentazoles <2002IC906>, azidotetrazoles <2005MI17>, tetrazolotetrazenes <2004MI325>, and *N*-nitroso- and *N*-nitraminetetrazoles <2006JOC1295>.

According to calculations performed by different procedures, aromatic tetrazole rings with any substituents in position 5 are absolutely planar in all possible prototropic forms. As seen from **Table 1**, the geometry of structures **19–23** is essentially different. The least variation of bond distances in the hetero-ring is found in forms **19**, **21**, and **23**. This observation is consistent with the data on aromaticity of the corresponding forms. The character of the substituent in position 5 significantly affects the geometry of the tetrazole ring <2004JMT(668)123>. On going from electron-donor to electron-withdrawing substituents the N(1)–N(2) bond considerably shortens with simultaneous elongation of the N(2)–N(3) bond, whereas the length of C–N bonds does not essentially change. This phenomenon is especially characteristic of tetrazolate anions where a satisfactory polynomial dependence between the values of N(1)–N(2) and N(2)–N(3) interatomic distances and Hammett σ_p -constants has been found. In 5-nitrotetrazolate, the N(2)–N(3) bond is notably longer than the N(1)–N(2) bond.

Table 1 Ring bond lengths of different forms of parent tetrazole **19–23** optimized by means of theoretical methods in the gas phase compared with X-ray diffraction data

Form	Method	1-2	2-3	3-4	4-5	5-1	Reference
19	B3LYP/6-31G*	1.353	1.325	1.353	1.340	1.340	2004JMT(668)123
	Experiment ^a	1.348	1.310	1.348	1.329	1.329	1984CHEC(4)791
20	B3LYP/6-31G	1.390	1.315	1.409	1.333	1.359	2000CPL(330)212
	B3LYP/6-31G*	1.353	1.292	1.366	1.315	1.348	2004JMT(668)123
	B3LYP/6-31++G**	1.351	1.287	1.363	1.312	1.346	
	MP2/6-311G**	1.343	1.315	1.359	1.323	1.348	1998JMT(453)65
	Experiment ^b	1.33	1.30	1.33	1.30	1.33	1974CSC321
21	B3LYP/6-31G*	1.329	1.329	1.311	1.357	1.329	2004JMT(668)123
	B3LYP/6-31++G**	1.326	1.326	1.307	1.355	1.326	2001JOC8737
	MP2/6-311G**	1.323	1.335	1.326	1.349	1.343	1998JMT(453)65
22	B3LYP/6-31G*	1.363	1.272	1.363	1.327	1.327	2004JMT(668)123
23	B3LYP/6-31G*	1.318	1.298	1.332	1.318	1.360	

^aFor sodium tetrazolate monohydrate; see also **Table 3**, Section 6.07.3.1.

^bFor monoclinic form; see **Table 3**, Section 6.07.3.1, for geometry of triclinic polar polymorph.

In general the difference in ring bond lengths optimized with the use of calculation methods including polarization functions is insignificant (**Table 1**). These calculations are also in fair agreement with the experimental data. It should be noted, however, that the bond lengths obtained from the X-ray crystallography considerably depend on the packing of molecules in the crystal (see **Table 3**, Section 6.07.3.1) and thus cannot be used as an absolute criterion of the validity of theoretical calculations of molecular geometry.

Geometries of tetrazoles containing conformationally nonrigid substituents were studied by different theoretical procedures by many research teams <2001AHC(81)1>. For instance, according to conformation analysis of crown-like macrocycles containing 2,5-disubstituted tetrazole moieties, 30 different conformations can be identified, one of which is similar to that found in the crystal structure <2001J(P2)417>. Electronic structure and geometry of 2-vinyl- and 5-vinyltetrazoles have been studied by means of HF and MP2 methods at the 6-31G* level <2004RJC134, 2004RJC409>.

6.07.2.2 Energetic Aspects

Reference data on total energies of forms **19–23** optimized by means of different theoretical methods in the gas phase are given in **Table 2**. Various energetic characteristics of tetrazoles can be successfully estimated. The vertical adiabatic ionization potentials of both neutral tautomers **20** and **21** were calculated for σ - and π -radical cations <2000CPL(330)212>. The standard molar thermodynamic functions (enthalpies, heat capacities, and entropies) of

tetrazole forms **20** and **21** in the temperature range 300–1000 K were calculated using frequencies at MP2/6-311G** level <1998JMT(453)65>. The calculated thermodynamic properties agree quite well with the experimental findings. By the same manner the properties of a series of isomeric chloro-, nitro-, and azidotetrazoles were calculated using HF and DFT (B3LYP) methods <1999JST(460)167, 1999JST(458)249, 1999JEM345>. The heats of formation for 49 tetrazoles have been calculated with B3LYP hybrid method by means of designed isodemic and isogyric reactions <1999PCA8062>. Some of these values are quite close to the corresponding experimental ones. Quantum-chemical theory at the MP2 level with a double-zeta basis set or G2 and G3 methods were used for the calculation of standard enthalpies of formation of 1,5-diaminotetrazolium salts <2004MI3, 2005IC4237>.

Table 2 Total energies of different forms of parent tetrazole **19–23** optimized by theoretical methods

Form	Method	E_{total} (a.u.)	Reference
19	B3LYP/6-31G*	–257.699 47	2004JMT(668)123
	CBS-QB3	–257.393 20 ^a	2005PCA5590
20	HF/6-31G*	–256.754 08	1998JOC2497
	B3LYP/6-31G	–258.133 35	2000CPL(330)212
	B3LYP/6-31G*	–258.250 90	2004JMT(668)123
	B3LYP/6-31+G**	–258.268 05	2000CPL(330)212
	B3LYP/6-31++G**	–258.324 26	
	CBS-QB3	–257.915 18 ^a	2005PCA5590
	B3LYP/6-311+G(3df,2p)	–258.344 38	2002NJC1567
	G2(MP2)	–257.870 77	
21	HF/6-31G*	–256.757 04	1998JOC2497
	B3LYP/6-31G	–258.136 21	2000CPL(330)212
	B3LYP/6-31G*	–258.255 39	2004JMT(668)123
	B3LYP/6-31+G**	–258.272 53	2000CPL(330)212
	B3LYP/6-31++G**	–258.328 90	
	CBS-QB3	–257.918 81 ^a	2005PCA5590
22	B3LYP/6-31G*	–258.586 40	2004JMT(668)123
	B3LYP/6-311+G(3df,2p)	–258.677 38	2002NJC1567
	G2(MP2)	–258.188 85	
	B3LYP/6-31G*	–258.586 52	2004JMT(668)123
23	B3LYP/6-311+G(3df,2p)	–258.677 07	2002NJC1567
	G2(MP2)	–257.187 29	

^aFree energies.

6.07.3 Experimental Structural Methods

6.07.3.1 X-Ray Crystal Structures

In the last decade, X-ray diffraction analysis has been actively exploited for identification and structural study of various tetrazole derivatives. This method was also applied to mechanistic studies of certain chemical reactions involving tetrazoles <2005CCR1201> and to evaluating the biological activity of tetrazole-containing compounds, which are novel thrombin inhibitors, by structural analysis of their complexes with thrombin <2005BML4411, 2006JME1346>. In this period, X-ray crystallography was applied to the examination of several tens of tetrazoles. In this section, the data on crystal structures of neutral tetrazoles and their ionic forms are compiled; for coordination compounds, see Section 6.07.5.3.4. It should be noted that according to the findings cited below the aromatic tetrazole ring is planar in all compounds studied, both neutral molecules and ionic forms.

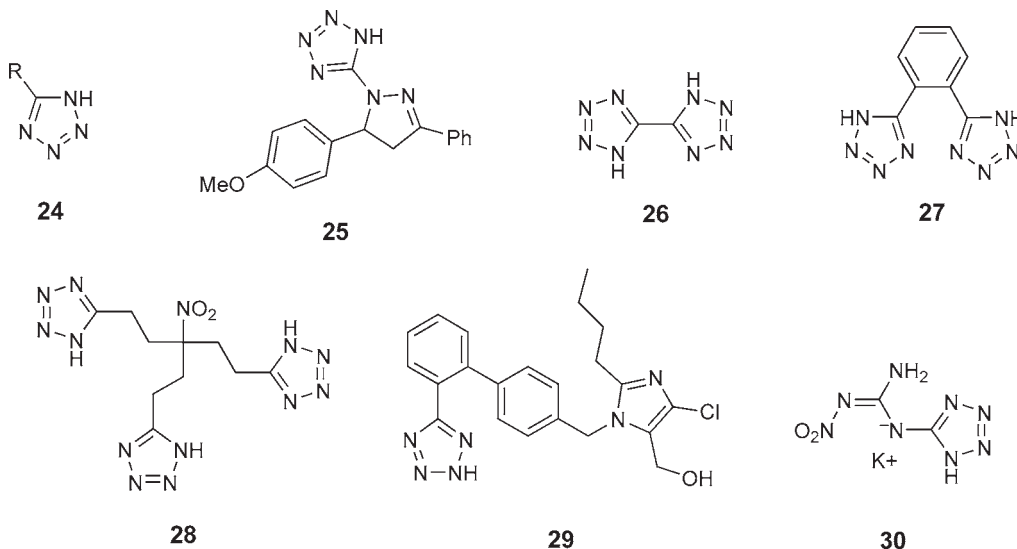
6.07.3.1.1 NH-Unsubstituted tetrazoles

The characteristic feature of the crystals of all NH-unsubstituted tetrazoles is the presence of strong intermolecular N–H···N hydrogen bonds, which govern mainly the molecular packing of these compounds. Goddard *et al.* have described the crystal structure of the parent tetrazole (**24**, R = H) with a triclinic crystal system (named α -tetrazole) <1997AXC590>. It was shown that the 1*H*-tetrazole molecules were connected by N(1)–H···N(4) hydrogen bonds with N···N distance of 2.804 Å forming chains which were linked together by C–H···N interactions into planar

sheets. The difference between the structures of α -tetrazole and monoclinic polymorph (β -tetrazole), which has been determined before, is due to the sheet orientation. In the case of α -tetrazole all molecules point in the same direction and form the polar polymorph, whereas in the case of β -tetrazole, in different directions. Two dimorphs of 5-methylsulfanyltetrazole (**24**: R = MeS) with monoclinic and orthorhombic crystal systems may be distinguished <2004AXCo47>. In both forms, the molecules occupy crystallographic mirror planes connected by the N–H···N hydrogen bonds. As in the case of unsubstituted tetrazole, the dimorphs (polar and nonpolar) differ from one another by packing. The crystal structures of a series of 5-R-tetrazoles with common formula **24** were also determined: 5-methyltetrazole <1999AXC1014>, 5-(1,1,2-trimethyl-2-cyanopropyl)tetrazole <2003AXCo388>, and co-crystals of 5-(*p*-hydroxyphenyl)tetrazole with water molecules <1997AXC143>. Weak intramolecular hydrogen bonds were observed in tetrazolopyrazoline **25** where both proton donor (NH-tetrazole ring) and acceptor fragments were present <2006JST(785)114>.

X-Ray diffraction methods were also used to determine the structure of some polynuclear compounds containing two and three NH-tetrazole fragments. For instance, 5,5'-bitetrazole **26** packs in chains held together by pairs of strong intermolecular hydrogen bonds characterized by an N(1)···N(4) distance of 2.805 Å <1996JCX399>. The relatively short inter-ring bond length suggests strong $\pi\pi$ -conjugation between the tetrazole rings. This compound is strictly coplanar and the molecule exists in a conformation that is *transoid* about an inter-ring bond. In the case of crystals of the tetrahydrate of 1,2-ditetrazolylbenzene **27**, the two tetrazole units are each twisted with respect to the central C₆H₄ ring (34–35°) to allow both heterocycles to engage in extensive hydrogen bonding <1999J(P1)3507>. Three-dimensional (3-D) N–H···N networks of intermolecular hydrogen bonds were also observed in the structure of tristetrazole **28**, where each molecule participates in six hydrogen bonds (in three bonds as donor and in three bonds as acceptor) with the N···N distance 2.78–2.90 Å <1997CHE1292>.

Some practically important compounds containing an NH-unsubstituted tetrazole fragment were also subjected to X-ray diffraction studies. Thus, structures of the well-known nonpeptide AII receptor antagonist losartan **29**, crystalline forms of its salts, and of some its analogs or precursors were established <1996AXC1019, 1998MI583, 1999AXC1345, 2002AXCm418, 2004AXCo821, 2004AXEo1830, 2005AXEm1686, 2005AXEo309>. Structural data of some energetic NH-tetrazoles are also available, including 5-azidotetrazole (**24**: R = N₃) <2005MI17> and the potassium salt of tetrazolynitroguanidine **30** <2005AXB435>.



It should be noted that virtually all 5-R-NH-unsubstituted tetrazoles, regardless of the substituent, exist in the crystalline state as individual *1H*-tautomers. Only losartan **29** containing a sterically strained (2'-tetrazol-5-ylbiphenyl-4-yl)methyl group was found to crystallize in the *2H*-form stabilized by intermolecular O–H···N and N–H···N hydrogen bonds <2004AXEo1830>.

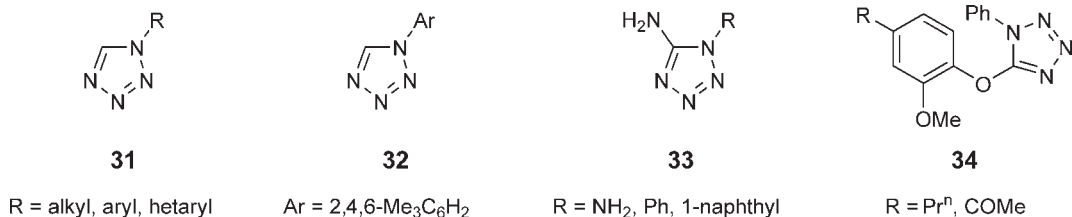
Bond distances within the NH-tetrazole ring differ significantly (Table 3). The shortest bond is observed between N-2 and N-3 and the longest is the N(3)–N(4) bond. In virtually all compounds studied, the C(5)–N(4) bond length is slightly shorter than the N(1)–C(5) distance, although in general this difference is insignificant. The parent *1H*-tetrazole is an exception, for the pattern therein is opposite. These distinctions may be mostly due to liberation

effects <1997AXC590>. In general, some discrepancies exist in ring bond lengths reported for various NH-tetrazoles in different publications, but they are not significant. The bond angles are reproduced very well in all studies.

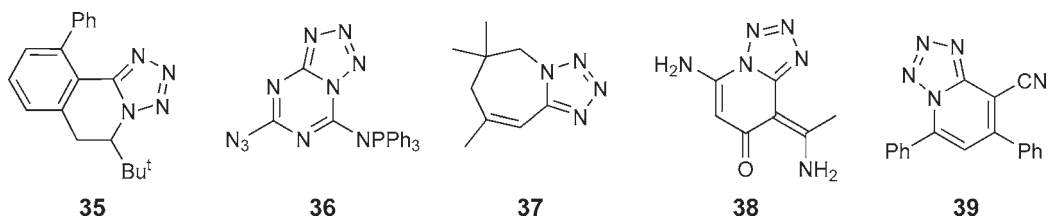
6.07.3.1.2 1-Substituted tetrazoles

Structures have been determined for a large number of 1-substituted tetrazoles. The number of studies dedicated to this type of compounds is larger than the overall number of all other publications. The great interest in 1-substituted **31** and 1,5-disubstituted tetrazoles **5** is mostly due to the biological activity of this type of compounds: the 1,5-disubstituted tetrazole fragment is an isosteric analog of ester and *cis*-amide groups.

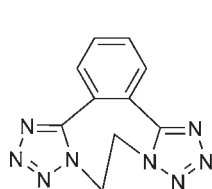
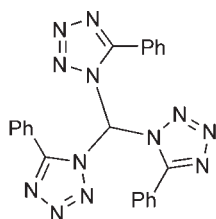
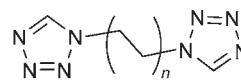
Structural data on 1-methyl- and 1-phenyltetrazoles (**31**: R = Me, Ph) are available <1996AXC2818, 1999AXC129>. As shown by examples of 1-haloethyl- and 1-aryltetrazoles (**31**: R = ClCH₂CH₂, BrCH₂CH₂, ICH₂CH₂, 2-naphthyl, pyridine-2-yl), C(5)–H···N angular interactions play an important role in the crystal packing of these molecules <2005JST(733)41>. For instance, in 1-(2-chloroethyl)- and 1-(2-bromoethyl)tetrazoles, the H···N distance was 2.64–2.66 Å. Similarly, C(5)–H···N bridges between tetrazole rings forming chains were observed in the case of 1-(2,4,6-trimethylphenyl)tetrazole **32** <2000AXC256>. In this compound, the tetrazole and phenyl rings are not coplanar with the mean planes inclined at 69° to each other due to a steric interaction. Also non-coplanar structures with a large distance between the rings were observed in the case of 1-aryltetrazoles **32** containing OH, NO₂, and COOH fragments in the benzene ring indicating a weak $\pi\pi$ -conjugation between the aryl and tetrazol-1-yl moieties <2001AXC1436, 2001AXC1204>. On the other hand, the aryl group in position 5 is in a strong $\pi\pi$ -conjugation with the tetrazol-5-yl fragment as was demonstrated by the example of some 1,5-disubstituted tetrazoles **5**. For instance, in 1-methyl-5-(pyrid-2-yl)tetrazole, the two heterocyclic rings are nearly coplanar <1996JXC399>. The crystal structures of 5-mesyImethoxy-1-(4-nitrophenyl)tetrazole <2006AXE0903> and 1-phenyl-5-(piperidomethyl)tetrazole <2004AXCo293> were established. Strong N(amino)–H···N(tetrazole) interactions characterized the molecular packing of 5-aminotetrazoles **33**. It was established that in 1,5-diaminotetrazole (**33**: R = NH₂) the 5-amino group is conjugated with the π -system of the tetrazole ring, whereas the 1-amino group is sp³-hybridized and nonconjugated <2001AXC185>. In the case of 1-aryl-5-aminotetrazoles (**33**: R = Ph, 1-naphthyl), dihedral angles between tetrazole and aryl rings are 45–65° <2003AXCo690>. It was shown for phenoxytetrazoles **34** that the O–C(5) bonds are 1.327–1.331 Å, which is shorter than the O–C(aryl) bond distances (1.417–1.418 Å), presumably due to relatively strong $n\pi$ -conjugation between the unshared electron pair of the oxygen and the tetrazole ring <2001CJC1201>. In general, as seen from Table 3, the hetero-ring geometry for 1-substituted tetrazoles **5**, **31**, and **33** does not significantly differ from that of NH-unsubstituted tetrazoles **24**, **25**, and **26**.



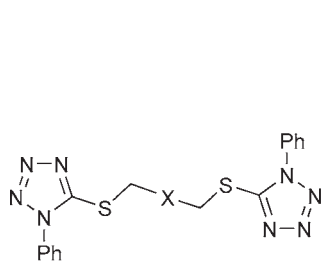
X-Ray analysis was applied to establish the crystal structures of compounds where the tetrazole ring is fused to various aromatic and nonaromatic rings: tricyclic tetrahydrotetrazolonaphthyridine **35** <2006T1849>, a derivative of tetrazolo[1,5-*a*][1,3,5]triazine **36** <2001IC1102>, dihydrotetrazolo[1,5-*a*]azepine **37** <2003AXE0643>, tetrazolo[1,5-*a*]pyridine-7-one **38** <2003AXE01589>, and tetrazolo[1,5-*a*]pyridine **39** <2002AXE0431>. It is shown in Table 3 by an example of heterocycle **39** that the 1,5-tetrazolediyl fragment insignificantly changes its geometry on conjugation. Only a slight elongation of the N(1)–N(2) and N(3)–N(4) bonds is observed, whereas the N(2)–N(3) bond shortens.



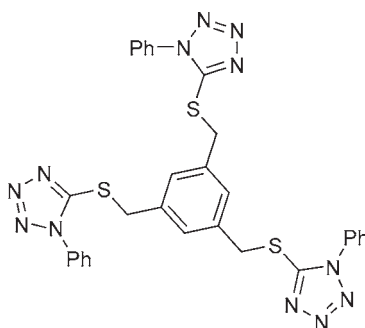
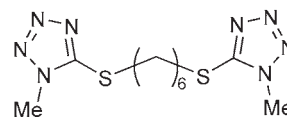
The crystal structures of various di- and trinuclear compounds containing 1-monosubstituted and 1,5-disubstituted tetrazole moieties have been determined. Thus an example of a tetrazole-containing cyclophane **40** with short aliphatic chain was described by Molloy and co-workers <1999J(P1)3507>. A symmetric highly polarized molecular structure was found in tristetrazolymethane **41** where two spatially separated fragments may be singled out: a polar one, including three tetrazole rings, and a nonpolar one including phenyl substituents oriented in one direction <2007CHE320>. Bridging ligands, for example, α,ω -di(tetrazol-1-yl)alkanes **42**, crystallize in centrosymmetric monoclinic lattices, but with rather different packing schemes <2002ICA(339)297, 2005JST(733)41>.

**40****41****42** $n = 1-6$

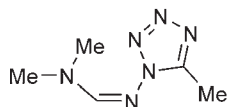
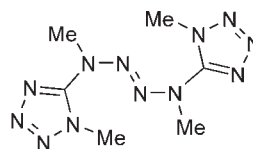
X-Ray diffraction analysis was successfully applied to bis- and tris-[(1-phenyltetrazol-5-ylsulfanyl)methyl] derivatives **43** and **44** with linkers of different nature <2004AXEo1279, 2004AXEo1979, 2004AXEo1107, 2005AXEo1639, 2005AXEo1163, 2005AXEo2623, 2005AXEo1161, 2005AXEo206, 2006AXEo603, 2006AXEo2817>, bis(tetrazolylsulfanyl)hexane **45** <2006AXEo402>, and some organotin-substituted bis(thiotetrazoles) <1998JCD3425>.

**43**

X = alkyl, alkenyl, aryl, hetaryl

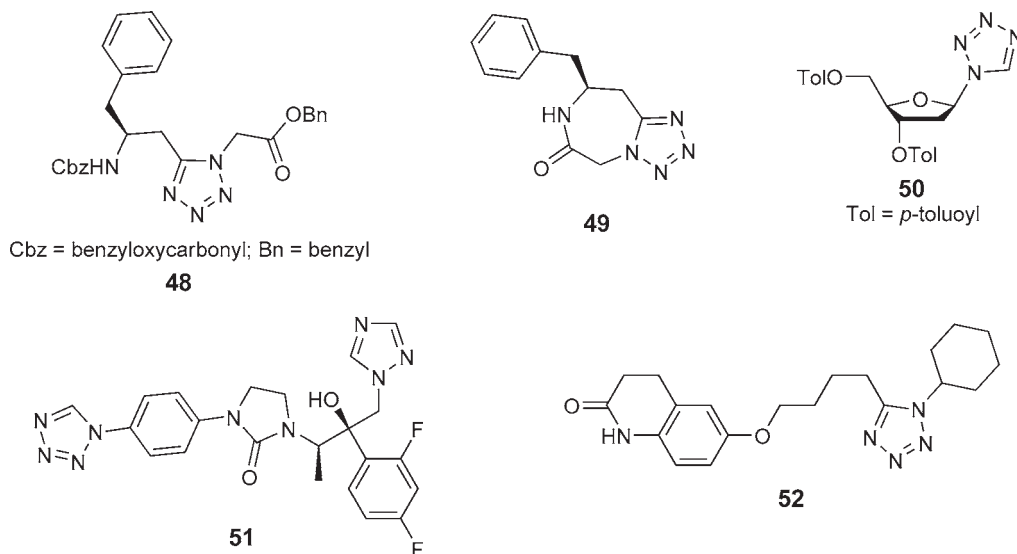
**44****45**

Stable crystals of some nitrogen-rich 1-substituted tetrazoles were analyzed by X-ray methods. It was found that in 5-azido-1-phenyltetrazole the azido and phenyl groups were in the same plane, and the phenyl group was at a torsion angle about 56° to the tetrazole plane <2005MI17>. The structures of the energetic derivative of tetrazole **46** and bistetrazolyltetrazene **47** were confirmed by X-ray crystallography <2005IC7009, 2004MI325>. The structure of compound **47** is nearly planar, revealing a good delocalization of the π -electron density over the molecule.

**46****47**

The crystal structures of a series of bioactive 1-substituted tetrazoles have been determined. Thus, May and Abell have described the structures of peptidomimetic **48** and some of its derivatives **49** <2001CC2080, 2002J(P1)172>.

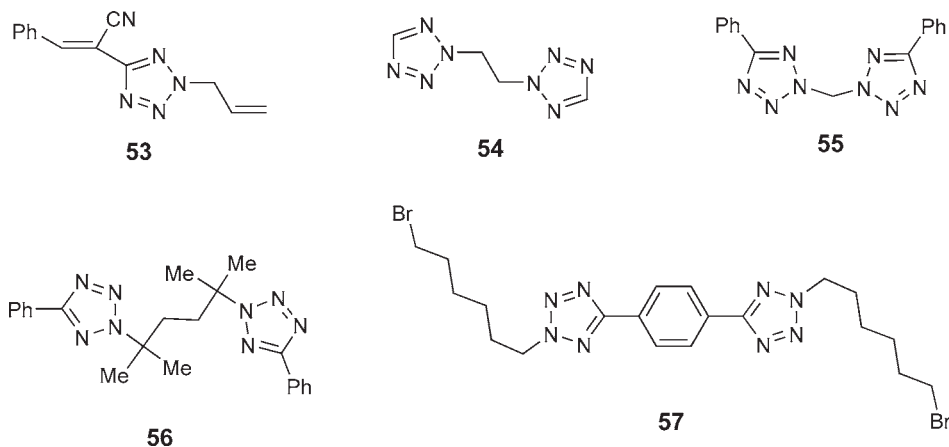
Müller *et al.* determined the structure of *p*-toluoyl-protected tetrazole nucleoside **50** <2005CEJ6246>. The structures of optically active stereoisomers of antifungal agent **51** were solved <2001CPB1110>. Two polymorphic forms of the drug cilostazol **52** (inhibitor of phosphodiesterase III) have been characterized <2002AXCo525>.

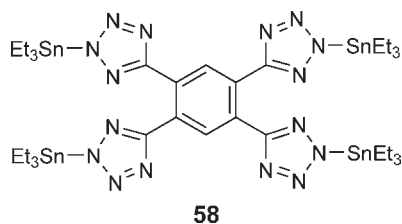


6.07.3.1.3 2-Substituted tetrazoles

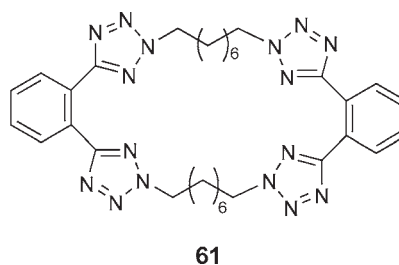
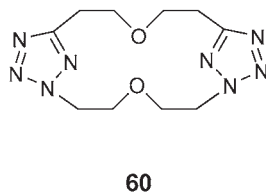
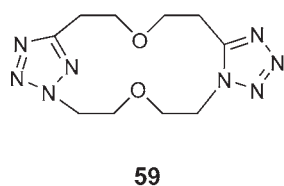
The crystals of different 2-substituted tetrazoles were examined by means of X-ray diffraction method. Strong conjugation between a 5-nitro group and the tetrazole ring was observed in the case of energetic 5-nitro-2-nitromethyltetrazole <2001AXC1101>. Coplanar conjugated systems, including phenyl, ethylene group, and tetrazole ring, exist in 2-allyltetrazole **53** <2000TL4193>.

Crystal structures of various linear binuclear tetrazol-2-yl alkanes were investigated recently. In di(tetrazol-2-yl)ethane **54**, the crystal structure is stabilized by C(tetrazole)–H···N(4) intermolecular contacts <2002ICA(340)215>. Hydrogen atoms of methylene groups also play an important role in the interactions between the molecules of bis(5-phenyltetrazol-2-yl)alkanes **55** and **56** <2002AXCo381, 2000CHE326>. The structure of compound **57** exhibits liquid crystal alignment in the gross array, enhanced by the presence of intermolecular Br···Br interactions <2004AXE0388>. Crystals with asymmetric units of tetrakis(2-stannyltetrazolyl)benzene **58** have been examined by Molloy and co-workers <1999JCD1951>.

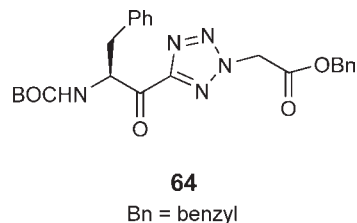
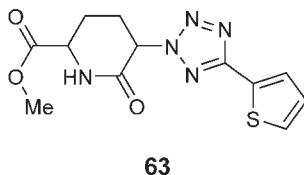
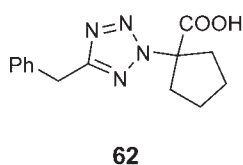




Structures of macrocyclic ligands **59**, **60**, and **61** containing 2,5-disubstituted tetrazole fragments capable of selectively binding metal ions have been investigated. Among 30 theoretically predicted conformations of macrocycle **60**, one is similar to that experimentally observed in the crystal structure [<2001J\(P2\)417>](#). The interior of the rectangular cavity of cyclophane **61** measures $11.2 \times 5.7 \text{ \AA}^2$ [<2001AXEo195>](#).



The geometries of different biologically active compounds containing 2,5-disubstituted tetrazole moieties have been described: tetrazolylcyclopentanecarboxylic acid **62** (a precursor in the synthesis of semisynthetic antibiotics based on penicillin and cephalosporin) [<2001KFZ49>](#), tetrazole-containing derivative of pipercolic acid **63** [<2005EJO326>](#), and α -keto tetrazole-based peptidomimetic **64** [<2001TL5641>](#).



As seen from [Table 3](#), the geometry of a 2-substituted tetrazole ring is unlike the structures of NH-unsubstituted and 1-substituted tetrazoles in that the bond lengths within the 2-substituted tetrazole ring are more uniform and more symmetric.

6.07.3.1.4 Nonconjugated tetrazoles

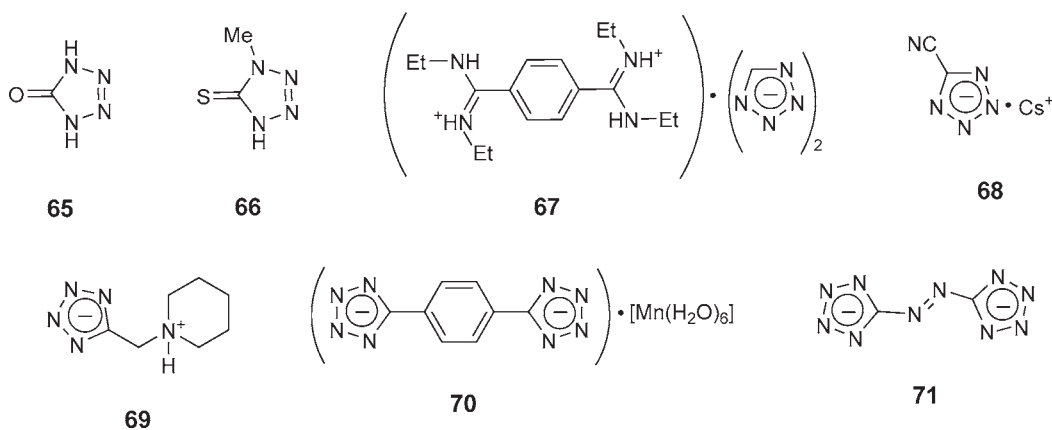
Structural parameters of 1,4-dihydropyridazine derivatives have been established. Compounds **65** and **66** in the crystalline state exist exclusively as tetrazol-5-ones and tetrazole-5-thiones [<1995HAC89, 1998AXC1160>](#). Although tetrazolone **65** has a nonaromatic character, the dihydropyridazine ring remains practically planar: the deviation from planarity results in a value of the corresponding dihedral angles of about 1° [<1998AXC1160>](#). In the crystals of this compound, strong intermolecular hydrogen bonds are present.

The data in [Table 3](#) show that the main difference between the geometry of the hetero-ring in tetrazolone **65** and that of the NH-unsubstituted tetrazoles consists of a slight elongation of the N(4)–C(5) and C(5)–N(1) bonds and a shortening of the N(2)–N(3) bond.

6.07.3.1.5 Tetrazolate anions

The tetrazole ring possesses a relatively high acidity (cf. Section 6.07.4.5.1). Tetrazolate anions generated by dissociation are capable of forming stable salts with various cations. Thus, the crystal structure of hydrogen-bonded complex of two molecules of parent tetrazolate anion with 4-bromo-*N,N'*-diethylbenzamidine and *N,N',N'',N'''*-tetraethylterephthalamidine cations have been described by Kraft and co-workers <2001JOC3291, 2002AXCo272>. The crystal structure of salt **67** contains an infinite network of hydrogen bonds with short N...N distances (2.820, 2.858 Å) between tetrazolate anion and amidinium cation <2002AXCo272>. Monoclinic crystals of cesium 5-cyanotetrazole **68** are described as a 3-D array of cations and anions connected by weak Cs⁺–N^{δ+} contacts of 3.3–3.6 Å and a tetrahedral arrangement of ions <2000IC1840>. 5-Piperidinomethyltetrazole **69** exists as a zwitterion structure where the H-atom of the tetrazole ring is transferred to the N-atom of the piperidine ring <2003AXCo22>. Hexaqua manganese(II) ditetrazolate **70** was obtained and structurally characterized <2005AXEm361>.

Structures of energetic salts of 5,5'-azotetrazolate **71** with sodium, *N*-methylurotropinium, azidoformamidinium, aminoguanidinium, and 1-methyl-4-amino-1,2,4-triazolium cations have been investigated <2005MI75, 2002ZFA2901, 2005CM3784, 2005CC2750>. The structure of the 5-nitrotetrazolate salts with sodium, potassium, ammonium, hydrazinium, 1,4-dimethyl-5-aminotetrazolium, guanidinium, aminoguanidinium, and tetraphenylphosphonium ions was also reported <2006MI631>.



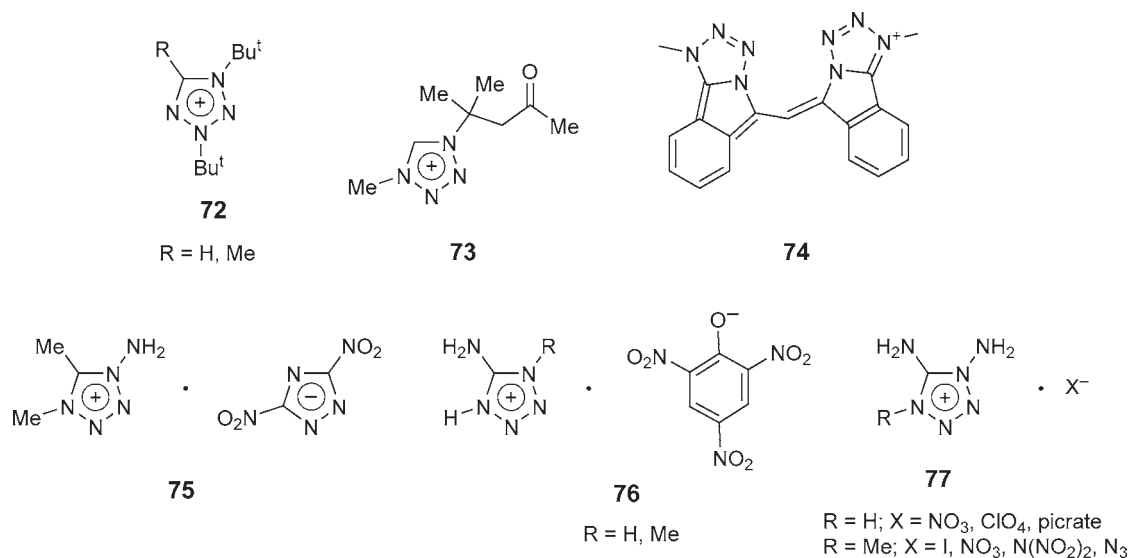
As seen from Table 3, the tetrazolate ring is a symmetric structure with nearly uniform bond lengths. The strong intermolecular hydrogen bonds inherent to these compounds can presumably considerably affect the geometry of the tetrazolate ring.

6.07.3.1.6 Tetrazolium ions

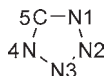
The structures of several 1,3- and 1,4-tetrazolium salts have been reported. Thus, crystal structures of 1,3-di-*tert*-butyltetrazolium picrate and perchlorate **72** as well as 1-*tert*-butyl-3-(1-methylvinyl)tetrazolium perchlorate were determined <1998CHE579, 2001CHE949>. In the case of tetrazolium perchlorate (**72**: R = H), two structurally nonequivalent tetrazolium cations and two perchlorate anions are present in the unit cell <2001CHE949>. X-Ray diffraction data obtained for hydrogen-bonded crystals of 1,4-disubstituted tetrazolium perchlorate **73** suggest that the positive charge is mainly localized on the N(4)–C(5)–N(1) fragment <1999CHE1078>. A propeller-like structure of tetrazolocyamine perchlorate **74** has been described <2004JST(707)193>.

The crystals of some energetic aminotetrazolium salts were suitable for X-ray analysis. Thus, the structural data of 1-amino-4,5-dimethyltetrazolium 3,5-dinitro-1,2,4-triazolate **75** at 85 K <2005JMC3459> and 5-aminotetrazolium picrate (**76**: R = H), which is readily quaternized at N-4, at 86 K <2005EJI3760> are available. Crystals of 5-amino-1-methyltetrazolium picrate (**76**: R = Me) contain cations and anions linked together by a complex set of hydrogen bonds, forming polymeric chains with van der Waals interaction between the chains <2005AXEo3645>. Salts of 1,5-diamino-tetrazolium **77** with various counterions were examined <2003JST(649)309, 2005JA2032, 2005IC4237>. As in the neutral 1,5-diaminotetrazole, in 1,5-diaminotetrazolium salts the amino groups attached to the endocyclic carbon and nitrogen are essentially different. The 5-amino group is strongly conjugated with the tetrazole ring ('aniline' type) and has a planar structure, whereas the 1-amino group is virtually nonconjugated ('hydrazinic' type), and its geometry is

close to tetrahedral. In all tetrazolium salts (**77**: R = H), the hydrogen is located exclusively at N-4 atom. In the crystals of these ions, the N(4)–H fragment plays the proton donor role in formation of strong intermolecular hydrogen bonds which are mainly responsible for the crystal packing of these salts.



The data in [Table 3](#) show that the ring geometries of isomeric 1,3- and 1,4-tetrazolium ions are somewhat different. The structural parameters of 1,3-tetrazolium ions are more like those of 2-substituted tetrazoles, whereas the 1,4-tetrazolium ions are close in structure to 1-isomers of the neutral molecules.



6.07.3.2 Microwave Spectroscopy

Krugh and Gold in an early study determined the rotational constants and dipole moment of the parent tetrazole by means of microwave spectroscopy in the gas phase: A 10667.3, B 10310.9, C 5240.4 MHz, dipole moment 2.19 D [<1974JSP423>](#). The results of calculations carried out by Fausto and co-workers using the B3LYP/6-31G* method are only consistent with the data for the 2*H*-tautomer of tetrazole confirming the prevalence of exactly this form of the compound in the gas phase [<2001PCP3541>](#).

6.07.3.3 NMR Spectroscopy

NMR spectroscopy is the principal spectral method used for elucidating the structures of tetrazole derivatives and especially in the identification of regioisomers and corresponding tautomers. Taking into account the structural features of the tetrazole ring containing up to two hydrogen atoms directly linked to nitrogen and carbon atoms of the ring, one carbon, and four nitrogen atoms, it is presumable that just nitrogen NMR spectroscopy would be the most informative. This was stated in many publications.

The features of NMR spectra of tetrazole derivatives registered on various nuclei and also examples of their application to the solution of actual chemical problems were considered in detail by Butler in CHEC(1984) [<1984CHEC\(4\)791>](#) and CHEC-II(1996) [<1996CHEC-II\(4\)621>](#). The main concepts remain unchanged; however, some new trends in this field may be revealed. Thus, considering the higher level of modern experimental technique, the recent publications are more concerned with long-range coupling constants and solid-state NMR spectroscopy. In treating NMR shieldings, the *ab initio* theoretical methods have acquired a significant place; they are used in particular for estimating the effect of intermolecular interactions on the spectral characteristics in question. In this section, we discuss some examples of the application of these approaches to various aspects of tetrazole chemistry.

Table 3 Selective X-ray diffraction data of cycle geometry of neutral tetrazoles, tetrazolate anions, and tetrazolium cations

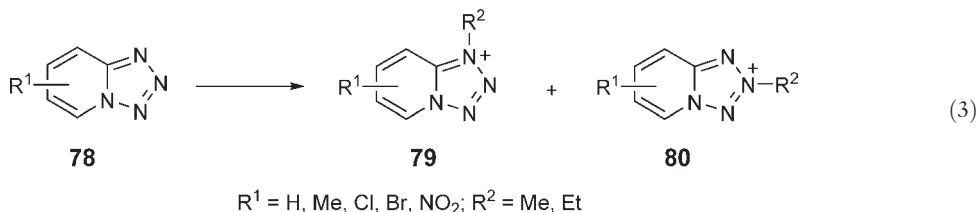
Structural type, substituent(s)	Crystal system	Space group	Bond lengths (Å)					Bond angles (deg)					Reference
			1–2	2–3	3–4	4–5	5–1	5–1–2	1–2–3	2–3–4	3–4–5	4–5–1	
NH-Unsubstituted tetrazoles													
24: ^a R = H	Triclinic	P1	1.332	1.295	1.346	1.315	1.308	109.2	106.0	110.5	105.5	108.8	1997AXC590
24: ^a R = Me	Monoclinic	C/c	1.342	1.285	1.358	1.316	1.333	109.4	106.2	110.6	106.5	107.4	1999AXC1014
24: ^a R = MeS	Orthorhombic	Pbcm	1.358	1.281	1.363	1.325	1.346	109.1	106.2	110.9	106.8	107.0	2004AXCo47
24·H ₂ O: ^a R = 4-OHC ₆ H ₄	Monoclinic	C2/c	1.344	1.286	1.360	1.325	1.338	109.3	106.4	110.7	106.3	107.4	1997AXC143
26 ^a	Monoclinic	P2 ₁ /n	1.344	1.297	1.360	1.315	1.330	107.9	106.8	110.4	105.4	109.5	1996JCX399
1-Substituted tetrazoles													
31: R = Me	Orthorhombic	Pnma	1.344	1.299	1.360	1.315	1.331	108.4	106.2	110.8	105.4	109.2	1996AXC2818
31: R = Ph	Monoclinic	P2 ₁ /a	1.348	1.298	1.354	1.302	1.344	107.3	106.6	110.7	105.8	109.6	1999AXC129
5: R ¹ = pyrid-2-yl; R ² = Me	Triclinic	P1	1.343	1.303	1.352	1.326	1.345	108.3	106.7	110.6	106.1	108.3	1996JCX399
33: R = NH ₂	Monoclinic	P2 ₁ /c	1.363	1.279	1.367	1.327	1.345	108.8	105.8	111.9	105.6	107.9	2001AXC185
39	Monoclinic	P2 ₁ /c	1.404	1.267	1.435	1.324	1.346	106.9	108.3	109.4	105.4	109.9	2002AXEo431
2-Substituted tetrazoles													
54	Monoclinic	P2 ₁ /n	1.333	1.323	1.326	1.348	1.328	101.4	114.0	106.0	105.9	112.8	2002ICA(340)215
55	Monoclinic	P2 ₁ /n	1.333	1.322	1.313	1.358	1.327	101.6	114.1	105.7	106.7	111.8	2002AXCo381
1,4-Dihydropyrazole													
65 ^b	Tetragonal	P4 ₁ /2 ₁ /2	1.351	1.275	1.351	1.348	1.348	111.0	107.8	107.8	111.0	102.4	1998AXC1160
Tetrazolate anions													
67	Monoclinic	P1 2 ₁ /n ₁	1.335	1.295	1.320	1.315	1.294	104.0	109.4	109.3	104.2	113.0	2002AXCo272
68	Monoclinic	C2/c	1.333	1.303	1.333	1.325	1.325	103.8	109.8	109.8	103.8	112.7	2000IC1840
69	Triclinic	P1	1.348	1.306	1.349	1.329	1.331	104.7	109.7	109.0	105.1	111.45	2003AXCo22
Tetrazolium cations													
72: ^d R = Me	Triclinic	P1	1.320	1.287	1.328	1.314	1.353	109.2	104.0	114.8	103.6	108.5	1998CHE579
73 ^c	Monoclinic	P2 ₁ /c	1.361	1.276	1.349	1.315	1.317	108.4	108.0	107.9	109.1	106.6	1999CHE1078
76: ^{d,e} R = Me	Triclinic	P1	1.364	1.268	1.354	1.329	1.334	109.2	108.0	108.1	109.9	104.8	2005AXEo3645
77: ^f R = H	Monoclinic	C2/c	1.366	1.260	1.354	1.336	1.324	110.4	107.2	108.7	110.0	103.7	2005IC4237
77: ^{c,g} R = H	Monoclinic	P2 ₁ /n	1.368	1.272	1.361	1.333	1.340	110.4	107.4	108.0	110.6	103.7	2005IC4237

^a1*H*-Tautomer.^bC(5)–O bond length 1.241 Å.^cPerchlorate.^dPicrate.^eC(5)–N_{am} bond length 1.316 Å.^fNitrate, C(5)–N_{am} and N(1)–N_{am} bond lengths: 1.302, 1.385 Å.^gC(5)–N_{am} and N(1)–N_{am} bond lengths: 1.304, 1.387 Å.

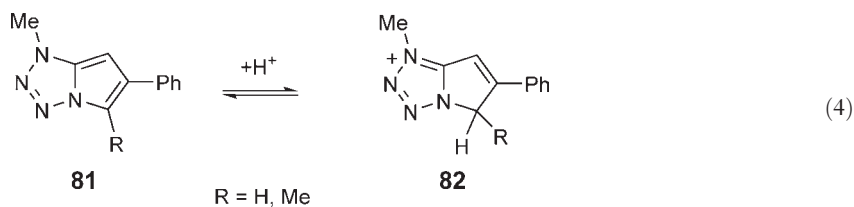
6.07.3.3.1 Proton NMR spectra

The signal of a proton associated with the nitrogen atom of the tetrazole ring appears as a broad band in the far downfield region and it can be seldom used for the solution of any practical problems. The hydrogen directly attached to C-5 exhibits acidic character that has been evaluated from the isotope exchange (H/D) rate on a series of N-substituted tetrazoles <2006RJO1585>. An NMR spectroscopy titration method based on the shift of the CH proton was successfully utilized in measuring the constants of protolytic equilibria of some tetrazoles <2006RJO1585>, and also in evaluating the stability constants of metal complexes with a 1-substituted-5*H*-tetrazole ligand in D₂O solution <2005CEJ6246>. The dependence of the CH singlet's chemical shift on concentration was exploited in estimating the constants of hydrogen-bonding association between unsubstituted tetrazolate and benzamidine salts <2001JOC3291>. The signal of this proton in the case of C-unsubstituted 1,4- and 1,3-tetrazolium salts is characterized by a downfield shift (11.1–11.9 ppm for 1,4-dialkyltetrazolium perchlorates and tetrafluoroborates and 10.2–10.9 ppm for 1,3-isomers in DMSO) in comparison with the neutral tetrazoles <2002RCR721>.

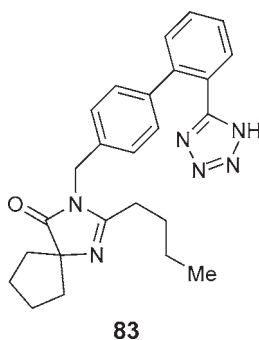
Characteristics of NMR spectra of various substituents (alkyl, aryl, hetaryl, etc.) at different nitrogen or carbon atoms can be successfully used for structural identification of tetrazole derivatives. In particular, polynuclear and complex compounds can be applied to the study and prediction of diverse tetrazoles properties. For instance, both theoretical and experimental proton NMR spectra were used for determining tetrazole–azide equilibrium constants and thermodynamic parameters for the tautomerism in CDCl₃ solution of tetrazolo[1,5-*a*]pyridines **78** and tetrazolo[1,5-*b*]pyridazine <1997MRC237, 1999MRC493, 1999JST(510)165>. It was found also that tetrazolo[1,5-*a*]pyridine (**78**: R¹ = H) and its derivatives upon alkylation gave mixtures of *N*¹- and *N*²-alkyl compounds **79** and **80** in different ratios (Equation 3) <1999JST(477)119>.



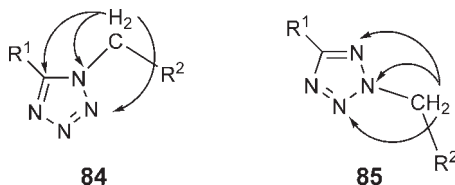
The chemical shifts of the signals of the α -methylene groups of α,ω -di(tetrazol-5-yl)alkanes correlate well with pK_a^1 and pK_a^2 (cf. Section 6.07.4.5.1) <2006CHE469>. The alkylation regioselectivity of bifunctional tetrazoles and also the structure of macrocyclic compounds can be successfully investigated with the use of ¹H NMR spectra. The signals of the α -methylene groups of alkyl substituents at the endocyclic N-1 and N-2 atoms are considerably different: the signal of the CH₂ group attached to N-2 appears downfield from the signal of such a group at N-1 <1999MC116, 2001J(P2)417>. It was shown by ¹H NMR spectroscopy that protonation, acylation, and alkylation of the pyrrolotetrazoles **81** occurred mainly at the carbon atom affording 5*H*-tautomers **82** (Equation 4) <2001J(P1)729>.



Winter and co-workers used the proton NMR spectra of niobium(v) complexes with 5-phenyltetrazolate ligand recorded at temperatures between –80 and +40 °C in toluene-*d*₈ for structural analysis <2001IC6451>. One- and two-dimensional ¹H NMR methods in solution and solid state were used for analyzing the structure of irbesartan **83** <1998J(P2)475> as well as for the analysis of the structure of coordination compounds of ruthenium(II) and iron(II) with 5-aryltetrazolates <2002OM3774, 2003JOM(669)135, 2006IC695>.

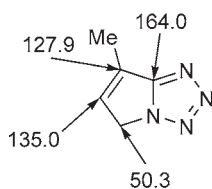


Two-dimensional NMR spectroscopy (^1H , ^{13}C and ^1H , ^{15}N heteronuclear multiple bond correlation (HMBC)) is also useful for identification of the regioisomers of tetrazoles. For instance, the patterns of cross-peaks in the spectra of the 1*H*- and 2*H*-tetrazoles **84** and **85** are essentially different. In 1-substituted derivatives **84**, a cross-peak resulted from a ^3J -coupling between the methylene protons and C-5, and two cross-peaks, from couplings ^2J and ^3J between the protons and N-1 and N-2 <2006T1849>. As regards the 2-alkyltetrazoles **85**, usually no cross-peaks ^1H - ^{13}C were observed, but three cross-peaks were registered in the ^1H - ^{15}N HMBC spectrum from couplings ^2J and ^3J between the protons and nitrogen atoms N-1, N-2, and N-3.

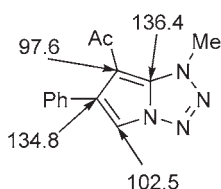


6.07.3.3.2 Carbon-13 NMR spectra

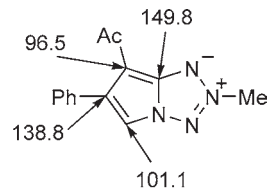
Signals of the tetrazole ring carbon in the ^{13}C NMR spectra are very sensitive to regioisomerism and other structural factors. For instance, the C-5 signal for 2,5-disubstituted tetrazoles is located downfield (162–167 and 151.9 ppm for 2-methyl-5*H*-tetrazole) from the corresponding signal of the 1,5-regioisomers (152–156 and 143.4 ppm for 1-methyl-5*H*-tetrazole) <1996CHEC-II(4)621>. This fact and also the presence of a single carbon atom in the tetrazole ring significantly facilitate the interpretation of the ^{13}C NMR spectra. ^{13}C NMR spectroscopy was used to prove the structure of various complex tetrazoles, including linear branched and macrocyclic systems <1999MC116, 2001J(P2)417>. Two crystal forms of irbesartan **83** have been examined using solid-state ^{13}C NMR spectroscopy and substantial differences between the spectra of the forms were observed <1998J(P2)475>. These differences were ascribed to the existence of one crystalline form as the 1*H*- and the other as the 2*H*-tautomer. Carbon spectra of compound **83** in solution prove that in this case the tetrazole ring is present only as the 1*H*-tautomer. The NMR signal of the endocyclic C-5 atom was used in proving the structure of various coordination compounds. For instance, Palazzi *et al.* showed that complexes of Fe(II) or Ru(II) with 5-aryltetrazolates had a structure where the metal forms a coordination bond with N-2 of the hetero-ring (carbon resonance at ca. 163.4 ppm) <2002OM3774, 2003JOM(669)135, 2006IC695>. On methylation and protonation of these complexes, the signal for C-5 shifted upfield to 156.4 ppm, and also a strong reduction of interannular conjugation between tetrazole and aryl rings was observed. The appropriateness of the application of this approach for proving the structure of various tetrazole-containing compounds was confirmed by independent methods, among them X-ray diffraction analysis. The signal of the endocyclic carbon in the ^{13}C NMR spectra correlates with $\text{p}K_{\text{a}}$ values of some tetrazoles <1997CHE1292, 2006RJO1585, 2006CHE469>. Some additional data on ^{13}C NMR spectra of the simplest tetrazole derivatives have been reported <1997MRC209, 2001H(55)2109>. ^{13}C NMR spectra of various types of tetrazoles and tetrazolines fused with the five- and six-membered heterocycles were published. Chemical shifts of carbons of some pyrrolotetrazoles registered in CDCl_3 are given in the formulas **86**, **87**, and **88** in ppm <1996JOC5646, 2001J(P1)720>. These spectral data were used for assigning the structure of compound **86** which might exist in various tautomeric forms.



86

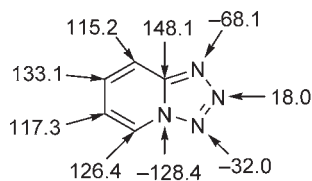


87

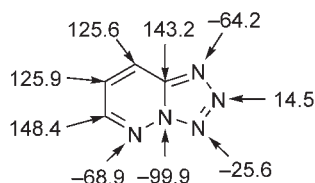


88

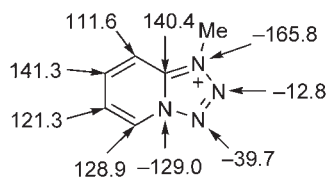
As seen from formulas **89** and **90** (chemical shifts measured in acetone and DMSO are given in ppm), the shielding of the nodal carbon atom belonging to both fused rings is close to that of the corresponding carbon in the 1-substituted-5*H*-tetrazoles <1999JST(477)119, 1999MRC493>. Alkylation of nitrogen causes significant changes in the spectral parameters as seen in formulas **91** and **92** (chemical shifts, ppm, measured in DMSO) <1999JST(477)119>. A good linear correlation between the experimental chemical shifts and the isotropic absolute shielding calculated by *ab initio* methods (GIAO-CHF) was found for compounds **89–92** and their derivatives <1999JST(477)119, 1999JST493, 1999MRC493>.



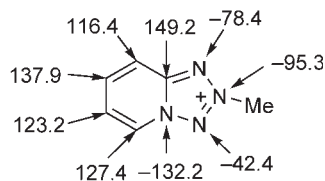
89



90



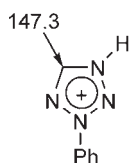
91



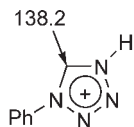
92

Isomeric N-methylated tetrazoles can also be distinguished based on the long-range ^{13}C , ^1H NMR coupling constants involving C-5 and protons of methyl substituents at N-1: for 1-methyltetrazoles the $^3J_{\text{C}(5),\text{N}(1)\text{Me}}$ value was 2.1–2.8 Hz, for 2-methyltetrazoles the $^4J_{\text{C}(5),\text{N}(2)\text{Me}}$ value was seldom possible to determine; for example, for 2-methyl-5-phenyltetrazole, this value equaled only 0.75 Hz <1997MRC209>. $^{13}\text{C}(5)$, ^{15}N ^1J -coupling constants for 1-alkyltetrazoles are smaller than the corresponding constants for 2-substituted derivatives by 1.9–2.1 Hz and presumably negative <1997MRC209>.

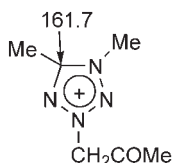
As for neutral tetrazoles, the ^{13}C NMR spectra of isomeric tetrazolium ions strongly depend on the isomer type. The signals for C-5 in 1,3-disubstituted tetrazolium salts are downfield by 7–16 ppm compared to the corresponding signals of 1,4-isomers (see formulas **93–96**, where the signals registered in H_2SO_4 for **93** and **94** and in D_2O for **95** and **96** are given in ppm) <2002RCR721>.



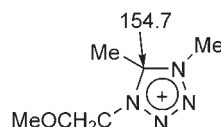
93



94



95



96

^{13}C NMR spectra of tetrazolate anions are similar to the spectra of 2-substituted tetrazoles. For instance, the chemical shift of the signal of tetrabutylammonium tetrazolate in CDCl_3 is 149.8 ppm <2001JOC3291>, and for the sodium 5-nitrotetrazolate in acetone- d_6 it is 167.5 ppm <2006MI631>.

Thus it is possible to conclude that in the ^{13}C NMR spectra of tetrazolate anions, 2*H*-tetrazoles, and 1,3-tetrazolium ions the signal of the endocyclic carbon atom is considerably shifted downfield compared to the corresponding signal in the spectra of 1-substituted neutral tetrazoles and 1,4-disubstituted tetrazolium ions, and also of the fused tetrazoloazines. It is just in the tetrazolate anions and tetrazole derivatives with a substituent at position 2 that a lesser variation in the bond distances in the ring and stronger aromaticity are observed (cf. Sections 6.07.3.1 and 6.07.4.1).

6.07.3.3.3 Nitrogen NMR spectra

The relationships described above between the signals in the ^1H and ^{13}C NMR spectra and the structure of regioisomers of tetrazole derivatives nevertheless are not always retained. Nitrogen NMR spectroscopy is the most informative and precise method for determining the structures of tetrazole derivatives <1997MRC209>.

Experimental values of the nitrogen chemical shifts in the ^{14}N NMR spectra of *N*-methyltetrazoles in various solvents are compiled in Table 4. There is a good linear relationship (regression coefficient $r = 0.997$) between the shieldings measured in dilute solutions in cyclohexane and theoretically calculated absolute shieldings (GIAO-CHF/6-31++G**) for isolated molecules of tetrazoles and some other azoles: $\sigma_{\text{exp.}} = 0.88\sigma_{\text{calc.}} + 112.6$ <1998MR54>. As seen in Table 4, the solvent considerably affects the nitrogen NMR shifts. The comparison of calculated *ab initio* nitrogen NMR spectral parameters of tetrazoles with experimental data was reported in other publications. For instance, Witanowski and co-workers and Catalan in more recent studies calculated nitrogen NMR spectral characteristics in various solvents <2000PCA1466, 2001J(P2)1117>. The solvent effect was examined in the light of solvent polarity/polarizability, solvent acidity, and solvent basicity scales, and fair agreement of the measured and calculated values was obtained <2001J(P2)1117>. A theoretical approach based on direct and indirect solvent effects on nitrogen NMR shieldings calculated by the DFT/PCM method was also able to reproduce the key aspects of the effects (PCM = polarizable continuum model), and a good agreement with the experimental data was observed <2000PCA9600>. ^{14}N NMR quadrupole coupling and the signal line widths of methyltetrazoles have been calculated theoretically by Jaszunski and Rizzo <1998ZNA362>.

Table 4 ^{14}N NMR shieldings in ppm referred to neat nitromethane and corrected for bulk susceptibility of *N*-methyl-5*H*-tetrazoles <1998MR54>

<i>Tetrazole</i>	<i>Solvent</i>	<i>N</i> -1	<i>N</i> -2	<i>N</i> -3	<i>N</i> -4
1-Methyl	Cyclohexane	159.55	8.42	−23.31	43.23
	Acetone	153.10	9.93	−15.27	48.61
	DMSO	150.92	10.35	−13.00	50.18
	CHCl_3	154.63	9.91	−14.61	49.71
	MeOH	151.99	10.35	−8.28	56.35
	Water	150.34	14.06	−1.75	60.33
2-Methyl	Cyclohexane	73.09	106.99	−3.41	41.30
	Acetone	72.86	102.93	−0.50	45.47
	DMSO	72.58	101.51	0.38	46.14
	CHCl_3	73.66	104.52	−0.28	47.31
	MeOH	73.35	102.78	0.68	51.41
	Water	77.56	102.34	6.00	56.36

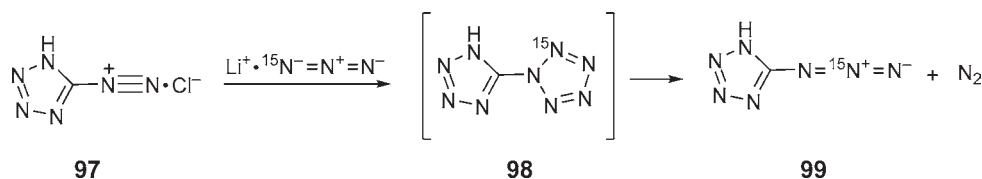
Selected data concerning ^{15}N NMR spectra of some *N*-substituted tetrazoles in solution, and also for *NH*-unsubstituted tetrazoles in the solid state published within the last decade, are presented in Table 5. The data on fused tetrazoloazines are given in formulas 89–92 (chemical shifts in ppm measured in acetone and DMSO). It was stated that the ^{15}N NMR chemical shifts become increasingly more negative in the order *N*-3 < *N*-2 < *N*-4 < *N*-1 for 1,5- and *N*-3 < *N*-4 < *N*-1 < *N*-2 for 2,5-substituted tetrazoles, and this rule is valid for a wide range of substituted tetrazoles <1997MRC209, 2006JOC1295>. The order of nitrogen shielding is consistent with the charges on the atoms, which are in a similar order (cf. Section 6.07.2.1).

Table 5 ^{15}N NMR shifts (ppm) of tetrazole derivatives referred to external nitromethane, and ^{15}N , ^1H coupling constants (Hz)

<i>Tetrazole</i>	<i>Solvent, state</i>	<i>N-1</i>	<i>N-2</i>	<i>N-3</i>	<i>N-4</i>	<i>Reference</i>
1-Me, 5-H	CDCl_3	$-151.35 \text{ d}, {}^2J = 9.3 \text{ d}, {}^2J = 2.0$	-8.29 m	$14.29 \text{ d}, {}^3J = 3.0$	$-48.64 \text{ d}, {}^2J = 12.1$	1997MRC209
1,5-diMe	CDCl_3	-153.67 m	$-7.49 \text{ q}, {}^3J = 1.9$	10.19 s	$-52.06 \text{ q}, {}^3J = 1.9$	1997MRC209
2,5-diMe	CDCl_3	-75.81 m	$-103.62 \text{ q}, {}^2J = 2.3$	$2.03 \text{ q}, {}^3J = 1.5$	$-48.00 \text{ q}, {}^3J = 1.1$	1997MRC209
1-Me, 5-Ph	CDCl_3	$-156.19 \text{ q}, {}^2J = 1.9$	$-5.26 \text{ q}, {}^3J = 1.8$	11.39 s	-50.36 s	1997MRC209
2-Me, 5-Ph	CDCl_3	$-79.49 \text{ q}, {}^3J = 1.7$	$-102.08 \text{ q}, {}^2J = 2.3$	$3.15 \text{ q}, {}^3J = 1.6$	-51.83 s	1997MRC209
1-Bu ^t , 5-H	CDCl_3	-117.43 m	$-11.36 \text{ d}, {}^3J = 1.1$	$13.77 \text{ d}, {}^3J = 3.4$	-50.39 m	1997MRC209
2-Bu ^t , 5-H	CDCl_3	$-76.57 \text{ d}, {}^2J = 15.3$	-71.52 m	-2.18 s	$-48.91 \text{ d}, {}^2J = 12.6$	1997MRC209
1-H, 5-Ph	Solid	-153.2	-16.9	5.1	-78.0	1998J(P2)475
1-H, 5-NH ₂	Solid	-117.9	-37.2	-13.0	-115.0	1998J(P2)475
1-H, 5-NH ₂	$\text{DMSO}-d_6$	-137.1	-13.1	-13.1	-137.1	2005IC4237
1-NH ₂ , 5-NH ₂	$\text{DMSO}-d_6$	$-167.0 {}^2J = 2.3$	-5.5	-20.8	-97.5	2005IC4237
1-Me, 5-NH(Me)	$\text{DMSO}-d_6$	$-186.8 {}^2J = 1.5$	$-21.8, {}^3J = 1.5$	1.8	$-94.9, {}^3J = 2.4$	2006JOC1295
1-Me, 5-NNO(Me)	$\text{DMSO}-d_6$	$-168.0 {}^2J = 2.0$	$-9.1 {}^3J = 1.7$	4.7	-72.8	2006JOC1295
1-Me, 5-NNO ₂ (Me)	$\text{DMSO}-d_6$	$-153.2 {}^2J = 1.3$	-5.9	10.2	$-58.9, {}^3J = 2.2$	2006JOC1295
<i>Tetrazolium salts</i>						
1-H, 4-H, 5-NH ₂ ^a	$\text{DMSO}-d_6$	-165.2	-24.5	-24.5	-165.2	2005IC4237
1-NH ₂ , 4-H, 5-NH ₂ ^a	CD_3OD	-164.9	-21.9	-33.1	-170.4	2005IC4237
1-NH ₂ , 4-Me, 5-NH ₂ ^b	$\text{DMSO}-d_6$	$-167.9 {}^2J = 1.7$	-24.0	$-35.3, {}^3J = 1.9$	$-186 {}^2J = 2.0$	2005IC4237
1-Ph, 3-Ph, 5-H ^c	CD_3CN	-129.8	-33.5	-92.4	-73.3	2000JST(523)103

^aNitrate.^bIodide.^cTetrafluoroborate.

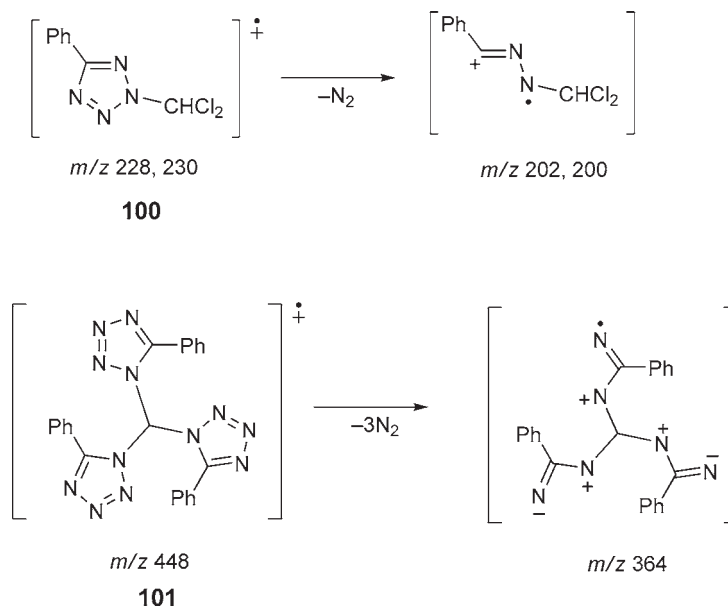
Experimental as well as theoretical approaches reveal that the ^{15}N NMR spectra of NH-unsubstituted tetrazoles are very sensitive to the intermolecular interactions, especially to hydrogen bonds <2001H(55)2109>. The spectra of the parent tetrazole and of compounds substituted only at carbon are strongly influenced by proton exchange; therefore, only two signals at averaged positions are seen <1998J(P2)475>. However, in the solid state, the spectra are more informative. Thus, in the case of different crystal forms of irbesartan **83**, it was shown using variable-temperature 2-D ^{15}N NMR experiments that an exchange process of simultaneous proton hopping is observed in only one of these forms <1998J(P2)475>. This spectroscopic procedure was used for structure determination of some compounds unstable under common conditions. For instance, the ^{15}N NMR spectra recorded at -70°C showed that the reaction of tetrazolyldiazonium chloride **97** with ^{15}N -labeled lithium azide forms an intermediate tetrazolylpentazole **98** that already at -50°C has decomposed, affording azidotetrazole **99** and N_2 (Scheme 1) <2005MI17>.

**Scheme 1**

As seen from Table 5, on going from neutral tetrazoles to tetrazolium ions, the ^{15}N NMR spectra significantly change. The protonation-induced shift shows that for all neutral tetrazoles protonation takes place at N-4. The pyrrole-type nitrogen appears most upfield compared with the signals of the pyridine-like nitrogens. A strong nuclear Overhauser effect (NOE) is observed for nitrogen atoms directly bonded to a proton and with increasing nitrogen–proton distance the NOE changes its sign and causes a decrease in the signal intensity <2005IC4237>. Thus NOE can be successfully used for interpretation of signals in the nitrogen NMR spectra and for identification of structures of various tetrazole derivatives. The nitrogen chemical shifts of 1,3-diphenyltetrazolium cations are characteristic of the class of compounds and are sensitive to changes in exocyclic groups bonded to C-5 <2000JST(523)103>. According to the nitrogen NMR spectroscopy data, the positive charge in the latter compounds is localized mainly on N-3 <1999PJC1719, 2000JST(523)103>.

6.07.3.4 Mass Spectrometry

The electron impact mass spectral fragmentation patterns of 1,5- and 2,5-disubstituted tetrazoles are essentially different, as has already been stated by Butler in CHEC(1984) and CHEC-II(1996) <1984CHEC(4)791, 1996CHEC-II(4)621>. In the case of 2,5-isomers **6**, the first stage of the molecular ion decomposition is usually a nitrogen molecule ejection followed by stepwise fragmentation and other transformations of the arising nitrile imine, although the decomposition of the molecular ion can also lead to the formation of $\text{R}^2\text{-N}_2$ and $\text{R}^1\text{-N}_2$ fragments. More patterns of fragmentation of the molecular ions are observed for 1,5-isomers **5** and also NH-unsubstituted tetrazoles, and N_2 elimination in the first stage is not always the governing route. The fragmentation routes were examined in recent studies. For instance, it is seen from the analysis of the mass spectra of 2*H*-tetrazole **100** and tristetrazole **101** (Scheme 2) that the decomposition of the tetrazole ring of compound **100** takes the classic route with ejection of the N_2 molecule, but it also turns out that the similar path with simultaneous liberation of three nitrogen molecules is also the main event for the unstable molecular ion **101** <2007CHE320>. This fragmentation scheme of polynuclear tetrazoles related in structure to **101** allows prediction of their importance as gas generator components.



Scheme 2

The fragmentation patterns of a series of neutral aryl/hetaryl tetrazoles have also been discussed <1999JIC565>. 1,4-Diaminotetrazolium and 1-phenyl-1*H*-tetrazol-5-ylthiolate salts were characterized by means of fast atom bombardment (FAB) mass spectrometry (MS) <2005IC4237, 2004ZFA1627>. Secondary dissociation reactions of some ions formed in the first stage of fragmentation were studied with the use of the charge separation MS technique <1996JMP1054>. The gas chromatography/mass spectrometry (GS/MS) method was useful in the study of thermal

decomposition products of some energetic tetrazoles revealing the mechanism of these processes <2005THE168>. Ion-cyclotron resonance (ICR) MS was applied to evaluation of the main acid–base characteristics of unsubstituted tetrazole in the gas phase (cf. Section 6.07.4.5), but 5-nitrotetrazole was unstable under these experimental conditions <2002NJC1567>. MS provides the possibility of studying other reactions involving tetrazoles. For instance, in the gas phase, 5-substituted tetrazoles react with acyl ions generated as the secondary reactive ionization plasma in the mass spectrometer to give through N-acylated intermediate the corresponding 2,5-disubstituted oxadiazoles <2001JMP1069>. While studying the characteristics of 1*H*-tetrazole as a catalyst in phosphoramidite coupling reactions, mass spectrometric analysis suggested that tetrazole acted as an acid and as nucleophilic catalyst in the pyrophosphate bond formation <1997JOC2144>. Liquid chromatography/electrospray–tandem mass spectrometry, LC/MS/MS, was used in the study of metabolism and detection of AII receptor antagonists and antibiotics containing a tetrazole heterocycle fragment in biological media <1996JMP873, 2004BCH86>. Hydrogen binding strength of noncovalent complexes between bisamidine and unsubstituted tetrazolate was estimated by electrospray MS <2001JOC3291>.

6.07.3.5 IR/Raman Spectroscopy

Characteristic absorption bands in vibration spectra of the unsubstituted tetrazole ring lie in the range 660–1530 cm^{−1} (Table 6). As had been previously reported <1984CHEC(4)791, 1996CHEC-II(4)621> and was frequently confirmed within the last decade, the vibration spectra of tetrazoles commonly contain absorption bands from vibrations of C=N, C–N, N=N, N–N, NCN, and NNN fragments. However, most of these bands cannot be unambiguously assigned to vibrations of a definite individual functional fragment or bond and involve vibrations of several bonds or bond groups. Besides, many of these bands are relatively weak. Nonetheless, the bands corresponding to these vibrations can be applied to estimating the structure of given compounds and to investigation of tautomerism and isomerism of tetrazoles in various media. For instance, Fausto and co-workers showed using detailed data on both observed and calculated vibration spectra that NH-unsubstituted tetrazole and 5-chlorotetrazole isolated in an argon matrix at low temperature exist predominantly as the 2*H*-tautomer, whereas in the crystalline state they exist as the 1*H*-tautomer <2001PCP3541, 2002PCP1725>. According to these data, the fraction of 1*H*-form of parent tetrazole in the argon matrix can be estimated at 10% with respect to the most stable tautomer. A comprehensive analysis of vibration spectra with the use of theoretical DFT calculations and also of experimental methods involving matrix isolation IR spectroscopy was carried out by the same authors for 1-phenyl-5-methoxytetrazole <2006JPH175>, 1-methyl-5-mercaptotetrazole <2006JST(786)182>, 1-phenyltetrazolone <2006JPH243>, and 2-methyl-5-amino-tetrazole <2005PCA7967>. The findings obtained were used for evaluation of the tautomeric composition of the mentioned heterocycles. The effect of the character of substituent in position 1 on the vibration spectra was subjected to analysis for a series of 1-substituted tetrazoles and α,ω-di(tetrazol-1-yl)alkanes 42 <2005JST(733)41>. As shown by Passmore and co-workers, in the case of cesium 5-cyanotetrazolate among the expected 15 vibrations of the tetrazole ring, 11 are observed in the FT-Raman spectrum and 13 in the FTIR spectrum <2000IC1840>. The peak positions are in good agreement with the calculated spectrum (RB3PW91/6-311+G*), and the IR frequencies are similar to those reported for some other tetrazolate anions. The Raman and IR spectra of 1,5-diaminotetrazolium salts have also been analyzed by Klapötke and co-workers <2005IC4237>. On formation of tetrazole complexes with metal ions, certain changes are observed in the IR region corresponding to the proper vibrations of the tetrazole ring. For instance, in the mid-range IR spectrum of complex 103, in contrast to the spectrum of the corresponding ligand, bands at 1507, 1454, and 1110 cm^{−1} were observed belonging to the combinations of stretching vibrations of bonds N-4 and N-4' in the coordinated tetrazole rings <2002ICA(339)297>. Analysis of the far-IR spectral region of the complex, also reported in the mentioned publication, demonstrated that due to the spin transition between a high and low spin state of the iron(II) two Fe–N stretching vibrations at 300 (for high spin state) and 430 cm^{−1} (for low spin state) may be observed. On raising the temperature from 100 to 298 K, the intensity of these bands dramatically changes.

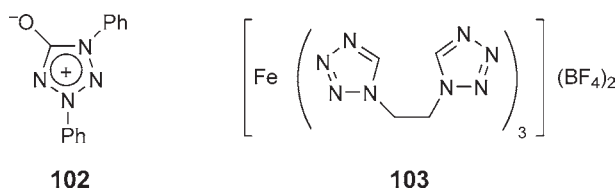


Table 6 Selected vibration frequencies (in cm^{-1}) observed in the argon matrix at 10 K and in the crystal state and calculated in the gas phase (B3LYP/6-31G*) of 1*H*- and 2*H*-tautomers of parent tetrazole <2001PCP3541>

Approximate description ^a	1 <i>H</i> -tetrazole				2 <i>H</i> -tetrazole	
	IR (argon)	IR (cryst.)	Raman (cryst.)	Calcd.	IR (argon)	Calcd.
$\nu(\text{N-H})$	3484.3	3500–2300 ^b	3200–2900 ^c	3512.0	3468.8	3504.7
$\nu(\text{C-H})$		3158.3	3158.5	3182.3		3184.7
$\nu(\text{C}\equiv\text{N})$	1467.6	1524.6	1530.3	1458.4	1481.6	1477.9
$\nu(\text{C-N})$	1428.2	1451.6, 1444.8	1448.9	1409.8	1279.6	1274.0
$\nu(\text{N}\equiv\text{N})$	1242.7	1259.3	1259.9	1248.8	1214.3, 1196.1	1206.8
$\delta(\text{N-H}) + \nu(\text{C}\equiv\text{N})$		1145.1	1144.5	1223.4	1359.2	1348.6
$\delta(\text{C-H}) + \nu(\text{C-N})$	1090.3	1085.3	1086.1	1107.1	1119.8	1114.3
$\nu(\text{N(3)-N(4)})$	1040.6	1049.6	1048.3	1029.2		
$\nu(\text{N(1)-N(2)})$	1010.5	1015.1, 999.2	1013.7	1005.6	1127.9	1139.1
$\nu(\text{N(2)-N(3)})$					1061.8	1063.4
$\delta(\text{NCN})$		951.5	947.2	972.1	989.0	971.7
$\delta(\text{NNN as.})$	938.4	937.1		932.7	1017.4	1000.6
$\gamma(\text{C-H})$	851.2	907.2	905.4	815.5	876.8	855.4
$\gamma(\text{ring 1})$		772.4		708.6	724.0	713.0
$\gamma(\text{ring 2})$	673.7	663.1	662.5	663.8	698.4	690.8
$\gamma(\text{N-H})$	573.4	884.4		543.4	592.6	559.4

^a ν , stretching; δ , in-plane bending; γ , out-of-plane bending; as, asymmetric.^bStrong broad band.^cWeak broad band.

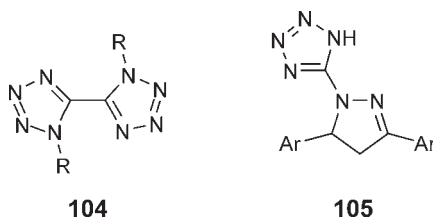
Raman spectroscopy was applied to measuring the $\text{p}K_{\text{BH}^+}$ value of unsubstituted tetrazole in aqueous solutions of sulfuric acid, and it was shown that the most probable basicity center was the nitrogen at position 4 of the ring <2006RJO1585>. Hydrogen-bonding basicity constants of some N-substituted tetrazoles in CCl_4 were determined using FTIR spectroscopy <2006RJO1059>. The significant changes found between the surface-enhanced Raman scattering and normal Raman spectra combined with the DFT theoretical data obtained for Ag-5-aminotetrazolate system demonstrated that the heterocycle was adsorbed on colloidal Ag-particles through the lone electron pair of the nitrogen atoms and assumed a tilted orientation <2005PCA9928>. The primary and secondary products of photochemical decomposition of some matrix-isolated tetrazoles were identified using IR spectroscopy <2006JPH175, 2005PCA7967, 2006JPH243, 2006JST(786)182>. The gaseous products of thermal and explosive decomposition of guanidinium 5-aminotetrazolate, as well as of azidoformamidinium and guanidinium 5,5'-azotetrazolate salts, were also identified using IR spectroscopy <2003MI181, 2005CM3784>. Raman and FTIR techniques were applied to examine the interaction between additives of the mesoionic tetrazole **102** and proton-conducting polymer gels <2001PCB9686>.

IR spectroscopy was successfully exploited in studies of ring-chain tetrazole-azide isomerism of some fused tetrazoles. The presence or absence of a peak near 2100 cm^{-1} corresponding to vibrations of an azide group, and also bands of the tetrazole ring in solid state and solutions, may be utilized for estimation of the dominant isomer and its relative amount <1999JST(510)165, 2006JOC4049>.

6.07.3.6 UV/Fluorescence Spectroscopy

The electronic spectrum of unsubstituted tetrazole is characterized by an absorption band with a maximum in the vacuum UV region (λ_{max} below 200 nm). However, substituents in the tetrazole ring capable of conjugation lead to a considerable redshift of the maximum into the normal UV range. UV spectra of isomeric 1- and 2-substituted tetrazoles are considerably different, for example, 1-methyl-5-phenyltetrazole (λ_{max} 232 nm), 2-methyl-5-phenyltetrazole (λ_{max} 240 nm), 1-phenyltetrazole (λ_{max} 236 nm), and 2-phenyltetrazole (λ_{max} 250 nm) <1996CHEC-II(4)621>. 2*H*-Tetrazoles absorb in more of the longwave region than the 1*H*-isomers. The situation is not so clear with NH-unsubstituted tetrazoles, as the position of the absorption bands in the electronic spectra is significantly affected by the intermolecular interactions. UV spectrophotometry was successfully exploited in measuring the acidity and basicity constants of aryl-substituted tetrazoles, 5-nitrotetrazole, and 5,5'-bitetrazoles, for the UV spectra of neutral heterocycles, tetrazolate anions, and tetrazolium ions are in general essentially different <2006RJO1585>. Electronic spectroscopy data reveal strong $\pi\pi$ -conjugation between the tetrazole ring and a substituent in the 5-position for 5-nitrotetrazole and

5,5'-bitetrazoles **104**. In the case of NH-unsubstituted 5,5'-bitetrazole **26**, the planar structure is retained in anionic, neutral, and also protonated forms. High fluorescence quantum yields (0.6–0.8) are typical for tetrazolopyrazolines **105** in toluene <2006JST(785)114>. The solvent considerably affects the electronic spectra of compounds **105** and is apparently caused by formation of multiple hydrogen bonds involving the heterocyclic fragments as well as by NH-dissociation of the molecules in the ground state.

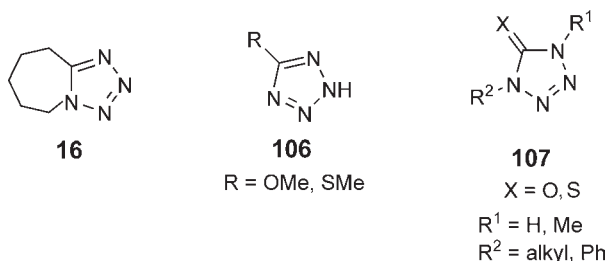


A time-dependent DFT method was utilized for calculating the electronic transition energies of a series of 5-aryl-NH-tetrazoles in solution, and the calculated absorption bands were compared with experimental data <2003CPH65>. However, Sadlej-Sosnowska *et al.* compared the theoretically calculated spectra of 2*H*-tautomers with the spectra measured in solutions where the prevalence of 1*H*-tautomers was well known.

The electronic spectra of tetrazoles are in general somewhat different from the spectra of their coordination compounds with metal ions. For instance, in the spectra of complexes alongside the bands corresponding to electron transitions in the tetrazole ligands, bands may appear belonging to metal-to-ligand charge-transfer transitions at the lowest energy. Thus, in the case of Ru(II) complexes with 5-aryltetrazolate, the broadened band corresponding to the transition $d(\text{Ru})-\pi^*(\text{ligand})$ is centered between 450 and 480 nm. The metal-to-ligand transitions appear also in the emission spectra of the Ru(II) complexes <2006IC695>. The temperature-dependent electronic absorption spectra of complex **106** in the range 100–293 K confirmed that the spin transition at the iron(II) coordination center changes the size of the energy gap between the d orbitals <2002ICA(339)297>. Strong fluorescent emission of various Zn(II) and Cd(II) complexes with tetrazolates in the solid state were reported <2004EJ13662, 2005IC3618, 2005IC5278, 2005JCS(D)1570>.

6.07.3.7 Photoelectron Spectroscopy

Ultraviolet photoelectron spectroscopy (UPS) has been used in the study of electronic structure, thermolysis, and tautomerism (see Sections 6.07.4.4.1 and 6.07.4.4.2) of tetrazoles in the gas phase. The electronic structure of the neutral tetrazole ring is characterized by three occupied π molecular orbitals and three n_N orbitals. The bands assigned to ionization from these orbitals may be observed in the photoelectron spectra <1996CHEC-II(4)621>. The spectra with the fine structure of the parent tetrazole and its monomethylated derivatives with higher resolution than those previously reported have been characterized and interpreted basing on Koopmans' approximation in conjunction with DFT and outer valence Green's function (OVGF) calculations by Novak *et al.* <2003SAA1725>. The lowest vertical ionization energies are: tetrazole (2*H*-tautomer) 11.35 eV, 1-methyltetrazole 11.0 eV, 5-methyltetrazole (2*H*-tautomer) 10.87 eV, 1,5-dimethyltetrazole 10.5 eV, pentamethylenetetrazole **16** 10.15 eV. The photoelectron spectra of a series of 5-substituted tetrazoles **106**, 1,4-dihydrotetrazol-5-ones, and 1,4-dihydrotetrazole-5-thiones **107** at various temperatures have been recorded <1997JHC113>. Tetrazoles **106** are characterized by the presence of high-lying occupied orbitals n_X ($R = \text{OMe}$ or SMe). 1,4-Dihydrotetrazoles **107** are characterized by three occupied π -type MOs of the tetrazene unit, two n -type orbitals centered on the azo group, and also by n_X ($X = \text{O}$ or S) orbitals, and their photoelectron spectra are essentially unlike those of compounds **16** and **106**. One of the π -orbitals is interpreted as the high-lying occupied orbital. Real-time gas analysis controlled by photoelectron spectroscopy proved to be an excellent method for studies of gas-phase thermolysis of tetrazole derivatives **106** and **107** <1997JHC113>.



The adsorption of N-substituted tetrazoles on surfaces was studied by means of the X-ray photoelectron spectroscopy technique <2000MI130, 2004MI1371>.

6.07.3.8 Dipole Moments

Dipole moments of 1*H*- and 2*H*-tetrazoles are essentially different as has been mentioned by Butler in CHEC(1984) and CHEC-II(1996) <1984CHEC(4)791, 1996CHEC-II(4)621>. Thus the dipole moments of the 1-substituted tetrazoles are significantly larger (above 5.3 D, 1-ethyltetrazole 5.46 D) than those of the 2-substituted isomers (under 2.65 D, 2-ethyltetrazole 2.65 D) <1984CHEC(4)791>. This fact has been successfully used in studying the tautomerism of NH-unsubstituted tetrazoles in various media. For instance, the dipole moment of unsubstituted tetrazole measured by microwave spectroscopy in the gas phase was 2.19 D <1984CHEC(4)791>, whereas in solution it was 5.14 D <2006RJO1585>, demonstrating that in the gas phase the 2*H*-tautomer dominated and in solution it is the 1*H*-tautomer. The theoretically calculated dipole moments are consistent with the experimental findings. These calculations give good results in both *ab initio* and semi-empirical procedures <2006RJO1585, 2003RJC275, 2004JMT(668)123>. However, it was demonstrated that the higher polarity of 1*H*-tetrazoles compared to that of 2*H*-tetrazoles is observed only when the substituents at the carbon atom are either electron donors, neutral, or weakly electron withdrawing <2004JMT(668)123>. With growing electron-acceptor power of the substituent, the dipole moment of the 2*H*-form increases whereas that of the 1*H*-tautomer diminishes. In 5-nitrotetrazole, the 2*H*-tautomer is the more polar. The dipole moments of 1*H*- and 2*H*-tautomers of 5-R-substituted tetrazoles correlate with the σ_p constants of the substituents (Table 7). It is assumed that in polar media the 1*H*-forms of 5R-tetrazoles containing electron-donor substituents are the better solvated, whereas in the case of 5-nitrotetrazole the opposite is true. This substituent effect evidently should also operate in the chemical reactions involving 5R-tetrazoles.

Table 7 Dipole moments (in D) of 5-R-NH-tetrazoles **24** calculated by means of DFT method at B3LYP/6-31G* level <2004JMT(668)123>^a

<i>R</i>	1 <i>H</i> -Tetrazoles	2 <i>H</i> -Tetrazoles
H	5.34	2.27
Me	5.74	2.11
Bu ^t	5.72	1.99
Ph	5.96	2.05
Cl	4.64	2.82
CF ₃	4.06	3.42
NO ₂	3.37	4.86

^aRelations of the dipole moments (μ) versus substituent constants:

$\mu_{1H} = 5.40 - 2.56 \sigma_p$, r 0.968, s 0.27, n 7; $\mu_{2H} = 2.33 + 2.72 \sigma_p$, r 0.962, s 0.31, n 7.

6.07.3.9 Other Methods

As previously reported, tetrazolynyl radicals have been studied by means of electron spin resonance (ESR) spectroscopy <1984CHEC(4)791, 1996CHEC-II(4)621>. This method was utilized for studying copper(II) complexes with 1-substituted tetrazole ligands <2003M255, 2003ICA(350)57, 2003JCD3628>. The radiolytic reactions of nitro blue tetrazolium chloride were studied by pulse radiolysis techniques in aqueous solution under reducing and oxidative conditions <1999MI795>. Under reducing conditions, the fast formation of the tetrazolynyl radical is observed and this is followed by the appearance of formazan, whereas the formazan formation is not found under oxidative conditions. According to ferroelectric tests, the complexes of Cd(II) ion with tetrazolate ligand exhibit moderate ferroelectric behavior <2005JCS(D)1570>. Magnetic susceptibility of copper(II) and iron(II) complexes with 1-(2-chloroethyl)tetrazole and some other 1-substituted tetrazoles has been examined in the temperature range 1.8–300 K <2002ICA(335)61, 2003M255, 2003ICA(350)57, 2002IC6468, 2002ICA(339)297, 2005EJI1678>. The ⁵⁷Fe Mössbauer spectra of several of the spin crossover iron(II) complexes with tetrazole ligands have been measured at different temperatures <2002ICA(335)61, 2002ICA(339)297>. The morphology of bis(5-nitrotetrazolato Λ^2)tetraammine cobalt(II) perchlorate and its copper(II), zinc(II), and nickel(II) analogs has been investigated by scanning electron microscopy <2005MI25>. The binding energies of these complexes have also been characterized by electron spectroscopy for chemical analysis (ESCA). The sharp peak in the spectrum with binding energy of 403–412 eV

may be attributed to the nitrogen atoms of the tetrazole ring <2005MI25>. The scanning tunneling microscopy technique was used to study the adsorption of 1-phenyl-5-mercaptotetrazole on copper electrode surface in sulfuric acid solution <2004MI1371>. The effect of the addition of tetrazoles on the corrosion of brass in nitric acid has been studied by electrochemical impedance spectroscopy (EIS) <2006MI2389>.

6.07.4 Thermodynamic Aspects

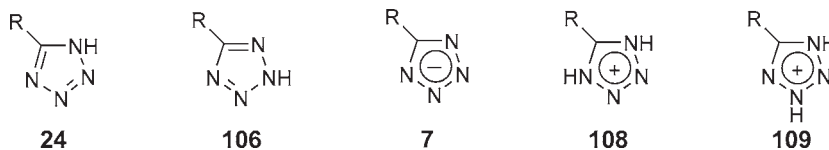
6.07.4.1 Aromaticity

Aromaticity is a fundamental characteristic of heterocyclic systems governing many of their chemical and physical properties. It can be quantitatively expressed through a number of criteria: energetic, geometrical, magnetic, and by analysis of electron delocalization. The scales of aromaticity of five-membered nitrogen-containing heterocycles have been thoroughly discussed in a number of surveys dedicated to this problem <2001CRV1421, 2004CRV2777, 2005CRV3561>. Although the tetrazole ring notably differs in structure from the other azoles (it contains four nitrogen heteroatoms and a single carbon), its aromaticity is very high. Moreover, certain forms of the tetrazole ring surpass the aromaticity of di- and triazoles <1998JOC2497>. Several comprehensive theoretical publications have appeared analyzing various aromaticity criteria of neutral 1*H*- and 2*H*-tautomers **24** and **106** of unsubstituted tetrazole <1998JOC2497, 2001JOC8737, 2004JPO303>. For instance, various aromaticity indexes estimated on the basis of calculations at the B3LYP/6-311++G** level for tautomeric forms **24** and **106** of unsubstituted tetrazole are as follows: geometric Bird's index (I_5), 74.74 and 89.49; aromatic stabilization energy (ASE), 14.48 and 23.06 kcal mol⁻¹; nuclear-independent chemical shift (NICS), -14.34 and -14.47 ppm <2001JOC8737>. NBO analyses for estimation of delocalization and aromaticity of tautomers **24** and **106** were performed independently by Bean and Sadlej-Sosnowska <1998JOC2497, 2001JOC8737>. Different magnetic aromaticity indices were calculated for various 5*R*-substituted tetrazoles by Sadlej-Sosnowska <2004JPO303>. Virtually all results obtained in these studies indicate that the 2*H*-tautomer is the most aromatic. The influence of substituents on the carbon atom on aromaticity of 5-*R*-tetrazoles is different and depends strongly on the type of aromaticity index <2001JOC8737>.

It is, however, very important to compare the aromaticity not only of neutral 1*H*- and 2*H*-tautomers of tetrazoles, but also of the charged forms. Thus Pozharskii's aromaticity index (Table 8) was calculated for all possible prototropic forms **7**, **24**, **106**, **108**, and **109** of a series of 5-*R*-tetrazoles based on the differences in bond orders optimized at the B3LYP/6-31G* level <2004JMT(668)123>. As seen from Table 8, the highest aromaticity corresponds to tetrazolate anions **7**. This is partly responsible for the relatively high acidity of the NH-unsubstituted tetrazoles and for the great thermal stability of metal tetrazolides (see Section 6.07.4.3). As was concluded previously based on the other aromaticity indexes, Pozharskii's index was also significantly higher for the 2*H*-tautomers **106** than for the 1*H*-tautomers **24** of the neutral 5-*R*-tetrazoles. Aromaticity of the 1*H*,3*H*⁺-cation **109** is considerably higher than that of the 1*H*,4*H*⁺-form **108**. Hence, the introduction of the proton in position 2(3) of the tetrazole ring considerably increases its aromaticity. These data are consistent with the findings of the X-ray analysis (see Section 6.07.3.1). The substituent attached to the ring hardly affects its aromaticity, and this effect is irregular (see Table 8). It should be mentioned, however, that the aromaticity of 5-phenyl- and 5-nitrotetrazolate anions is somewhat higher than that of the other 5-*R*-tetrazoles, probably due to the conjugation effect.

Table 8 Aromaticity (in %, benzene 100%, cyclopentadiene 0%) of different prototropic forms **7**, **24**, **106**, **108**, and **109** of 5-*R*-tetrazoles calculated from differences in bond orders (Δn) based on geometry optimized at B3LYP/6-31G* level <2004JMT(668)123>

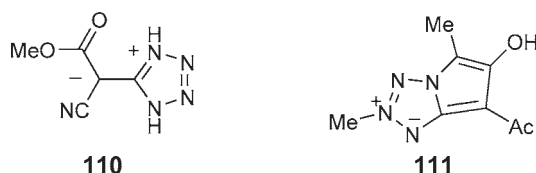
<i>R</i>	24	106	7	108	109
H	62	84	84	56	75
Me	64	81	85	57	72
Bu ^t	65	80	85	57	75
Ph	68	81	96	58	74
Cl	61	85	76	58	73
CF ₃	65	83	89	57	75
NO ₂	67	83	91	60	75



6.07.4.2 Intermolecular Forces

6.07.4.2.1 Melting and boiling points

The fullest systematization of the values of melting and boiling points of tetrazoles known up to 1947 includes over 300 compounds and was done by Benson <1947CRV411>. The laws that he outlined for the influence of substituents have not become out of date, even 60 years later. This conclusion is also supported by Butler's review <1996CHEC-II(4)621>. To obtain primary information on the subject of this subsection, the reader should refer to these excellent reviews <1947CRV411, 1996CHEC-II(4)621>. The melting points of numerous tetrazole derivatives were indicated in recent publications cited in this chapter (cf. Sections 6.07.5–6.07.8, etc.). Leaving out rare cases, these data are consistent with the general laws <1947CRV411>. We will consider further only some new comparable findings. Butler drew attention to the fact that some tetrazole ylide structures, for example **110**, possess generally very high melting points (m.p. 330 °C) <1996CHEC-II(4)621>. However Moderhack *et al.* <2001J(P1)720> showed that the melting points of 1*H*- and (mesoionic) 2*H*-pyrrolotetrazoles, for example, of compound **111** (m.p. 163–164 °C), were not so high.



The comparison of melting and/or boiling points and decomposition temperatures not only indicates the regular trends in unimolecular thermal reactions (cf. Section 6.07.5.2) but also is absolutely indispensable for forecasting the application parameters of the energy-rich tetrazoles (cf. Sections 6.07.4.3 and 6.07.12.2). Interesting studies in this respect have been published <1999MI168>, shedding light on the interconnection between the above parameters. A selection of 17 from the 35 tetrazoles investigated <1999MI168> is given in Table 9. The values of the decomposition enthalpies <1999MI168> are discussed further in Section 6.07.5.2.1.

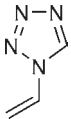
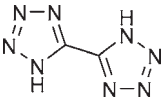
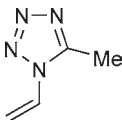
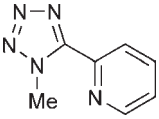
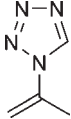
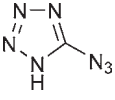
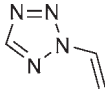
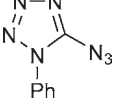
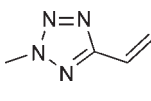
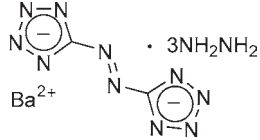
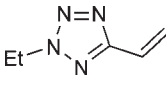
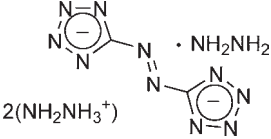
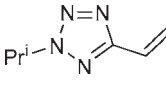
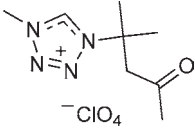
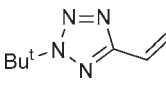
Table 9 DSC data of tetrazoles <1999MI168>

Compound	N (mass %)	m.p. (°C)	Decomposition temperature	
			Onset temperature (°C)	Temperature at maximum heat flow (°C)
Tetrazole	79.9	156	180–183	216
5,5'-Bitetrazole	81.1	No melting	252	257
5-Methyltetrazole	66.6	145	Vaporization	
5-Cyanotetrazole	73.6	101	During melting	111 (max 1) 126 (max 2)
5-Chlorotetrazole	53.6	65	131	146
Copper(I)-5-chlorotetrazole	33.5	No melting	284	302
5-Aminotetrazole monohydrate	82.3	201	Vaporization	
5-Methoxycarbonyltetrazole	43.7	147	174	179
5-Phenyltetrazole	38.3	216	During melting	221 (max 1) 243 (max 2)
5-Benzyltetrazole	35.0	123	214	250
5- <i>N</i> -(2,4,6-Trinitroanilino)tetrazole	37.8	No melting	208	212
1-Methyl-5-methoxycarbonyltetrazole	39.4	48	196	205
1-Methyl-5-phenyltetrazole	35.0	102	Vaporization	
2-Methyl-5-phenyltetrazole	35.0	48	Vaporization	
2,5-Diphenyltetrazole	25.2	101	166	192
3,6-Di(tetrazol-5-yl)benzene	52.3	No melting	283	294
3,6-Bis(tetrazol-5-yl)-1,2,4,5-tetrazine	77.0	No melting	231	236

6.07.4.2.2 Solubility, density

The most comprehensive information on solubility of tetrazoles of various structural types (cf. [Section 6.07.1.3](#)) in water and different organic solvents was given in the review of Benson [<1947CRV1>](#). These data are sufficient for predicting the solubility of the majority of tetrazole derivatives even not mentioned in the large tables of this classical survey [<1947CR1>](#). In contrast, systematic data on the density of tetrazole and its derivatives are lacking in the available literature. The density values of tetrazoles from recent publications are given in [Table 10](#).

Table 10 Density of tetrazoles

<i>Compound</i>	<i>Density</i> (g cm ⁻³)	<i>References</i>	<i>Compound</i>	<i>Density</i> (g cm ⁻³)	<i>References</i>
	1.632	1999THS(3)467		1.179	2003RCR143
	1.738	1996JCX399		1.085	2003RCR143
	1.444	1996JCX399		1.100	2003RCR143
	1.670	2005MI17 , 2003MI65		1.131	2003RCR143
	1.515	2005MI17		1.085	2003RCR143
	2.109	2003ZFA2117		1.041	2003RCR143
	1.484	2003ZFA2117		1.007	2003RCR143
	1.460	1999CHE1078		0.987	2003RCR143

The single crystal density and the ‘compression density’ of a charge of explosive compound are necessary for discussing the parameters of energetic tetrazole detonation. These data were published for tetrazole [<1999THS\(3\)467>](#), 5-nitrotetrazole [<1997RJO1771>](#), which was given the maximum attainable charge compression density, diaminotetrazole [33](#) derivatives [<2005IC4237, 2005THE168>](#), 5-nitraminotetrazole derivatives [<2006JOC1295>](#), azotetrazole [4](#) derivatives (see [Section 6.07.4.3.2](#)), energetic salts of iminobis(5-tetrazole), and of 5,5'-bistetrazole [26](#) [<2005CC2750>](#) (see [Section](#)

6.07.4.3.1). The cited data indicate that among the molecular forms the highest density corresponds to NH-unsubstituted tetrazoles, stable under normal conditions in the crystalline state. The densities of NH-unsubstituted tetrazoles are in the range 1.6–1.8 g cm⁻³. The density of the N-substituted tetrazoles, especially those stable under normal conditions in the liquid phase, for example, of vinyltetrazoles (Table 10), is considerably lower. The density of tetrazolate salts depends essentially on the nature of cation and can be very large (about 2 g cm⁻³) (Table 10). In more complex molecular structures of coordination compounds containing tetrazole ligands, the density is governed by the combination of various factors: stoichiometric composition of the complex, nature of the metal, structure of the tetrazole fragment, the presence of molecules in the external coordination sphere, etc. For instance, the densities of the coordination compounds of zinc with NH-unsubstituted tetrazol-5-yl ligands [Zn(CH₃CN₄)₂]₃H₂O and [Zn(HCN₄)₂] equal 1.736 and 2.089 g cm⁻³, respectively <2005IC5278>. The densities of certain coordination compounds containing N-substituted tetrazol-1-yl or tetrazol-2-yl ligands exceed 2 g cm⁻³. Thus, for [Cu(teec)₅]₂[Cu(teec)₆][PMo₁₂O₄₀]₂·2H₂O, where teec is 1-(2-chloroethyl) tetrazole (cf. Section 6.07.5.3.4), $\rho = 2.5 \text{ g cm}^{-3}$ <2003M255>. The density of new 2-D polymeric compound bis(1,5-diaminotetrazole)dichlorocopper(II) is 2.106 g cm⁻³ <2005ICA(358)2549>. The density values close to 2 g cm⁻³ were also found for dinuclear [CuLn(tza)₄(H₂O)₅Cl] complexes (tza is tetrazol-1-yl-acetic acid) <2005IC559>.

6.07.4.2.3 Chromatographic behavior

Various thin-layer and column chromatography procedures are extensively used in solving both analytical and preparative problems relating to tetrazoles. As already mentioned, the polarities of 1*H*- and 2*H*-tetrazoles are essentially different (see Section 6.07.3.8). In particular, this is manifested in significant differences in the retention times of these regioisomers in chromatographic systems. For instance, in reversed-phase column chromatography, the retention time of 2-isomers is longer than that of 1-isomers, and vice versa in the case of direct-phase chromatography. Reversed-phase high-performance liquid chromatography (HPLC) has proved to be a convenient instrument for investigation of kinetics and mechanism of tetrazole alkylations providing the possibility of determining the kinetic parameters both by accumulation of the products, 1- and 2-alkyltetrazoles, in the course of the reaction and by consumption of the initial compound <2006UP2>. The values of chromatographic hydrophobicity index and the retention times of 5-phenyltetrazole at pH 2.0, 7.4, and 10.5 were analyzed by means of a fast gradient reversed-phase liquid chromatography with both UV and MS detection <2001ANC3716>. Good linear correlations between these parameters were found for a wide range of compounds. Identification of complex biologically active molecules and drugs containing the tetrazole moiety and the study of their metabolism were frequently performed using HPLC and LC/MS <1997JCH(702)149, 2001CPB1110, 2003BMC2551, 2006JME1346, 2006JLC553> (see also Section 6.07.3.4).

6.07.4.3 Thermochemical Properties

The difference in the molecular weights (MWs) of all parent azoles does not exceed 3 units. However, in going from 1,2-diazole (pyrazole) to tetrazole, both the nitrogen content in the heterocycle and the enthalpy of formation increase considerably (nearly twofold) (Table 11).

Table 11 Properties of azoles <1999THS(3)467>

Compound	<i>m.p.</i> (°C)	MW	N (%)	ΔH_f° , <i>cryst.</i> (kcal kg ⁻¹)
Pyrazole	69	68.08	41.15	413.9
1,2,3-Triazole	23	69.07	60.84	642.5
1,2,4-Triazole	121	69.07	60.84	380.4
Tetrazole 2	157	70.05	79.98	805.1

Thus among the parent azoles that are stable in the crystalline state, tetrazole is the absolute champion both by the amount of the bound nitrogen and by the chemical energy accumulated in the ring. The value of the enthalpy of formation is especially striking. It competes in this most important thermochemical parameter only with HN₃ and the simplest aliphatic azides. A higher thermodynamic stability of the cyclic (tetrazolic) form as compared to the open-chain (azidoazomethine) form has been discussed <1999THS(3)467>. The values of the basic performance parameters of the energy-rich substances (impulse of rocket formulation, detonation velocity, etc.) are known to be proportional to the enthalpy of formation. The energy evolved at combustion, detonation, and thermal decomposition of compounds

possessing a high ΔH_f° can be applied to performing useful work. This is also favored by evolution of a large amount of gaseous products of a low molecular weight, predominantly N_2 , resulting from the corresponding chemical processes (cf. Section 6.07.5.2). In Sections 6.07.4.3.1 and 6.07.4.3.2, the thermochemical, explosive, and combustion parameters of tetrazoles are considered. Experimentally obtained values are preferred: combustion enthalpy, detonation velocity (at definite density) (ΔH_{comb} , D_p), or enthalpy of formation (ΔH_f°), evaluated directly from the experimental data (ΔH_{comb}). The ΔH_f° values calculated by theoretical methods are cited only when it is necessary for the uniformity of treating the material. In other cases, the theoretically calculated thermochemical parameters can be found in the publications cited in Section 6.07.2.2 and also in the available database *ICT-Thermodynamic Code*, Version 1.0; Fraunhofer-Institut für Chemische Technologie (ICT): Pfinztal/Berghausen, Germany, 1988–2000.

6.07.4.3.1 Enthalpies of formation and related parameters

A quantitative experimental measurement of the thermochemical parameters for a series of tetrazoles was carried out by McEwan *et al.* <1951JA4725, 1957JPC26>. These studies performed over 50 years ago are regarded as classical (Table 12) <1999THS(3)467>.

Table 12 Thermochemical properties of some tetrazoles <1951JA4725, 1957JPC26, 1999THS(3)467>

Compound	$-\Delta H_{comb}$ (kcal mol ⁻¹)	ΔH_f° , <i>cryst.</i> (kcal mol ⁻¹)	Compound	$-\Delta H_{comb}$ (kcal mol ⁻¹)	ΔH_f° , <i>cryst.</i> (kcal mol ⁻¹)
Tetrazole	219.0	56.7	5-Aminotetrazole	224.1	49.7
1,5-Dimethyltetrazole	532.1	45.1	5-Nitroaminotetrazole	222.6	62.0
1-Phenyltetrazole	949.8	86.5	5-Cyanotetrazole	318.4	96.1
5-Phenyltetrazole	933.1	69.9	<i>trans</i> -1,1'-Dimethyl-5,5'-azoditetrazole	770.5	189.3
1,5-Diphenyltetrazole	1664	99.3	<i>cis</i> -1,1'-Dimethyl-5,5'-azoditetrazole	769.8	188.6
2,5-Diphenyltetrazole	1659	95.4	<i>trans</i> -2,2'-Dimethyl-5,5'-azoditetrazole	761.4	180.3

In Table 13, results are compiled on evaluation of the ΔH_f° values for some tetrazoles, published 20 years later by Lebedev and co-workers <B-1977MI93>. In this study, refined values of the thermochemical parameters measured with the use of precision calorimeters were reported. The refined data proved the high reliability of the experimental findings of McEwan *et al.* (Table 13) <1951JA4725, 1957JPC26>.

Table 13 Thermochemical properties of some tetrazoles <B-1977MI93, 1999THS(3)467>

Compound	$-\Delta H_{comb}$, (kcal mol ⁻¹)	ΔH_f° , <i>cryst.</i> (kcal mol ⁻¹)	ΔH_f° , <i>gas</i> (kcal mol ⁻¹)
Tetrazole	218.8	56.4	76.6
1-Phenyltetrazole	945.5	82.3	107.1
5-Phenyltetrazole	934.6	82.3	98.7
1,5-Diphenyltetrazole	1662	97.2	125.9

Enthalpies of formation of tetrazoles containing simple substituents <1990ZFK656> are presented in a review <1999THS(3)467>. Names of compounds and the values of ΔH_f° (gas) (kcal mol⁻¹) (in parentheses) are as follows: 1-methyltetrazole (77.2), 2-methyltetrazole (78.4), 5-methyltetrazole (67.0), 1,5-dimethyltetrazole (65.2), 2,5-dimethyltetrazole (60.0), 1-methyl-5-aminotetrazole (72.2), 2-methyl-5-aminotetrazole (71.4), 5-vinyltetrazole (71.4), 1-methyl-5-vinyltetrazole (73.2), 2-methyl-5-vinyltetrazole (72.2), 2-ethyl-5-vinyltetrazole (63.6), 2-Prⁱ-5-vinyltetrazole (55.2), 2-Buⁱ-5-vinyltetrazole (48.5). The enthalpy of formation of 5,5'-bitetrazole **26** ΔH_f° (cryst.) is 127.1 kcal mol⁻¹ <1979CED4>. The enthalpy of combustion and enthalpy of formation of 2,2'-bis(hydroxymethyl)-5,5'-ditetrazole dinitrate is ΔH_{comb} 599 kcal mol⁻¹, ΔH_f° (cryst.) 103.2 kcal mol⁻¹, of 1,1'-bis(2-chloroethyl)-5,5'-bitetrazole, ΔH_f° (cryst.) 979 kcal kg⁻¹ <1999THS(3)467>, and, finally, of unsubstituted 5-nitrotetrazole, ΔH_f° (cryst.) 62.3 kcal mol⁻¹, ΔH_f° (gas) 89.2 kcal mol⁻¹ <1997RJO1771, 1999THS(3)467>.

As follows from the above data, the values of enthalpies of formation for isomeric N-substituted tetrazoles differ somewhat, decreasing in the sequence N-1, N-2, C-5. Difference between ΔH_f° values of N¹- and N²-isomers does

not exceed $1.5\text{--}3.5\text{ kcal mol}^{-1}$. The experimental and calculated modified neglect of diatomic overlap (MNDO) values of ΔH_f° linearly correlate: $\Delta H_f^\circ(\text{exp.}) = 0.942\Delta H_f^\circ(\text{calc.}) + 26.44$ <1992IJQ813>. Note the growing number of theoretical studies applying modern *ab initio* quantum-chemical procedures to the calculation of the thermochemical properties of tetrazoles. For instance, the heats of formation (HOFs) for 49 tetrazole derivatives were calculated using the DFT B3LYP method by means of designed isodemic and isogyric reactions <1999PCA8062>. The average absolute deviation for five compounds for which the experimental HOFs are available is less than 2 kcal mol^{-1} , which is a target accuracy of G-2 theory. Theoretical calculations of the energy and thermochemical properties of tetrazoles (cf. Section 6.07.2.2) are indispensable when experimental measurements of the thermochemical properties of tetrazole are difficult or impossible, for example, when the compounds are unstable or their handling dangerous. For instance, *ab initio* MO (at HF/6-31G* level) and thermodynamic calculations were carried out for the azido derivatives of tetrazole that are hardly available for the experiments due to the high impact and friction sensitivity <1999JST(458)249>. However, in this section, attention is primarily drawn to the experimental investigation of the thermochemical properties of tetrazoles. Regretfully, we did not find many experimental studies on this problem in accessible sources. It follows from the data of Table 12 that the derivatives of azotetrazole **4** (*trans*-1,1'-dimethyl-5,5'-azoditetrazole, *cis*-1,1'-dimethyl-5,5'-azoditetrazole, and *trans*-2,2'-dimethyl-5,5'-azoditetrazole) possess high positive values of the enthalpy of formation. The attention of researchers was focused recently on the 5,5'-azotetrazolate **71** salts. Enthalpies of formation of hydrazinium, guanidinium, triaminoguanidinium, and ammonium 5,5'-azotetrazolates were measured at ΔH_f° (kcal kg⁻¹): 889 <2001IC3570>, 344 <2000MI3>, 686 <1998JEM119, 2004AGE4924>, and 529 <2000MI3>, respectively. Energetic ionic salts of azotetrazolate **112–118**, iminobi(5-tetrazolate) **119**, and 5,5'-bitetrazole **120** have been synthesized and studied (Table 14) <2005CC2750>.

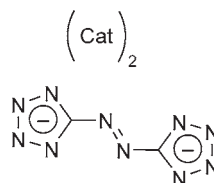
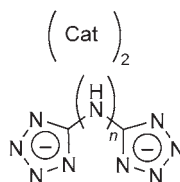
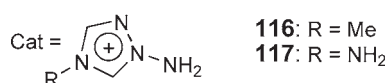
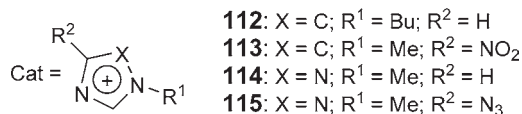
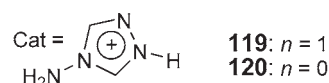
**112–118****119, 120**

Table 14 Properties of energetic salts **112–120** <2005CC2750>

Compound	<i>m.p.</i> (°C)	Density (g cm ⁻³)	−Δ <i>H</i> _f ^o (kcal mol ⁻¹)	−Δ <i>H</i> _f ^o (kcal kg ⁻¹)
112	3	1.26	240.3	542.9
113	145	1.54	321.2	716.3
114	182	1.42	290.4	805.8
115	155	1.55	341.3	771.4
116	180	1.57	377.4	1041
117	^a	1.59	407.2	1118
118	189	1.46	144.3	369.5
119	175	1.59	118.5	368.5
120	131	1.61	226.4	739.2

^aMelting point not observed, decomposes violently at 134 °C.

6.07.4.3.2 Explosive and combustion parameters

Detonation velocity, impact and friction sensitivity, and also enthalpy of combustion of various tetrazole derivatives are presented in this section with emphasis on experimentally found values. The only exception is the detonation velocity: here *D* values that are theoretically calculated are mentioned. Regretfully, not so many experimentally obtained *D* values could be found in accessible publications.

6.07.4.3.2(i) Tetrazole

The most complete information on the thermochemical properties of unsubstituted tetrazole was compiled in a review <1999THS(3)467>. Among the data were given the explosive and combustion parameters: Δ*H*_{comb} −218.8 kcal mol⁻¹ (see also **Table 13**); onset temperature 180–183 °C <1999MI168>, ignition temperature 272 °C (with a 5 s delay); *D* (ρ 1.51 g cm⁻³) 4770 m s⁻¹; impact sensitivity, 28% of explosion (weight 10 kg, height 25 cm); impact sensitivity is close to trinitrotoluene (TNT); friction sensitivity (pressure 2120 kg cm⁻², middle point, and 5320 kg cm⁻², lower limit) <1999THS(3)467>.

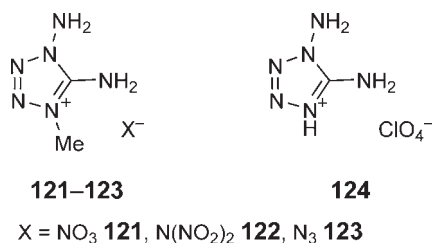
6.07.4.3.2(ii) 5-Nitrotetrazole

Impact sensitivity (dropping hammer, weight 10 kg, height 25 cm) 100% of explosions; *D* (ρ 1.73 g cm⁻³) 8900 m sec⁻¹; detonation velocity exceeds that of TNT and RDX; intensive decomposition (DTA) with the loss of 75% of weight, 115–120 °C <1997RJO1771, 1999THS(3)467>.

6.07.4.3.2(iii) Derivatives of 1,5-diamino-1*H*-tetrazole

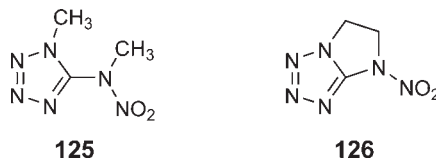
The enthalpies of combustion (Δ*H*_{comb}) of compounds **121–123** were determined experimentally using oxygen bomb calorimetry. Δ*H*_{comb} (kcal kg⁻¹) (compound number): −2456 **121**, −2135 **122**, and −3594 **123** <2005IC4237, 2005THE168>.

The detonation velocities (*D*, m s⁻¹) and detonation pressures (*P*, GPa) were calculated using the empirical equations of Kamlet and Jacobs: *D* 7682, *P* 23.4 **121**; *D* 8827, *P* 33.6 **122**; *D* 7405, *P* 20.8 **123**. The above-mentioned values of *D* <2005IC4237, 2005THE168> were apparently calculated for the single crystals density ρ, g cm⁻³: 1.506 **121**, 1.719 **122**, and 1.417 **123**. For compound **124**, the value of *D*, 8383 m s⁻¹ (ρ 1.902 g cm⁻³), and *P*, 32.2 GPa, have been reported <2005IC4237, 2005THE168>. Impact and friction sensitivity of compound **122** are notably higher than for compounds **121** and **123**. For this reason compound **122** is not safe to transport <2005THE168>.



6.07.4.3.2(iv) Derivatives of *N*-nitraminotetrazoles

For compounds **125** and **126**, the experimental values of the enthalpy of combustion are given, ΔH_f° (gas) are calculated at the basis B3LYP/6-31G, and the detonation velocity is calculated by the method of Kamlet and Jacobs <2006JOC1295>.



For compound **125**, ΔH_{comb} is $-489.9 \text{ kcal mol}^{-1}$, D (ρ 1.522 g cm^{-3}) 5988 m s^{-1} ; for **126**, ΔH_{comb} is $-503.9 \text{ kcal mol}^{-1}$, D (ρ 1.690 g cm^{-3}) 7181 m s^{-1} <2006JOC1295>.

It should be noted in conclusion that a thermoanalytical screening of 35 tetrazoles based on the data of differential scanning calorimetry (DSC), thermogravimetric analysis (TGA), and evolved gas analysis (EGA) has been performed <1999MI168> (cf. Section 6.07.5.2.1).

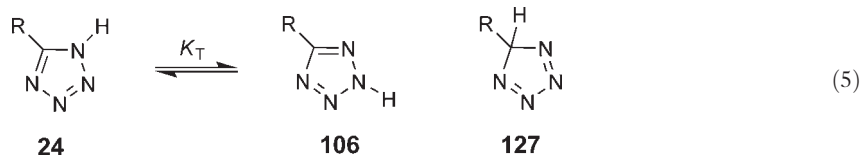
6.07.4.4 Tautomerism

6.07.4.4.1 Annular tautomerism

Annular tautomerism inherent to NH-unsubstituted tetrazoles and tetrazolium ions governs many chemical and physicochemical properties of these compounds. Since the 1950s, this type of protolytic equilibrium has been investigated by various teams. In this section, we analyze the results of experimental and theoretical studies on the annular tautomerism of NH-tetrazoles and their conjugate acids. The results of investigations published within the last decade are considered from the viewpoint of the classical concepts based on earlier research.

6.07.4.4.1(i) Neutral NH-tetrazoles

Presumably the NH-tetrazoles with no functional substituents on the endocyclic carbon can exist in three tautomeric forms, which are the *1H*-, *2H*-, and *5H*-tautomers **24**, **106**, and **127**, respectively (Equation 5).



The hypothetical nonaromatic *5H*-form **127** is a very unstable species that has not been experimentally detected. According to the results of theoretical calculations for the gas phase performed by the QCISD(T)/6-311G+(2d,2p) and G3 methods, form **127** is approximately 20 kcal mol^{-1} more energy-rich than forms **24** and **106** <2000AHC(76)157, 2002PCP4314, 2001AHC(81)1>. Note, however, that the nonaromatic cyclic species, such as form **127**, may participate as intermediates in the ring-chain transformations of azoles <1996LA1041, 2000H(52)291>. Thus the study of the annular tautomerism in uncharged NH-unsubstituted tetrazoles comes to the investigation of a tautomeric equilibrium **24** $\rightleftharpoons$ **106**.

1H/2H-Tautomerism of tetrazoles was experimentally investigated in the gas phase and in solutions in some detail. The tautomers prevailing in the crystalline state were also established for many 5-substituted tetrazoles. The equilibrium in the gas phase was studied by microwave, photoelectron spectroscopy, and MS, and in solution by NMR on various nuclei (^1H , ^{13}C , ^{14}N , ^{15}N), by UV spectroscopy, and also using dipole moments and acidity constants of model compounds. In the crystalline state, the studies were performed with the use of NMR and IR spectroscopy, and by X-ray diffraction analysis. The results of research concerning the tautomerism of neutral NH-tetrazoles carried out prior to the twenty-first century were summarized in a number of reviews and monographs dedicated to both tetrazoles and protolytic equilibria in nitrogen-containing heterocycles in general <1976AHC, 1977AHC(21)323, 1984CHEC(4)791, 1988KGS579, 1994RCR797, 1996CHEC-II(4)621, B-2000MI1, 2000AHC(76)1, 2000AHC(76)157, 2005CRV3561, 2006RJO1585>.

According to the data of photoelectron, mass, and microwave spectroscopy and also to the findings of some other experimental methods, the *2H*-tautomer prevails in the gas phase <1984CHEC(4)791, 1988KGS579, 1994RCR797, 1996CHEC-II(4)621, 2000AHC(76)157, 2006RJO1585>. However, some studies indicate the simultaneous presence in the gas phase of both *1H*- and *2H*-forms of 5R-tetrazoles (R = H, CH₃, CD₃, CF₃, NH₂) <1994RCR797, 2000AHC(76)157>. In a recent investigation <2003SAA1725>, it was confirmed by UV photoelectron spectroscopy that tetrazole in the gas phase exists predominantly as a *2H*-tautomer **106**. Similar results were obtained with unsubstituted and 5-chlorotetrazoles isolated in an argon matrix at low temperature (8–12 K), where the experimental and calculated (BLYP/6-31G^{*}) IR spectra were compared and excellent correlation between computed and experimentally determined intensities was obtained only for the case of *2H*-tetrazoles **106** <1996LA1041, 2001PCP3541, 2002PCP1725>. Enthalpy difference between the tautomers **24** and **106** for 5-chlorotetrazole was estimated from the matrix experiment (ΔH 1.9 kcal mol⁻¹) <2002PCP1725>. However, in the case of the parent tetrazole, although the *2H*-tautomer **106** was observed as the dominating form, a minor contribution (10%) of the *1H*-form **24** was also found to be present in low-temperature inert matrices <2001PCP3541>.

Experimental investigations of the annular tautomerism of tetrazoles in solutions were carried out applying various procedures, but the most significant and reproducible results were obtained by NMR spectroscopy on the ¹³C and ¹⁵N nuclei, and by the use of dipole moments <1984CHEC(4)791, 1996CHEC-II(4)621, 2006RJO1585>. Just the distinctions in the NMR spectra and dipole moments of the different tautomeric forms of the NH-unsubstituted tetrazoles are the most characteristic. *1H*-Tetrazoles are as a rule more polar than the *2H*-isomers, and the chemical shift of the carbon belonging to the ring in the ¹³C NMR spectra of *2H*-tetrazoles is located downfield with respect to that of the *1H*-form <1996CHEC-II(4)621, 2006RJO1585, 1997MRC209>. The ¹⁵N and ¹⁴N NMR spectra of *1H*- and *2H*-tautomers also markedly differ and are differently affected by solvents <1996CHEC-II(4)621, 2000PCA1466, 2000PCA9600> (cf. Section 6.07.3.3 for details). According to these results, *1H*-tautomer **24** prevails in various solvents. It was, however, noted that in solutions of some 5-substituted tetrazoles the content of *2H*-tautomer can be considerable and reach 15–20% <1996CHEC-II(4)621, 2006RJO1585>. The enhanced relative content of the *2H*-form is possible in the following cases: (1) decrease in the dielectric permittivity of the medium; (2) increased electron-withdrawing properties of the substituent in position 5; (3) steric effects of the substituent at the endocyclic carbon. The considerable shift of the tautomeric equilibrium presented in Equation (5) may also be caused by the intramolecular and intermolecular hydrogen bonds involving the NH-protons of the hetero-ring <1984CHEC(4)791, 1996CHEC-II(4)621, 2006RJO1585>.

In the crystalline state, *1H*-tetrazole and some of its 5R-derivatives were shown by X-ray diffraction analysis, vibration spectroscopy, and ¹³C NMR spectroscopy to be individual *1H*-tautomers <1984CHEC(4)791, 1996CHEC-II(4)621, 2000AHC(76)157, 2005CRV3561, 2006RJO1585, 1997AXC590, 1996JCX399, 2002PCP1725>. However, in the case of losartan and some of its derivatives, the *2H*-forms of the tetrazole ring were also detected (cf. Section 6.07.3.1). Some 5R-tetrazoles are capable apparently of forming hybrid crystals containing both *1H*- and *2H*-tautomers. The *1H*-form is additionally stabilized in the crystal by formation of N–H···N hydrogen bonds to give dimers, trimers, and other agglomerates.

Since 1970, the annular tautomerism of tetrazoles has been subjected to numerous theoretical studies applying various theoretical procedures. As shown previously, the results of calculations performed by semi-empirical as well as *ab initio* theoretical methods at low basis set levels were in poor agreement with the experimental findings due to the underestimation of the reciprocal repulsion of the unshared electron pairs of the endocyclic vicinal nitrogen atoms <2006RJO1585>. For instance, using the HF method, only calculations in the basis 3-21G and higher show that in the gas phase the *2H*-form **106** of the unsubstituted tetrazole is more energetically favorable compared to the *1H*-form. Within the last decade, relatively large numbers of theoretical publications appeared on the prototropic tautomerism of tetrazoles. Results of some of these studies are presented in Table 15. The results of calculations performed by different procedures are fairly consistent. Virtually all calculations show for all 5-substituted tetrazoles in the gas phase that the energy of the *2H*-form **106** is lower than that of the *1H*-tautomer **24** by 1.5–3 kcal mol⁻¹. The exceptions are the data for 5-methoxycarbonyl- and 5-pyrrolidin-2-yltetrazoles obtained at B3LYP/6-31G+^{**} and B3LYP/6-31G^{**} levels and the data of the semi-empirical calculations <2005STC507, 2005TA2764, 1997RJO1767>. With growing temperature, the relative thermodynamic stability of the *1H*-tautomer of the unsubstituted tetrazole somewhat increases <1998JMT(453)65>. A theoretical investigation of the effect of solvation on the tautomeric equilibrium presented in Equation (6) has been performed <2000CPL(330)212, 2002PCP4314, 2005PCA5590, 2005TA2764, 2005MP209>. The solvation was shown to decrease to a larger extent the energy of the more polar tautomers of the 5-R-NH-unsubstituted tetrazoles (*1H*-tautomer of unsubstituted tetrazole and of 5R-tetrazoles with electron-donor or neutral substituents, and *2H*-tautomer of 5-nitrotetrazole or other tetrazoles with strong electron-withdrawing substituents at position 5 of the hetero-ring) (cf. Section 6.07.3.8). Therewith, the effect is stronger when

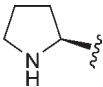
the dielectric permittivity of the simulated medium is greater. According to these studies, in the event of the unsubstituted heterocycle in the media of high polarity, the thermodynamical stability of the 1*H*-form is higher than that of the 2*H*-form <2000CPL(330)212>, whereas with 5-nitrotetrazole in the polar media just the 2*H*-form is stabilized to a greater extent <2005PCA5590>. Thus the experimentally observed effect of growing proportions of the 2*H*-tautomer in solutions with increasing electron-withdrawing properties of the substituent at position 5 is evidently due to the medium effect. As seen from **Table 15**, in the gas phase, the substituent at position 5 of the heterocycle does not significantly and systematically affect the relative thermodynamical stability of different tautomers of the NH-unsubstituted tetrazoles. Exceptions are the tetrazol-5-ylcarboxylic acids and their esters where the annular tautomerism is characteristically affected by various intramolecular interactions between the tetrazole ring and the carboxy group <2005STC507>. The ring aromaticity is considerably enhanced on going from 1*H*- to 2*H*-prototropic form of various 5*R*-tetrazoles <1998JOC2497, 2001JOC8737, 2004JMT(668)123>.

Table 15 Difference between energies of 1*H*- and 2*H*-tautomers **24** and **106** (ΔE_T in kcal mol⁻¹) of 5*R*-NH-tetrazoles calculated by theoretical methods in the gas phase

<i>R</i>	ΔE_T^a (kcal mol ⁻¹)	Calculation method	Reference
H	1.86	HF/6-31G*	1998JOC2497
	1.80 ^c	HF/6-31G*	1998JOC2497
	0.4	B3LYP/3-21G	2000CPL(330)212
	1.8	B3LYP/6-31G	2000CPL(330)212
	2.8	B3LYP/6-31G*	2000CPL(330)212
	2.81	B3LYP/6-31G*	2004JMT(668)123
	2.37 ^d	B3LYP/6-31G*	2001JST(567)59
	2.81	B3LYP/6-31+G**	2005STC507
	2.8	B3LYP/6-31+G**	2000CPL(330)212
	2.34 ^b	B3LYP/6-31+G**	2005STC507
	2.38 ^d	B3LYP/6-31++G**	2002PCP1725
	2.9	B3LYP/6-311++G**	2000CPL(330)212
	2.91	B3LYP/6-311++G**	2001JOC8737
	1.98 ^c	G3	2002PCP4314
	1.93 ^b	G3	2002PCP4314
	2.28 ^b	CBS-QB3	2005PCA5590
	1.9	QCISD(T)/6-311+G(2d,2p)	2001AHC(81)1
	-3.3 (in H ₂ O)	IEF-PCM/HF/6-31+G(d)	2002PCP4314
	-2.11 (in DMSO)	IPCM//6-311+G(2d,p)// B3LYP/6-31G*	2005MP209
	3.76 ^b (at 300 K)	MP2/6-311G*	1998JMT(453)65
	3.63 ^b (at 700 K)	MP2/6-311G*	1998JMT(453)65
	3.49 ^b (at 1000 K)	MP2/6-311G*	1998JMT(453)65
OCH ₃	0.94	B3LYP/6-311++G**	2001JOC8737
CH ₃	2.20	B3LYP/6-31G*	2004JMT(668)123
	2.06	B3LYP/6-31G*	1999PCA8062
	1.51 ^c	B3LYP/6-31G*	1999PCA8062
	2.65	B3LYP/6-311++G**	2001JOC8737
	2.19 ^b	CBS-QB3	2005PCA5590
C ₂ H ₅	1.95 ^b	CBS-QB3	2005PCA5590
C(CH ₃) ₃	2.01	B3LYP/6-31G*	2004JMT(668)123
Ph	2.84	B3LYP/6-31G*	2004JMT(668)123
Br	3.02	B3LYP/6-311++G**	2001JOC8737
	2.04 ^b	CBS-QB3	2005PCA5590
Cl	3.36	B3LYP/6-31G*	2004JMT(668)123
	3.38	B3LYP/6-31G*	1999PCA8062
	2.85 ^c	B3LYP/6-31G*	1999PCA8062
	3.01 ^d	B3LYP/6-31G*	2002PCP1725
	3.13 ^d	B3LYP/6-31++G**	2002PCP1725
	3.56	B3LYP/6-311++G**	2001JOC8737
	2.80 ^b	CBS-QB3	2005PCA5590
F	5.24	B3LYP/6-311++G**	2001JOC8737
CN	3.64	B3LYP/6-31G*	1999PCA8062

(Continued)

Table 15 (Continued)

<i>R</i>	ΔE_T^a (kcal mol ⁻¹)	Calculation method	Reference
N ₃	3.08 ^c	B3LYP/6-31G*	1999PCA8062
	3.89	B3LYP/6-311++G**	2001JOC8737
	-1.20	HF/6-31G*	1999JST(458)249
	3.86	MP2/6-31G*//HF/6-31G*	1999JST(458)249
COOH	0.18 ^c	B3LYP/6-31+G**	2005STC507
COOCH ₃	-0.40 ^c	B3LYP/6-31+G**	2005STC507
CF ₃	3.07	B3LYP/6-31G*	2004JMT(668)123
NO ₂	-1.9	MNDO	1997RJO1767
	-3.4	AM1	1997RJO1767
	-2.9	PM3	1997RJO1767
	2.70	HF/6-31G*	1999JST(460)167
	2.64	B3LYP/6-31G*	2004JMT(668)123
	2.67	B3LYP/6-31G*	1999JST(460)167
	0.7 ^c	B3LYP/6-31G*	1999JST(460)167
	3.00	B3LYP/6-311++G**	2001JOC8737
	2.52 ^b	CBS-QB3	2005PCA5590
	3.18	MP2/6-31G*//B3LYP/6-31G*	1999JST(460)167
	-2.35	B3LYP/6-31G**	2005TA2764
	-3.34 (in DMSO)	PCM/B3LYP/6-31+G**	2005TA2764

^aEnergy of 2*H*-tautomer is equal to 0.

^bThermodynamic value calculated as difference of free energies.

^cThermodynamic value calculated as difference of heats of formation.

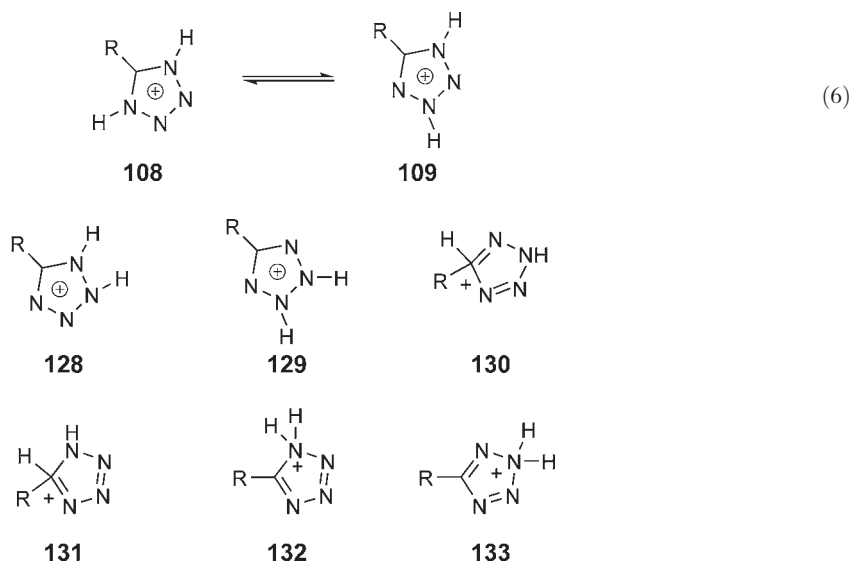
^dCalculated as difference of ZPE-corrected energies.

^eFor the most stable conformers.

We wish to stress that the process of 1*H*/2*H*-tautomeric conversion (Equation 5) is sufficiently fast and easily reversible when it occurs by an intermolecular mechanism involving the solvent or the second heterocycle molecule <1998J(P2)2671, 2000AHC(76)1>. The energy of the intramolecular transfer is quite high <1998JMT(453)65, 1998J(P2)2671>. Therefore, under the conditions favoring the intermolecular proton transfer, both prototropic forms, or the one that is more reactive, may participate in the chemical or other transformations. For instance, it has been shown <1996RCB2101> by the study of the unimolecular thermal decomposition of tetrazole and its 5-substituted derivatives that in both the gas phase and in melts and solutions, the reaction mechanism corresponds to decomposition of only the 2*H*-form, although in the condensed phase the 1*H*-form initially prevails.

6.07.4.4.1(ii) Tetrazolium ions

The general concepts regarding the annular tautomerism of the protonated forms of 5*R*-substituted tetrazoles are even more sophisticated than that of the neutral forms. It is theoretically possible that the aromatic tetrazolium cation may exist in four forms **108**, **109**, **128**, and **129** originating from a proton addition to the unshared electron pair of one of nitrogens in the heterocycle, and four nonaromatic cations **130–133** may also be present. These forms are essentially different in their thermodynamic stability. As shown by *ab initio* calculations (HF/6-31G*//6-31G, B3LYP/6-311+G(3df,2p), G2(MP2), and G3) 1*H*,2*H*⁺- and 2*H*,3*H*⁺-forms **128** and **129** are 15–20 kcal mol⁻¹ thermodynamically less favorable than the more stable 1*H*,3*H*⁺- and 1*H*,4*H*⁺-forms **108** and **109** (Equation 6) <1986JPC5597, 2002PCP4314, 2002NJC1567>. This effect is due to repulsion of vicinal NH-fragments in the heterocyclic system. According to the theoretical calculations, the nonaromatic forms **130–133** are even more energy-rich than the aromatic species. For instance, the energy of the hypothetical cation **131** with pentacoordinated carbon is higher by approximately 50 kcal mol⁻¹ than that of cations **108** and **109** <2002PCP4314, 2002NJC1567>. Some of these forms cannot be optimized in a cyclic form. For example, cation **132** according to the theoretical calculations should exist as a protonated imidoyl azide <2002NJC1567>.



Thus discussion of the annular tautomerism of the tetrazolium ions is limited by Equation (6). As shown by the theoretical calculations, the energies of the two tautomeric forms of tetrazolium cation **108** and **109** have close values (Table 16). It has been indicated <2004JMT(668)123> that, according to structural criteria, 1*H*,3*H*⁺-form **109** possess a higher aromaticity compared to 1*H*,4*H*⁺-cation **108**. Depending on the applied calculation procedure, the energies of 1*H*,3*H*⁺- and 1*H*,4*H*⁺-tautomers of the unsubstituted tetrazole either are virtually equal or form **108** was slightly more feasible than form **109**. The 1*H*,4*H*⁺-form **108** is also more stable than the 1*H*,3*H*⁺-form **109** of the tetrazolium cation in the presence of the electron-donor substituents. With electron-withdrawing substituents, on the contrary, the more favorable is the 1*H*,3*H*⁺-form of cation **109**. According to the theoretical calculations, the solvation energy of form **108** is considerably higher than that of form **109**, and that should additionally stabilize the former in solution <2002PCP4314>.

Table 16 Relative total energies of tautomeric tetrazolium ions **108** and **109** (1*H*,3*H*⁺- vs. 1*H*,4*H*⁺-forms) of 5*R*-NH-tetrazoles calculated by theoretical methods in the gas phase

<i>R</i>	ΔE_T^a (kcal mol ⁻¹)	Calculation method	Reference
H	2.2	HF/6-31G*//6-31G	1986JPC5597
	-0.08	B3LYP/6-31G*	2004JMT(668)123
	0.20	B3LYP/6-311+G(3df,2p)	2002NJC1567
	0.98	G2(MP2)	2002NJC1567
	0.86 ^b	G3	2002PCP4314
CH ₃	0.86	B3LYP/6-31G*	2004JMT(668)123
C(CH ₃) ₃	1.83	B3LYP/6-31G*	2004JMT(668)123
Ph	1.94	B3LYP/6-31G*	2004JMT(668)123
Cl	-0.19	B3LYP/6-31G*	2004JMT(668)123
CF ₃	-1.02	B3LYP/6-31G*	2004JMT(668)123
NO ₂	-1.97	B3LYP/6-31G*	2004JMT(668)123
	-1.66	B3LYP/6-311+G(3df,2p)	2002NJC1567
	-0.88	G2(MP2)	2002NJC1567

^aEnergy of 1*H*,4*H*⁺-form **108** is equal to 0.

^bThermodynamic value calculated as difference of heats of formation.

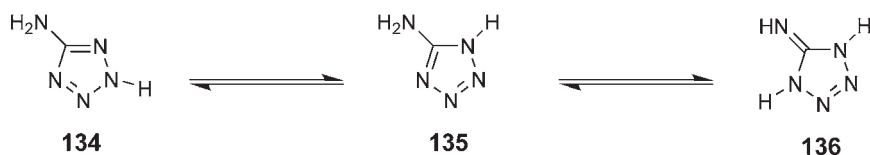
The theoretical calculations are consistent with the experimental findings. The data from NMR and Raman spectroscopy for NH-unsubstituted as well as 1-substituted tetrazoles in solutions of strong mineral acids show that the protonation of these heterocycles occurs at the nitrogen atom at position 4 leading correspondingly to the formation of 1*H*,4*H*⁺-tetrazolium ions **108**; the protonation of 2-substituted tetrazoles in turn resulted in ions **109** <1997MRC237, 2006RJO1585>. This conclusion was also supported by X-ray diffraction analysis of some crystals of tetrazolium salts

<2003JST(649)309, 2005IC4237> and by correlation analysis <2006RJO1585>. Thus, in a condensed phase the $1H,4H^+$ -form **108** is slightly more thermodynamically favorable compared to $1H,3H^+$ -form **109**. This is manifested in particular in the lower basicity of N^2 -substituted tetrazoles whose protonation yields $1H,3H^+$ -tetrazolim cations as compared to the basicity of the corresponding N^1 -isomers that on protonation give $1H,4H^+$ -cations (cf. Section 6.07.4.5.2).

6.07.4.4.2 Ring substituent

6.07.4.4.2(i) 5-Aminotetrazole and its derivatives

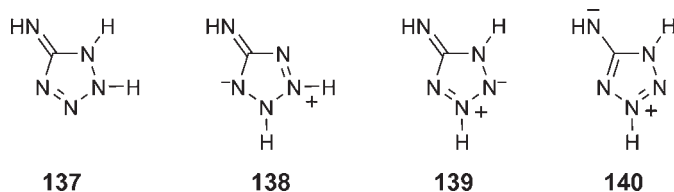
The most probable tautomeric equilibrium of 5-aminotetrazole and its N-substituted derivatives is represented by **Scheme 3**. The character of the annular tautomerism of 5-aminotetrazole is similar to that described in Section 6.07.4.4.1: in the gas phase the $2H$ -form is preferable, whereas taking into account solvation the polar $1H$ -tautomer **135** becomes more feasible in solution <2006RJO1585>.



Scheme 3

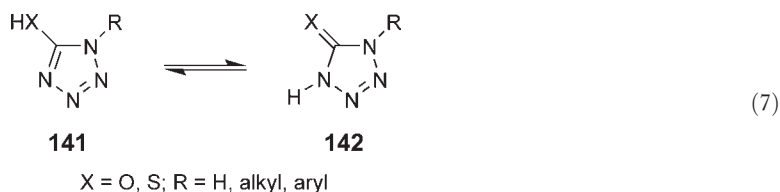
Certain early publications contained various data on the amine–imine tautomerism of 5-aminotetrazole and its derivatives <1977AHC(21)323, 1984CHEC(4)791, 1976AHC, 2000AHC(76)157>. However, already in CHEC-II(1996), Butler indicated that these compounds exist in various media exclusively in the amino- $1H$ -form **135** <1996CHEC-II(4)621>. This conclusion has been confirmed many times in publications during the last decade. Thus X-ray studies (see Section 6.07.3.1) did not discover an imino form **136** either in neutral 5-aminotetrazole derivatives or in 5-aminotetrazolium salts. FTIR, normal Raman, and surface-enhanced Raman, spectra of 5-aminotetrazole show that this compound in the crystalline state, in aqueous solution, and adsorbed on silver nanoparticles exists only in the amino form **135**, both in the case of the neutral molecule and the tetrazolate anion <2005PCA9928>. Also, IR spectra of 2-methyl-5-aminotetrazole isolated in a solid argon matrix give no evidence of the presence of any imine tautomers <2005PCA7967>. The experimental data agree well with results of DFT calculation <2005PCA9928, 2005PCA7967, 2006RJO1585>. Thus, according to the calculations for the gas phase at the B3LYP/LANL2DZ level, the amino form **135** was found to be more stable by about 9 kcal mol⁻¹ compared to the imino form **136** <2005PCA9928>. Qualitatively similar results were obtained when solvation effects were taken into consideration <2005PCA9928>.

Note that for 5-aminotetrazole and its derivatives, besides tautomers **135**, **134**, and **136**, some other prototropic forms might be taken into consideration, for example, forms **137–140**. The presumed number of such tautomers, including mesoionic and zwitterionic forms, may be very large, but none of these have been observed experimentally. Theoretical calculations show that the energy of these forms is quite large, but some of them may be regarded as intermediates in the thermal and photochemical decomposition of 5-aminotetrazole and its derivatives <2006RJO1585, 2005PCA7967, 2002THE233>.

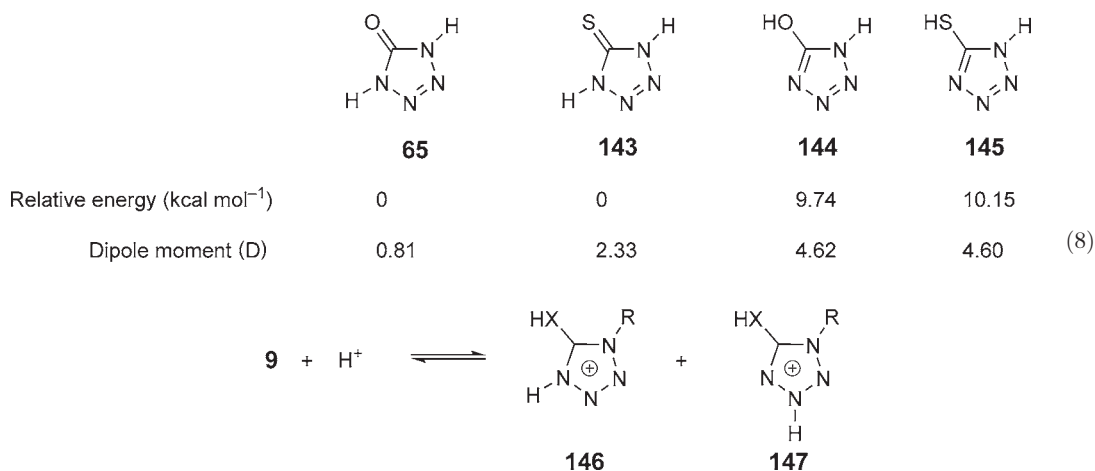


6.07.4.4.2(ii) 5-Hydroxy- and 5-mercaptotetrazoles

5-Hydroxy- and 5-mercaptotetrazoles and their mono- N^1 -substituted derivatives can be involved into keto–enol and thiol–thione tautomeric equilibria (Equation 7). This is the reason for significant differences in chemical and physical properties of these compounds from other 5R-tetrazoles.



This kind of prototropic tautomerism of tetrazole derivatives is well documented. Using X-ray crystallography, IR, Raman, UV, NMR (^1H , ^{13}C , ^{15}N), photoelectron spectroscopy, and some other methods, tetrazol-5-ones (thiones) have been shown to exist in the solid phase, in solutions, and in the gas phase exclusively in form **65** <1977AHC(21)323, 1984CHEC(4)791, 1976AHC, 1996CHEC-II(4)621, 2000AHC(76)157, 1996UK326, 1997JHC113, 1998AXC1160, 2006RJO1585>. On the basis of Fourier IR spectroscopy, 1-phenyl-5-hydroxytetrazole and 1-methyl-5-mercaptopotetrazole were shown to be present also in a matrix of solid argon at low temperature exclusively in the form of 1-phenyl-1,4-dihydro-5*H*-tetrazol-5-one and 1-methyl-1,4-dihydro-5*H*-tetrazole-5-thione <2006JPH243, 2006JST(786)182>. The calculations carried out in these and some other studies by *ab initio* and hybrid methods are totally consistent with the experimental data <2006RJO1585>. However, it has been shown <2000RJO1788> that HF/6-31G** calculations attribute to 5-hydroxy and 5-mercapto forms **144** and **145** considerably higher dipole moments compared to the thermodynamically more favorable 5-one(thione) tautomers **65** and **143**. It is presumed that in polar media the forms with aromatic tetrazole rings **144** and **145** are more strongly stabilized by intermolecular interactions and this might result in increasing their relative content. It was also shown in this study that the protonation of forms **142** should occur at the exocyclic heteroatom (O or S) giving 1,3-*H*,*H*⁺- and 1,4-*H*,*H*⁺-cations of tetrazolium **146** and **147** possessing close energies (Equation 8).

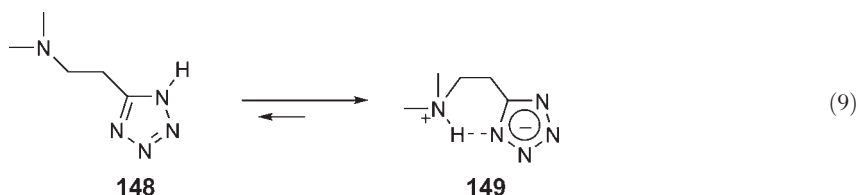


Interestingly, although the thione form of neutral tetrazoles prevails, the alkylation and acylation of tetrazole-5-thione anions afford exclusively products of addition to the sulfur atom (cf. Section 6.07.7.5), suggesting that under specific conditions formation of the 5-mercapto form is possible.

6.07.4.4.2(iii) Other kinds of tautomerism

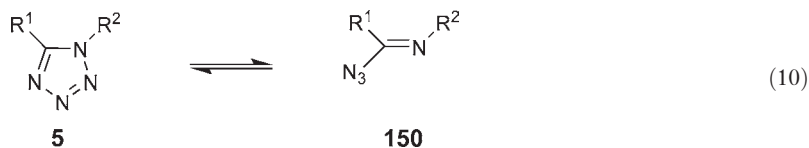
An interesting protolytic equilibrium involving the tetrazole ring is the tautomerism of azolotetrazoles. The best known among these compounds are pyrrolotetrazoles that can exist in various tautomeric forms, where both conjugated heterocycles cannot be aromatic simultaneously <1998JPR687>. It is shown by *ab initio* calculations that the nature of substituents on the pyrrole ring governs the structure of the prevailing tautomer: pyrrolotetrazole derivatives with electron-donor substituents and unsubstituted pyrrolotetrazole exist predominantly as the 5*H*-form, whereas the pyrrolotetrazoles with electron-withdrawing substituents are more stable in the 1*H*-form (Equation 2) <2006UP1>.

In 5-aminoalkyltetrazoles, an intramolecular proton transfer is possible from the NH-tetrazole fragment to the amino group. For instance, 5-(2,2-dimethylaminoethyl)tetrazole **148** is known to exist both in crystals and in solution predominantly as a zwitterion **149** (Equation 9) <1998RJO870>.

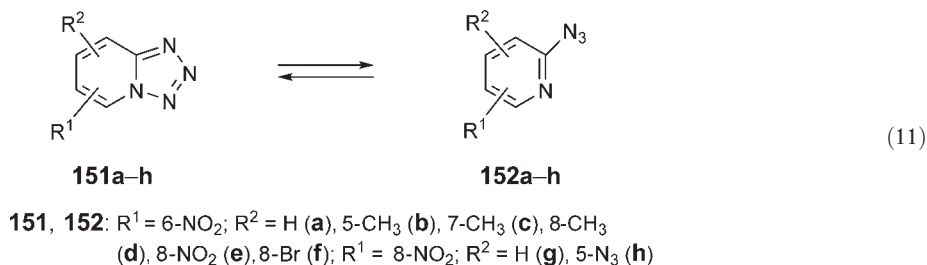


6.07.4.4.3 Ring-chain tautomerism

Ring-chain tautomerism is one of the main synthetic routes to tetrazole derivatives. This equilibrium governs not only the process of ring formation (cf. Section 6.07.9), but also ring fragmentation (cf. Section 6.07.5.1), rearrangements of the Schmidt type, Dimroth reactions (cf. Section 6.07.5.2.3), etc. In surveys by Koldobskii *et al.* <1975KGS723> and Pochinok *et al.* <1975UK1028>, the results of theoretical and experimental (including kinetic) investigations of ring-chain tautomerism performed 30 years ago and earlier were summarized. Later, Butler paid attention to this problem <1996CHEC-II(4)621>. Noodleman *et al.* recently <2004CRV459> compared the mechanisms of two principal processes leading to the formation of the tetrazole ring: cycloaddition of HN_3 (or its salts and complexes) to nitriles (cf. Section 6.07.9.4.1), and isomerization of imidoil azides in tetrazoles (cf. Section 6.07.9.1). The position of the imidoil azide-tetrazole equilibrium (Equation 10) (cf. Section 6.07.9.1) is known to be affected by the relative thermodynamic stability of the ring (tetrazole) **5** and chain (azido) form **150**, electronic and steric (*cis*-, *trans*-) effects of substituents R^1 and R^2 , solvation involving hydrogen bonds and/or protonation of the nitrogen of the $\text{C}=\text{N}$ group, polarity of solvent, temperature, etc. <1975KGS723, 1996CHEC-II(4)621, 1998JOC2354, 2000JOC7284, 2004CRV459>. Electron-withdrawing groups on the nitrogen of the imino group were shown to favor the azido isomer while the opposite effect is observed for electron-donating substituents <2000JOC7284>. Whereas the azido species is the most stable in the gas phase and nonpolar solvents, the equilibrium is displaced toward the tetrazole species as the polarity of the solvent increases. If the stabilization enthalpy of the tetrazole species is not large enough to compensate the entropy loss from the ring closure, the equilibrium is displaced toward the azido form <1998JOC2354>. A necessary condition for imidoil azide cyclization to tetrazole is the reciprocal *cis*-position of R^1 and R^2 substituents (Equation 10) <1975KGS723>.

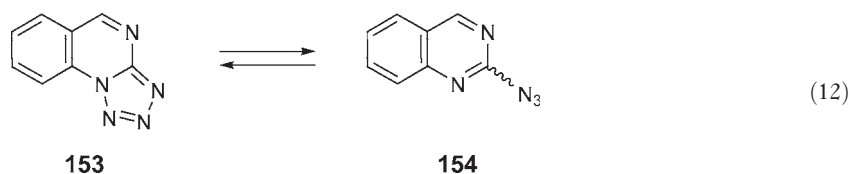


Recently, a series of theoretical and experimental studies were performed on the ring-chain tautomerism of fused systems containing tetrazole and imidoil structures. Wentrup and co-workers showed that tetrazolo[1,5-*a*]pyridines are a convenient model for theoretical and experimental investigation of the ring-chain tautomerism <1996JA4009>. Cmoch *et al.* examined the tetrazole-azide tautomerism of substituted tetrazolo[1,5-*a*]pyridines **13** by NMR, IR spectroscopy, and MO calculations <1997MRC237, 1999JST(510)165>. 6-Nitro and 8-nitro groups in the tetrazolo[1,5-*a*]pyridine molecules **151** exhibit completely different influences on the tetrazole **151**-azide **152** equilibrium. Introduction of methyl, nitro, azido groups or a bromine atom in positions 5, 6, 7, or 8 of the nitrotetrazolopyridine produces changes in the equilibrium constants (Equation 11). In the solid state, the tetrazole structure was assigned to almost all the compounds studied. Only one of them, 2,6-diazo-3-nitropyridine **152h**, exists in a diazo form in the solid state (Equation 11) <1999JST(510)165>. Information on the effect of different factors on the position of the tetrazole-azide isomerization equilibrium in tetrazolo[1,5-*a*]pyridines **151** was supplemented by the findings of Coutinho and Kanyalkar, showing that a high temperature favored the azide state <2000T8775>.

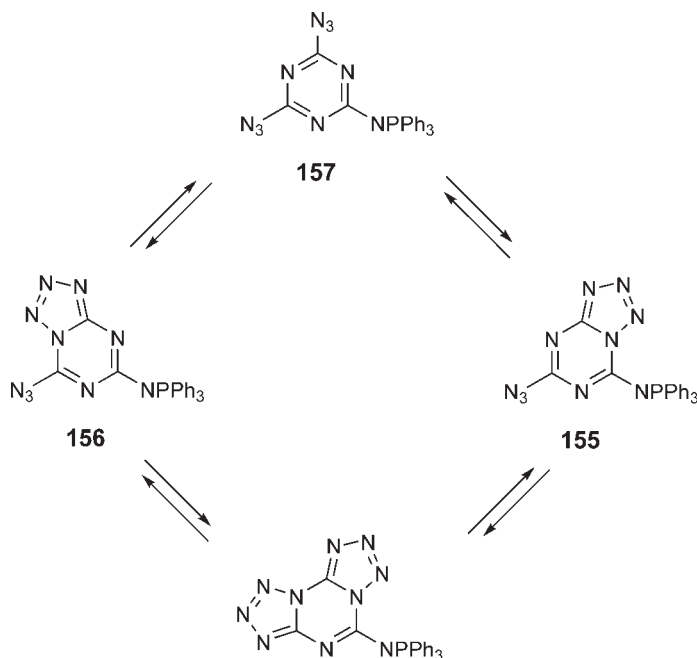


Note that other data <1999JST(510)165> are in agreement with conclusions previously made by Wentrup and co-workers <1996JA4009> that the tetrazolo[1,5-*a*]pyridines **13**, **78**, **151**–2-azidopyridines equilibrium is governed by entropy. The ^1H , ^{13}C , and ^{15}N NMR spectra of 6-substituted tetrazolo[1,5-*b*]pyridazines show that in DMSO at room temperature they exist only in the tetrazole form. According to CHF-GIAO *ab initio* calculations, the greater the electron-donating nature of the substituent at position 6, the higher is the stability of the tetrazole ring in tetrazolo[1,5-*b*] pyridazines <1999MRC493>.

The views on the effect of different factors on the ring–chain tautomerism formulated by an example of tetrazolo[1,5-*a*]pyridines **13**, **78**, **151** <1996JA4009, 1999JST(510)165, 2000T8775> and tetrazolo[1,5-*b*]pyridazines <1999MRC493, 2005JST(751)65> isomerization may be apparently extended to other similar heterocyclic systems. Wentrup and co-workers recently reported on the analysis of the tetrazole–azide equilibrium for tetrazolo[1,5-*a*]quinazoline **153** <2006JOC4049>. According to their findings, the formation from tetrazolo[1,5-*a*]quinazoline **153** of the corresponding azide **154** on heating can be ascribed to an entropy effect (Equation 12) <2006JOC4049>.



The approach used in the above-cited studies also proved to be useful in more complex events of ring–chain tautomerism, like the formation and isomerization of 2-triphenylphosphanimino-4-azidotetrazolo[5,1-*a*]-[1,3,5]triazine **155**. Schulz and co-workers by spectral studies (NMR, Raman) revealed an equilibrium between the tetrazole and the open-chain azide isomer. The azide groups of compounds **155**–**157** are capable of attacking a N-atom of the triazine ring, forming a tetrazole ring system (Scheme 4). These reactions are therefore not electrostatically controlled but are orbital controlled <2001IC1102>.



Scheme 4

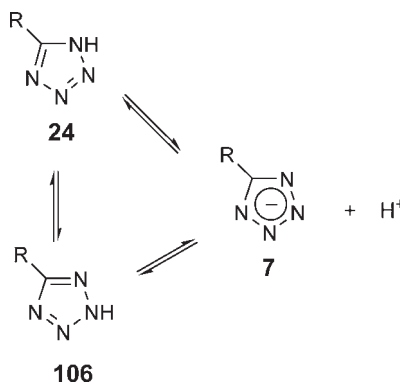
As seen from this discussion, the problem of ring-chain tautomerism has been the object of extensive theoretical investigations performed by modern *ab initio* methods (cf. Section 6.07.2.1). An example is the publication by Tian and co-workers aimed at a theoretical prediction of properties of triazidotri-*s*-triazine and its azido-tetrazole isomerism <2004PCA840>. The concepts on mechanism and laws of the ring-chain tautomerism obtained from the experimental and theoretical studies allowed a forecast of the properties and reactivity of tetrazoles in a number of cases. In particular, such data proved to be useful in the study of photoreactions of tetrazolo[1,5-*a*]pyrimidine (cf. Section 6.07.5.2.1) <1998JPO478>. Note in conclusion that the ring-chain tautomerism of pyrrolotetrazoles has not been previously investigated and the attempt to fill this gap was recently reported by Moderhack and co-workers <2006UP1>.

6.07.4.5 Acid-Base Equilibrium

Tetrazoles, compared with the other azoles, possess an abnormally high acidity and very weak basicity. Nowadays, a sufficiently large experimental and theoretical database covers the acid-base characteristics of tetrazoles. Not only have dozens of fundamental constants inherent to the compounds of this series been determined by various methods, but also the effect of different factors on these constants has been analyzed.

6.07.4.5.1 Acidity

Unsubstituted tetrazole behaves as an organic acid with acidity close to that of acetic acid. In general, depending on the substituent in position 5, tetrazole ionization occurs in the range from -0.8 unit of the H_0 scale to 7 unit of the pH scale. Proton elimination from 1*H*- and 2*H*-tetrazoles **24** and **106** results in formation of the tetrazolate anion (tetrazolide) **7** (Scheme 5) characterized by high aromaticity and good π -electron delocalization.



Scheme 5

At present, pK_a values are known for dozens of 5*R*-substituted tetrazoles both in water and in organic solvent–water systems <1987AHC(41)187, 2006RJO1585, 2001CED939>. Some of these data are presented in Table 17. The acidity constants were estimated by applying various physicochemical methods, but the most useful proved to be potentiometric titration and UV spectrophotometry. The table contains experimental data on NH-acidity of 5-substituted tetrazoles in water <1987AHC(41)187, 2006RJO1585>. Commonly the difference in pK_a values measured by various experimental procedures is insignificant. The thermodynamic parameters of the acid dissociation equilibrium of unsubstituted tetrazole (ΔH 3.3 kcal mol $^{-1}$, ΔS^0 -10 kcal mol $^{-1}$ K $^{-1}$) and some of its derivatives estimated pH-metrically by Boraci <2001CED939> are consistent with the earlier results obtained by calorimetry <1987AHC(41)187>.

For some tetrazoles, the pK_a values were evaluated in mixtures of organic solvent and water and also in pure organic solvents (methanol, ethanol, DMSO, dimethylformamide (DMF), and acetone) <1996CHEC-II(4)621, 1987AHC(41)187, 2001CED939, 2003CHE1317, 2006CHE469, 2006JST(785)114, 2002PSA4333, 1999J(P2)2551>. As expected, the pK_a of tetrazoles in mixed solvents grew with the content of the organic component and consequently with decrease in the dielectric permittivity of the medium <2001CED939, 2003CHE1317, 2006CHE469>. For instance, the pK_a of unsubstituted tetrazole in DMSO is 8.23 <1987AHC(41)187>.

Table 17 Acidity constants in water and basicity constants in H₂SO₄/H₂O mixtures (determined using H₀ acidity function) of selected 5-R-tetrazoles at 25 °C <2006RJO1585>

<i>Tetrazole</i>	pK_a (method) ^a	pK_{BH+} (method) ^a
Parent tetrazole 2	4.86 (P) ^b 4.70 (P)	−2.68 (NMR) ^c −3.01 (R)
1-H, 5-Me	5.50 (P) 5.56 (P)	−1.83 (NMR)
1-H, 5-NH ₂	6.00 (P)	
1-H, 5-Ph	4.83 (P) ^d	−2.28 (UV) ^e −2.32 (UV) ^f
1-H, 5-CF ₃	1.70 (P)	
1-H, 5-Cl	2.07 (P)	
1-H, 5-Br	2.13 (P)	−5.20 (UV)
1-H, 5-I	2.85 (P)	−4.40 (UV)
1-H, 5-NO ₂	−0.83 (UV)	−9.26 (UV)
5,5′-Bitetrazole 26	pK_a^1 1.41; pK_a^2 4.25 (UV)	pK_{BH+}^1 −5.47; pK_{BH+}^2 −10.91 ^g (UV)
1-Me, 5-H		−3.00 (NMR)
1,5-Di-Me		−1.68 (NMR)
1-Me, 5-Ph		−2.50 (UV) ^h
1-Me, 5-NO ₂		−9.31 (UV)
1-Ph, 5-H		−3.41 (UV)
1-Ph, 5-Me		−1.96 (NMR)
1,5-Di-Ph		−2.96 (UV)
2-Me, 5-H		−3.25 (NMR)
2-Me, 5-Ph		−3.27 (UV) ⁱ
2-Me, 5-NO ₂		−9.06 (UV)

^aP, potentiometric titration; UV, ultraviolet spectroscopy; NMR, ¹H NMR spectroscopy; R, Raman spectroscopy.

^bFor 5-R-NH-tetrazoles: $pK_a = -6.65\sigma_p + 4.46$; r 0.98, n 6, s 0.5.

^cFor 5-R-NH-tetrazoles: $pK_{BH+} = -7.83\sigma_p - 2.88$; r 0.99, n 6, s 0.40.

^dFor 5-aryl-NH-tetrazoles: $pK_a = -1.27\sigma^0 + 4.40$; r 0.99, n 6, s 0.09.

^eFor 5-aryl-NH-tetrazoles: $pK_{BH+} = -1.80\sigma - 2.24$; r 0.98, n 8, s 0.15.

^fIn HClO₄/H₂O mixtures.

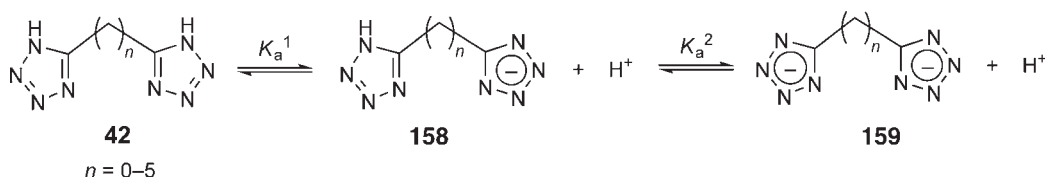
^gDetermined using H_0 acidity function.

^hFor 1-methyl-5-aryltetrazoles: $pK_{BH+} = -1.63\sigma - 2.43$; r 0.99, n 7, s 0.05.

ⁱFor 2-methyl-5-aryltetrazoles: $pK_{BH+} = -1.25\sigma - 3.19$; r 0.97 n 10, s 0.11.

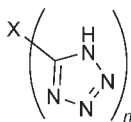
Fluorimetric titration in water was applied to estimate acidity constants of some well-known antihypertensive drugs containing in their structure an NH-unsubstituted tetrazole fragment governing their acid properties: pK_a 3.15 (losartan **29**), 4.70 (irbesartan **83**), and some others <2001MI477>.

Acidity constants for several series of di-, tri-, and tetrabasic heterocyclic NH-acids have been published <2006RJO1585, 2003CHE1317, 2006CHE469, 2004RJO1528>. For instance, 5,5′-bitetrazole and α,ω -ditetrazol-5-ylalkanes **42** are capable of stepwise dissociation forming mono- and dianions **158** and **159** (Scheme 6).

**Scheme 6**

5,5′-Bitetrazole **26** is a strong dibasic acid close in acidity to oxalic acid (see Table 17). From the values of pK_a^1 and pK_a^2 of 5,5′-bitetrazole **26** and other 5-substituted tetrazoles (Table 17), σ -constants for the tetrazole ring as a substituent were determined: for the NH-tetrazole-5-yl group σ_1 0.45, σ_m 0.46, for the corresponding anion, σ_1 0.12, σ_m 0.09 <2006RJO1585>. The tetrazolyl fragment is like a phenyl group in the character of conjugation, and like a picryl group with respect to electronegativity.

The pK_a values of α,ω -ditetrazol-5-ylalkanes **42** (Scheme 6) with a number of methylene groups n from 1 to 5 are close to the corresponding characteristics of dicarboxylic acids: for ditetrazolymethane ($n = 1$) pK_a^1 and pK_a^2 are 3.42 and 5.30, respectively <2006CHE469>. A characteristic trend is observed in increasing pK_a value with the growing number of the bridging methylene groups n , and at $n = 5$ the difference between the pK_a^1 and pK_a^2 values approaches a statistical factor. Using the Bjerrum distribution function, pK_a^1 , pK_a^2 , pK_a^3 , and pK_a^4 values were determined by potentiometric method for a series of polynuclear podand-like tetrazoles **160**; the values obtained were in the range 3.5–7.5 pH units <2003CHE1317>. These data led to the conclusion that the terminal tetrazole fragments notably affect each other even at a long distance.

**160**

X = alkyl, aryl, hetaryl

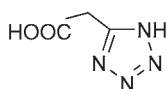
 $n = 2-4$

According to the data of Taft, the Gibbs free energy value of deprotonated unsubstituted 2*H*-tetrazole **106** and the proton affinity of the corresponding anion **7** in the gas phase determined by means of ion cyclotron resonance are ΔG_{acid}^0 326.7 and PA^- 333.7 kcal mol⁻¹ <B-2003M12>. These values are in a good agreement with analogous characteristics calculated by the DFT method using the basis B3LYP/6-31G* (ΔG_{acid}^0 324.6 kcal mol⁻¹) and G3 (PA^- 329.6 kcal mol⁻¹) <1998IJM51, 2005MP209>.

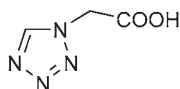
In numerous studies, the pK_a values of 5*R*-substituted tetrazoles **24** were shown to correlate with various physicochemical and spectral parameters of these heterocycles <1987AHC(41)187, 2006RJO1585>. Good correlation was found between pK_a of 5*R*-tetrazoles **24** containing substituents both in the hetero-ring and in a phenyl ring of 5-aryltetrazoles and the σ -constants of the substituents (Table 17). The value of the transmission factor (π' 0.19) shows that in 5-aryltetrazoles the phenyl ring reduces the electronic effect of the substituent on the reaction center to a significant degree. The dependence of pK_a values of some tetrazoles on the dielectric permittivity of the medium has been discussed <2001CED939, 2006CHE469>. Good correlations were found between the pK_a of ditetrazolylalkanes **42** and the chemical shifts of the endocyclic carbon of tetrazole ring in the ¹³C NMR spectra and also the chemical shifts of the carbon in the α -methylene groups <2006CHE469>.

The NH-acidity of unsubstituted tetrazole and some 5*R*-tetrazoles **24** was estimated using quantum-chemical HF, DFT, and MP2 methods <2005PCA5590, 1999PCA8062, 2004JMT(668)123, 2000IJQ27>. It has been shown <2004JMT(668)123> at the B3LYP/6-31G* level that for 5*R*-tetrazoles **24** (R = H, Me, Bu^t, Cl, CF₃, NO₂) the protonation energy in the gas phase of the respective anions (PE^-) correlates well with the experimental values of pK_a measured in water: $PE^- = (328.2 \pm 0.7) + (4.1 \pm 0.2) pK_a$; r 0.996, s 1.1, n 6. Parallel changes in the acid–base properties of nitrogen-containing heterocycles in solution and in the gas phase are often observed <1998IJM51, 2006RJO1585>. Applying HF and DFT procedures and also PCM method accounting for solvation in basis sets 6-31+G* and 6-31++G**, pK_a values in water and other solvents have been calculated for several series of 5*R*-tetrazoles (R = H, Hlg, Alk, N₃, NO₂, OCH₃) <2005PCA5590, 2005MP209, 2005JOC9677, 2002PCA1327>. In a number of cases, these calculated pK_a values considerably deviated from the experimental findings. For instance, the pK_a of unsubstituted tetrazole in DMSO calculated theoretically (IPCM/B3LYP/6-311+G(2d,p)//B3LYP/6-31G*) differed from the experimental value by 0.6 units <2005MP209>.

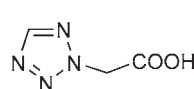
The acidity of tetrazolyl-substituted carboxylic acids has been discussed in several publications. For example, the pK_a values of tetrazolylacetic acids **161–163** in water were reported <2006RJO1585>. In tetrazolylacetic acid **161** with two centers capable of ionization, only the carboxy group possesses high acidity.

**161** pK_a

3.10

**162**

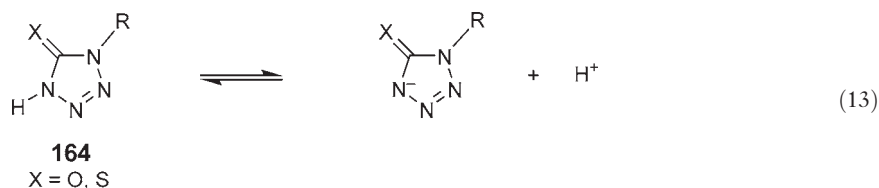
2.27

**163**

2.12

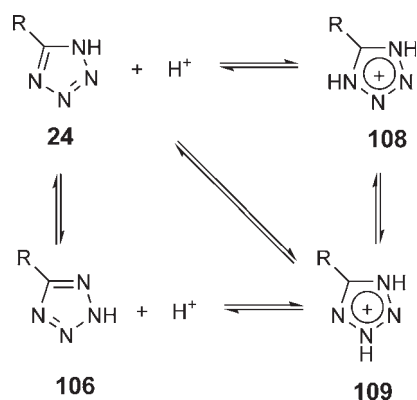
Acidity constants of the carboxy group have been measured in tetrazole-containing analogs of natural amino acids (phenylalanine, tryptophan, etc.) <2004RJO1528, 2004RJO1532>.

Acidities of tetrazol-5-ones (thiones) **11**, **65**, **143**, and **164** are in the same range as the acidities of NH-tetrazoles, although in these compounds dissociation occurs not at the OH or SH groups but at the nonaromatic 1,4-dihydro-tetrazole ring (Equation 13) <2006RJO1585>.



6.07.4.5.2 Basicity

Protonation of the tetrazole ring is depicted in Scheme 7 (taking into account the information from Section 6.07.4.4.1).



Scheme 7

Tetrazoles behave as weak bases: they are protonated only in media whose acidity is described by empirical scales of acidity functions. Nowadays basicity constants are known for several dozens of both NH-unsubstituted **24** and 1- and 2-alkyl(aryl)tetrazoles **5**, **6**, **31**. The data given in the table were obtained employing a calculation of all pK_{BH^+} values by the Yates–McClelland method using acidity function H_0 <2006RJO1585>. Most tetrazoles behave as typical Hammett bases. The protonation of 5R-tetrazoles, depending on substituent (Table 17), occurs in a wide range of values of the acidity function H_0 , from -1 to -10 <2006RJO1585, 1998RJO870>. The basicity constants of unsubstituted tetrazole determined by various methods are in good agreement. Basicity constants of some 5-aryl-tetrazoles measured in sulfuric and perchloric acids had close values evidencing the insignificant role of solvation factors in protonation of these compounds <2006RJO1585>. The basicity of 2-methyl-5-aryltetrazoles is somewhat lower than that of 1-methyl-5-aryltetrazole (Table 17). Evidently this is due to the different structures of the conjugate acids formed on protonation: the thermodynamic stability of the $1H,3H^+$ -form is slightly lower than that of the $1H,4H^+$ -form (cf. Section 6.07.4.4.1). 5-Nitro derivatives are an exception and in this case an opposite pattern is observed. According to X-ray diffraction analysis, NMR and Raman spectroscopy, and also to calculations by MP2 and DFT methods in the basis set 6-31G*, the protonation of 1,5-diaminotetrazole **33** occurs at the endocyclic nitrogen in position 4 but not at the amino group <2003JST(649)309, 2005IC4237, 2005EJI3760>. 5,5'-Bitetrazole **26** is a considerably weaker base than unsubstituted tetrazole: the protonation of the first tetrazole ring decreases the basicity constant of the other by more than 5 orders of magnitude (Table 17). 1,1'-Disubstituted-5,5'-bitetrazoles are even weaker bases than NH-unsubstituted 5,5'-bitetrazole **26** (Table 17) <1999RJO1824>. The protonation of isomeric 1*H*- **162**, 2*H*- **163**, and 5*H*-tetrazolylacetic acids **161** was investigated by IR, UV, and ^1H NMR spectroscopy <2006RJO1585>. As for *N*-methyl(aryl)tetrazoles, the proton addition to all these compounds occurs at the nitrogen at position 4 of the tetrazole ring.

Just as with pK_a values, good correlations are obtained between σ_p - and σ -constants of substituents and pK_{BH^+} values of 5-R-NH-tetrazoles **24** that have substituents attached directly to the heterocyclic ring or to the aryl group of 5-aryl-NH-tetrazoles (Table 17). The data on the basicity of 5,5'-bitetrazole **26**, which have several possible protonation sites, have been used to calculate the σ_p -constants of a neutral and protonated tetrazol-5-yl group, equaling 0.31 and 1.02, respectively <2006RJO1585>. Using the same equations, the transmission factor of the phenyl group was calculated as π' 0.23, the value close to that obtained from the correlation equation of pK_a and σ -constants. It was stated, that in general the effect of substituents on acidity and basicity of 5-substituted tetrazoles **24** follows the same direction. A good linear correlation is observed between pK_{BH^+} and pK_a <2006RJO1585>: $pK_a = 0.78, pK_{BH^+} + 6.37; r 0.98, n 11, s 0.3$. The pK_{BH^+} of 1- and 2-methyl-5-aryltetrazoles correlate well with the σ -constants of substituents (see Table 17). The slopes of the correlation equations for NH- and 1-methyltetrazoles have close values, additionally confirming that in solution the NH-unsubstituted tetrazole exists predominantly as the 1H-tautomer. Good and fair correlations between the basicity constants and substituents constants were also observed for several series of 1-aryltetrazoles (Table 17). The analysis of these relationships revealed that the electronic effect of the substituent was to a lesser extent transferred through the phenyl group in position 1 of the hetero-ring than through a phenyl at position 5.

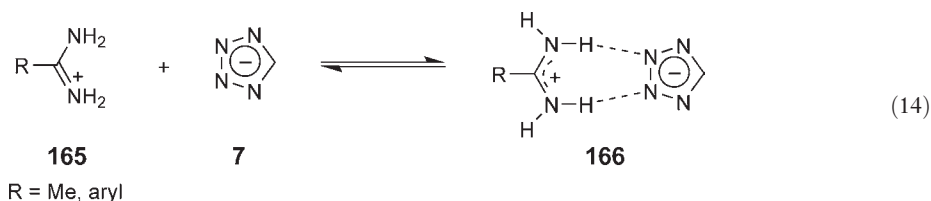
Taft by means of ion cyclotron resonance measured in the gas phase the quantitative characteristics of basicity of unsubstituted tetrazole **2**: PA 198.2, GB 190.2 kcal mol⁻¹ <B-2003MI2>. In a series of publications, the basicity of tetrazoles in the gas phase was calculated by theoretical methods <1986JPC5597, 2004JMT(668)123, 2002NJC1567, 1998IJM51>. For a series of 5R-tetrazoles **106**, an investigation was carried out into the effect of ring substituents on the protonation energy in the gas phase by applying calculations at the level of B3LYP/6-31G* <2004JMT(668)123>. Satchell and Smith attempted to calculate the pK_{BH^+} of unsubstituted tetrazole in solution by applying exclusively theoretical methods: method G3 for energy calculation, and methods PCM, iterative Langevin dipole (iLD), and Poisson–Boltzmann (PB) for taking into account the solvation effects <2002PCP4314>. These calculated pK_{BH^+} values significantly deviated from the experimental findings.

The thermodynamic parameters characterizing the basicity of the tetrazole ring with respect to lithium cation in the gas phase have been obtained experimentally (ion cyclotron resonance) and by calculations ((G2, G2(MP2), B3LYP/6-31+G**)) <2000PCA2824, 2004JCI1727, 2004PCA4812>.

6.07.4.5.3 Hydrogen bonding

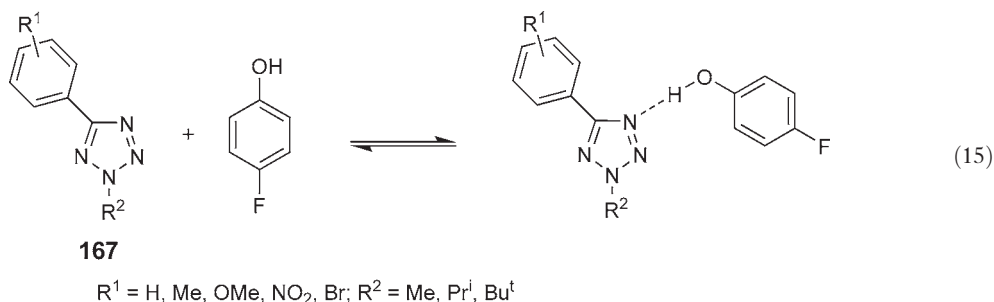
It has been frequently stated that virtually all prototropic forms of tetrazoles could be involved in hydrogen bonds both with donors and acceptors. These interactions considerably influence the crystal packing of tetrazoles and significantly affect many spectral and other characteristics (see Section 6.07.3). The ability of tetrazoles to form stable hydrogen bonds should essentially govern their biological activity, reactivity, and other properties. Nonetheless, the quantitative data describing the hydrogen bonding involving the tetrazole ring as a thermodynamic equilibrium are very few. Alkorta *et al.* using DFT calculations investigated the effect of intramolecular and intermolecular hydrogen bonds on tautomerism and proton-transfer processes involving the tetrazole ring, as well as on conformations of some 5R-tetrazoles **24** <1998J(P2)2675, 2005STC507>. Thomas *et al.* using the same calculation method optimized complexes of 5-aminotetrazole with a water molecule forming hydrogen bonds <2005PCA9928>.

Kraft and co-workers quantitatively investigated the association of unsubstituted tetrazolate with amidines **165** in organic solvents (Equation 14) using ¹H NMR spectroscopy <2001JOC3291, 2006OL1279>. The association constants and structures of complexes **166** (Equation 14) were compared with known data on amidinium carboxylates complexes. Tetrazolate was found to be a weaker ligand than carboxylates.



Fourier IR spectroscopy has been exploited for the evaluation of hydrogen-bonding basicity constants (pK_{HB}) in a series of 2-alkyl-5-aryltetrazoles **167** with respect to a reference proton donor (*p*-fluorophenol) in tetrachloromethane solution, and also for estimation of some thermodynamic parameters of the equilibrium presented at Equation (15) <2006RJO1059>. The determined pK_{HB} values of tetrazoles **167** fell into the range 0.9–1.4. These compounds

exhibit the quality of hydrogen-bond acceptors of medium strength comparable with diazines. Thus the hydrogen-bonding basicity of the tetrazole ring differs fundamentally from its normal basicity.



6.07.5 Reactivity of Fully Conjugated Ring

6.07.5.1 General Survey

This section includes results on two groups of chemical reactions, both of extreme importance for tetrazole chemistry. The first group deals with processes occurring on heating or under photochemical pulses and significant progress in understanding the mechanisms has been achieved in the last decade. This has led to an increasing number of publications treating these problems and has improved the quality of discussion of experimental data on the fragmentation of N-unsubstituted and N-substituted tetrazoles (cf. [Sections 6.07.5.2.1 and 6.07.5.2.2](#)). The second group of reactions is even more important and concerns electrophilic attack on the endocyclic nitrogen (cf. [Section 6.07.5.3](#)). The usual problem in these reactions is the low selectivity of the electrophilic attack. Since the 1990s, systematic investigations of these processes have been performed, both theoretical and experimental, and these provide the possibility of more reliable selection of substrates, reagents, and reaction conditions ensuring the desired regioselectivity level when introducing substituents at nitrogen. Compared to these achievements, the results obtained in the field of the electrophilic and nucleophilic attack at the endocyclic carbon (cf. [Sections 6.07.5.4 and 6.07.5.5](#)) are less spectacular. Since original theoretical and experimental publications on this topic are rare, we have been obliged to turn sometimes to the reviews of other authors treating this exotic line of the tetrazole chemistry in order to conserve the integrity of the discussion. The above is also true for [Sections 6.07.5.2.3 and 6.07.5.7](#). We found only a few papers on these subjects and, therefore, their analysis and generalization are untimely. We have been confronted with quite a different situation in an attempt to systematize the data on the formation of complexes with metal ions (cf. [Section 6.07.5.3.4](#)). Although abundant publications have appeared recently on this topic, it is difficult to find a reasonable algorithm for putting them into a system and for generalization of the material. Probably this difficulty hampered the publication on this urgent and important subject of reviews, which are in fact relatively few. In contrast, the exhaustive analysis of the other group of tetrazole reactions, those with radicals and electron-deficient species, reactions at surfaces, and reduction (cf. [Section 6.07.5.7](#)), is not possible because of insufficient information. Taking into account the significance of these lines in modern tetrazole chemistry, we discuss in [Section 6.07.5.7](#) the rare articles published until now on this subject.

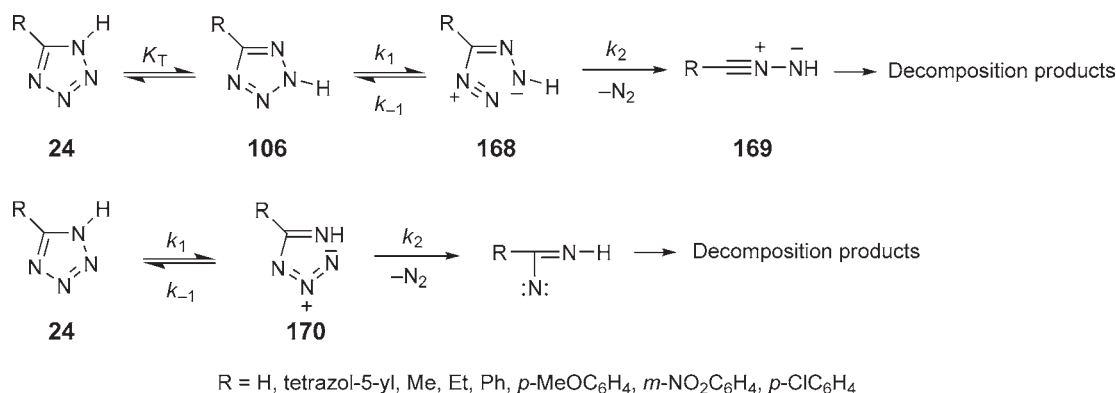
6.07.5.2 Unimolecular Thermal and Photochemical Reactions

Unimolecular thermal and photochemical reactions may be tentatively divided into two groups. The first includes reactions occurring with decomposition of the hetero-ring. These reactions involve evolution of gaseous products and liberation of the stored chemical energy (cf. [Section 6.07.5.2.1 and 6.07.5.2.2](#)). The second group includes rearrangement processes (cf. [Section 6.07.5.2.3](#)) occurring with retention of the tetrazole ring.

6.07.5.2.1 Fragmentation of N-unsubstituted and 1-substituted tetrazoles

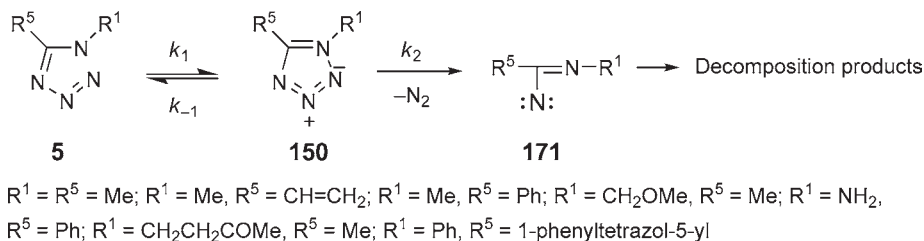
Thermal decomposition of tetrazoles is accompanied by the release of a large amount of energy utilizable for useful work <1999THS(3)467>. Thiele started investigation of thermal decomposition of tetrazoles shortly after the discovery of tetrazole by Bladin <1992THE427>. Since then, numerous studies have been devoted to the process. Attempts to generalize the results were undertaken in a review <1992THE427> and a monograph <B-1996MI87>.

Butler called attention to thermolysis, photolysis, and related transformations of tetrazoles <1996CHEC-II(4)621>. Within the last decade, interest in this problem has grown, and studies have been published on theoretical, kinetic, and thermodynamic aspects of the problem. Kinetic parameters of the thermal decomposition of tetrazole, 5,5'-bitetrazole **26**, 5-alkyl- and 5-aryltetrazoles **24** in the temperature range 150–230 °C were determined by a manometric method in melt and in nitrobenzene solution <1996RCB2101>. The first-order rate constants as well as activation parameters have been determined and characterize the decomposition proceeding via elimination of the molecular nitrogen (2 mol of N₂ is evolved in the case of 5,5'-bitetrazole) **26**. The principal conclusion drawn is that the prototropic tautomerism of tetrazole **2** and 5-substituted NH-tetrazoles **24** play a significant role in the decomposition process (Scheme 8) <1996RCB2101>.



Scheme 8

In the gas phase, the N²-tautomer **106** of tetrazoles predominates and suffers cleavage of the N(2)–N(3) bond to form a reactive intermediate **168**. Subsequent elimination of N₂ leads to the formation of reactive nitrilimines **169** and then the final products. On passing from the gas phase to melt or solution, the rate constants of thermal decomposition of NH-unsubstituted tetrazoles **24** substantially decrease. It has been suggested that this is due to changes in the mechanism of decomposition in a polar medium in which the prototropic equilibrium is shifted to the more polar N¹-tautomer **24**, whose decomposition involves isomerization into azidoazomethine **170** and subsequent elimination of N₂ (Scheme 8) <1996RCB2101>. The molten tetrazole starts to decompose at a lower temperature than in the gas phase. The nature of tetrazole decomposition depends not only on its aggregation state but also on the reaction temperature. Reaction temperature and gas-phase reaction products (in parentheses) are as follows: 225 °C (HCN, HN₃), 280 °C (N₂, HCN, H₂), 800 °C, flash photolysis (N₂, NH₂CN, CH₂N₂) <1992THE427, 1997JHC113, 1999THS(3)467, 2005PCA7967, 2005PCA7967>. The kinetics and mechanism of unimolecular thermal decomposition of 1,5-disubstituted tetrazoles **5** under isothermal conditions have been discussed <1996RCB2094>. The activation energy of the decomposition of N-substituted tetrazoles **5** is higher than that of N-unsubstituted tetrazoles **24**. Whereas the activation entropies are similar, the mechanism of thermal decomposition of 1,5-disubstituted tetrazoles **5** involves a stage of reversible ring opening to form intermediate imidoazides **150**. The elimination of a nitrogen molecule from intermediate **150** affords nitrenes **171** (Scheme 9, Table 18) <1996RCB2094, B-1996MI87, 1996RCB2094, 1999SC2847, 1999THS(3)467>.



Scheme 9

Table 18 Kinetic parameters of thermal decomposition of 1,5-disubstituted tetrazoles **5** <B-1996MI87>

R^5	R^1	Gas phase or nitrobenzene solution	Decomposition interval ($^{\circ}\text{C}$)	E (kcal mol^{-1})	$\lg A$ (s^{-1})
Me	Me	Gas	270–320	47.1	14.97
$\text{CH}_2=\text{CH}$	Me	Gas	270–330	47.5	15.05
Ph	Me	Gas	240–290	47.7	15.56
Me	CH_2OCH_3	Gas	230–280	47.8	15.20
Ph	NH_2	Nitrobenzene	160–210	39.8	14.34
Me	$\text{CH}_2\text{CH}_2\text{COCH}_3$	Nitrobenzene	190–210	44.5	15.31
Ph	1-Phenyltetrazol-5-yl	Nitrobenzene	200–240	44.7	15.66

A mechanism implying nitrene **171** formation (Scheme 9) makes understandable the appearance at later stages of thermal decomposition compounds such as isodiaziridines (resulting from the additive cyclization of the nitrene), carbodiimides (sextet rearrangement), and their disproportionation products (benzimidazoles have been found among the decomposition products of *N*-aryltetrazoles), polycyanamides, and also compounds of low molecular weight (NH_2CN , CH_2N_2 , HCN , N_2 , etc.) forming in the final stages of the decomposition <1992THE427, 1996RCB2094, B-1996MI87, 1999THS(3)467>.

The thermal decomposition of a large series of NH-unsubstituted **24**, 1-substituted **31**, and 1,5-disubstituted tetrazoles **5** have been investigated using DSC, TGA, and EGA <1999MI168>. Löbbecke *et al.* <1999MI168> have suggested a mechanism of thermal decomposition of tetrazoles consistent in general with earlier results <1996RCB2094, B-1996MI87>. However, quantitative values of the activation parameters of the thermal decomposition in two publications <1996RCB2094, 1999MI168> are notably different. For instance, the activation energy of the tetrazole thermal decomposition in the gas phase calculated from the kinetic data obtained by the manometric method <1996RCB2094> was $32.3 \text{ kcal mol}^{-1}$, whereas the activation enthalpy of the process according to another group <1999MI168> amounted only to $9.2 \text{ kcal mol}^{-1}$. For the thermal decomposition of 5,5'-bitetrazole **26** in nitrobenzene solution, the reported activation energy equaled $40.8 \text{ kcal mol}^{-1}$ <1996RCB2094>, whereas the activation enthalpy of the process published elsewhere <1999MI168> was $50.3 \text{ kcal mol}^{-1}$. The values of the activation energies of 5-substituted and 1,5-disubstituted **5** tetrazoles differed insignificantly on changing the substituent at position 5 of the heterocycle <1996RCB2094>. At the same time, the activation enthalpy of the thermal decomposition of tetrazoles ($\Delta H_{\text{decomp.}}$) <1999MI168> essentially depends on the character of the substituents (in kcal mol^{-1}): tetrazole 9.3; 5,5'-bitetrazole 50.3; 5-phenyltetrazole 21.7; 1,4-(ditetrazol-5-yl)benzene 53.7. The cause of the discrepancy in the activation parameters obtained <1996RCB2094, 1999MI168> is not clear. The difference may originate from dissimilar assignments of the activation parameters to a certain limiting stage of the process, and also from the specific features of the experimental measurements and calculation procedures.

The thermal decomposition of 5-aminotetrazole, 1-methyl-5-aminotetrazole, 1,5-diaminotetrazole, poly-1-vinyl-5-aminotetrazole, and the sodium salt of 5-aminotetrazole have been studied by thermogravimetry, thermal volumetric analysis (DSC, DTA, TVA), and EGA (Tables 19 and 20) <2002THE233>.

Table 19 Characteristic parameters of the first stage of thermal decomposition of aminotetrazoles <2002THE233>

Compound	<i>m.p.</i> (K)	Decomposition interval (K)	$-\Delta H_{\text{decomp.}}^a$ (kcal mol^{-1})	Gas evolution ($\text{cm}^3 \text{ g}^{-1}$)	Weight loss (%)
5-Aminotetrazole	478	480–610	2.03	130	50
1-Methyl-5-aminotetrazole	495	520–620	52.5	240	65
1,5-Diaminotetrazole	460	470–540	203.0	550	85
Poly-1-vinyl-5-aminotetrazole		493–615	16.7	250	40
Sodium salt of 5-aminotetrazole		563–635		230	35

^aMeasured in DSC experiments, heating rate: 10 K min^{-1} ; nitrogen pressure: 10 bar.

Thermal properties of guanidinium 5-aminotetrazolate, decomposition pathways, and volatile decomposition products have been investigated by thermal analysis <2003MI181>. The thermal decomposition of guanidinium 5-aminotetrazolate is initiated by the ring opening of the tetrazole. The release of hydrogen azide is typical for the thermolysis of substituted 5-aminotetrazoles <2003MI181>.

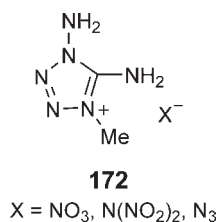
Table 20 Gaseous and volatile condensed products of thermal decomposition of aminotetrazoles <2002THE233>

Compound	Gaseous products	Volatile condensed products
5-Aminotetrazole	N ₂ , HN ₃ , NH ₃	NH ₄ N ₃ , melamine
1-Methyl-5-aminotetrazole	N ₂ , HN ₃ , NH ₃ , HCN, CH ₃ NH ₂	NH ₄ N ₃ , CH ₃ NH ₂ –HN ₃ , trimethylmelamine
1,5-Diaminotetrazole	N ₂ , HN ₃ , NH ₃ , HCN	NH ₄ N ₃ , 1,2,4-triazole
Poly-1-vinyl-5-aminotetrazole	N ₂ , HN ₃ , NH ₃	NH ₄ N ₃ , melamine
Sodium salt of 5-aminotetrazole	N ₂ , HN ₃ , NH ₃	NH ₄ N ₃ , melamine

Experimental studies as well as data on amino–imino tautomerism are in agreement with the suggested mechanism of decomposition of the tetrazole ring. It has been shown that secondary reactions significantly increase the number of products of thermal decomposition of aminotetrazoles <2002THE233, 2003MI181>.

The thermal decomposition of the azidoformamidinium and guanidinium 5,5'-azotetrazolate salts was monitored by DSC, and the gaseous products of the explosions of all compounds were identified by MS and IR spectroscopy <2005CM3784>. The activation energy of thermal decomposition of 5,5'-azotetrazolate salts are sensitive to the nature of the cation and vary from 38.2 kcal mol^{−1} for bis(azidoformamidinium) salt to 50.5 kcal mol^{−1} for bis(amino-guanidinium) salt. The decomposition gives a large amount of gaseous product, 911 and 999 ml g^{−1}, respectively <2005CM3784>.

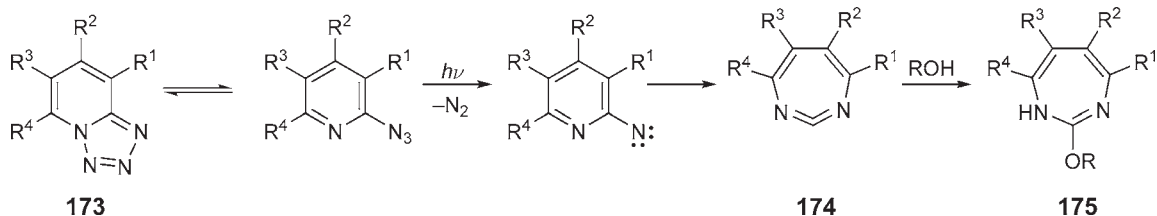
Thermal decomposition of the 1,5-diamino-4-methyl-1*H*-tetrazolium salts **172** was investigated by TGA and DSC <2005THE168>. The decomposition temperatures of salts **172** with X = NO₃ and N(NO₂)₂ are significantly higher than with X = N₃ and are consistent with the activation energy evaluated according to the method of Ozawa and Kissinger (Table 21) <2005THE168>.

**Table 21** Properties of 1,5-diamino-4-methyltetrazolium salts **172** (C₂H₇N₆⁺X[−]) evaluated by DSC and TGA measurements <2005THE168>

X	<i>m.p.</i> (°C)	<i>T</i> _{decomp} (°C)	<i>T</i> _{int.} ^a (°C)	Mass loss (%)
NO ₃	121	181	185–250	33 (150–195 °C) 58 (195–275 °C)
N(NO ₂) ₂	85	184	150–230	90 (150–250 °C)
N ₃	133	137	137–310	34 (105–160 °C) 36 (160–185 °C) 19 (185–310 °C)

^aRange of decomposition.

Transformations of the tetrazole ring on heating or irradiation occurring with formation of nitrenes of type **171** and their further conversion (Scheme 9) frequently provide the possibility of making uncommon compounds that are unavailable by other procedures. Studies of the reactions that were carried out before 1997 have been reviewed by Moderhack <1998JPR687>. Interest to these processes is still high. Tetrazolo[1,5-*a*]pyridines **173** undergo a photochemical nitrogen elimination and ring expansion to give 1,3-diazacyclohepta-1,2,4,6-tetraenes **174** <2004OBC246, 2004OBC1227>, which react with alcohols to afford 2-alkoxy-1*H*-1,3-diazepines **175** (Scheme 10; Table 22) <2004OBC1227>.

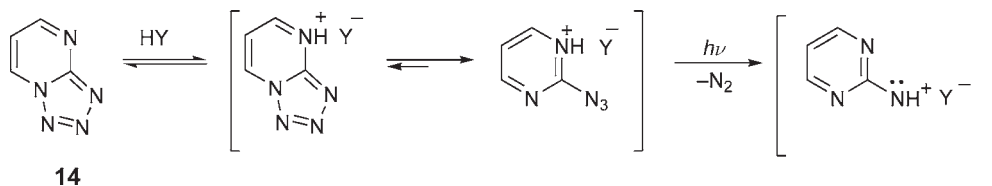


Scheme 10

Table 22 1*H*-1,3-Diazepines **175** from reactions of derivatives of tetrazoles **173** with alcohols ROH <2004OBC1227>

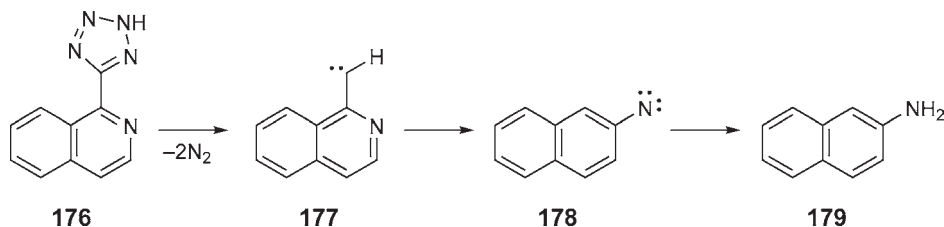
R^1	R^2	R^3	R^4	OR	Yield (%)
H	H	H	H	OMe	53
H	H	H	H	OE _t	72
H	CF ₃	H	H	OMe	72
CF ₃	H	H	H	OBu ^t	94
CF ₃	H	H	CF ₃	OMe	93

Another example is the photoreaction of tetrazolo[1,5-*a*]pyrimidine **14** with aromatic compounds in the presence of trifluoroacetic acid (TFA) to give 2-(2-, 3-, and 4-substituted anilino)pyrimidines together with 2-aminopyridine and biphenyl or diarylmethanes. Here the key intermediate is also the 2-pyrimidynitrenium ion originating from the photochemical decomposition of an imidoil azide. This ion, depending on the reaction conditions, is present either in the singlet or triplet state and this governs the composition of the products (Scheme 11) <1998JPO478>.



Scheme 11

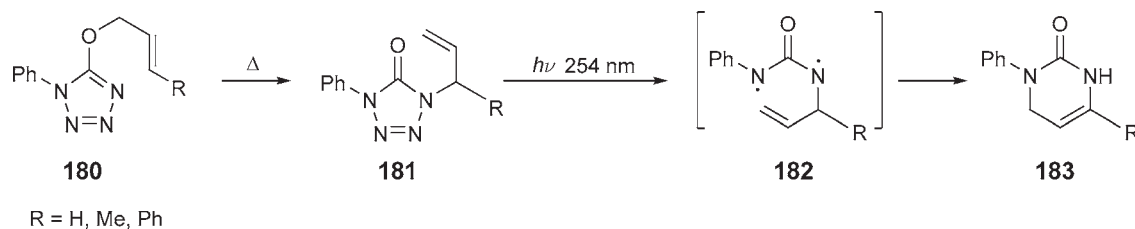
The results of a study of the flash vacuum thermolysis (FVT) of 2-(5-tetrazolyl)quinoline and 1-(5-tetrazolyl)isoquinoline **176** have been summarized <2004JOC2033>. By various methods, in particular, by ¹³C labeling experiment with 1-(5-tetrazolyl)-5-¹³C isoquinoline **176**, the tetrazole ring was shown to lose two nitrogen molecules under FVT conditions furnishing carbene **177**. Carbene **177** at 400 °C affords 2-aminonaphthalene **179** and other compounds (not shown in the scheme) expected from 2-naphthylnitrene **178** (Scheme 12) <2004JOC2033>.



Scheme 12

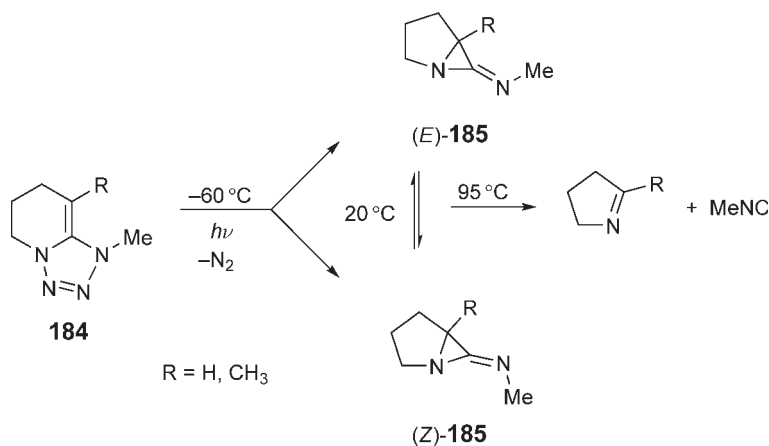
A series of investigations by Cristiano *et al.* were directed to special features of the thermal decomposition and photochemical behavior of 5-oxytetrazole derivatives **65** <1996J(P1)1453, 1997JCM164, 1997J(P2)489, 2002MI213, 2005PCA7967, 2005JPH243, 2006JOC3583>. On heating, 1-phenyl-5-allyloxytetrazoles **180** isomerize to the

corresponding 4-allyl-tetrazolones **181**. Photolysis (λ 254 nm) of 4-allyltetrazolones **181** was carried out in methanol, 1-propanol, 1-hexanol, acetonitrile, and cyclohexane. The photocleavage of 4-allyltetrazolones probably leads to a caged triplet radical pair **182**. The only primary photochemical process identified was molecular nitrogen elimination with formation of pyrimidinones **183** (Scheme 13) <2006JOC3583>.



Scheme 13

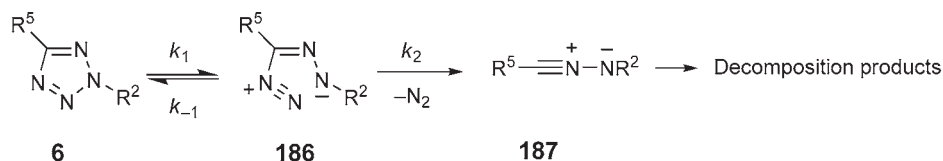
A study by Quast *et al.* on photochemical synthesis of iminoaziridines **185** from 5-alkylidendi-hydro tetrazoles **184** should be mentioned <1998EJO317>. The irradiation ($\lambda \geq 320$ nm) of compound **184** (R = H) in [*d*₈]-toluene at -60°C afforded exclusively product (*E*)-**185**, while a mixture of isomers (*E*)- and (*Z*)-**185** (66:34) was obtained at 20°C through diastereoisomerization of the initially formed (*E*)-**185** (Scheme 14) <1998EJO317>.



Scheme 14

6.07.5.2.2 Fragmentations of 2-substituted tetrazoles

The kinetic parameters of thermal decomposition of several 2,5-disubstituted tetrazoles **6** in the gas phase and in nitrobenzene solution have been determined using manometric methods. Limiting stages of the stepwise unimolecular decomposition that determine the experimental rate of nitrogen evolution include reversible formation and subsequent breakdown of the azo-diazo intermediates **186** (Scheme 15) <1996RCB2094>.



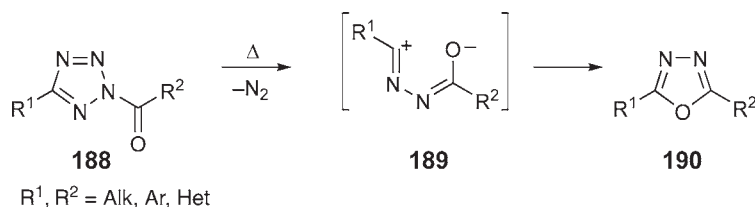
Scheme 15

2,5-Disubstituted tetrazoles **6** are usually less stable than 1,5-disubstituted tetrazoles **5** <B-1996MI87> (Table 23). This is due to three main reasons: (1) an energy barrier decrease in the initial stage of transformation molecule **6** into intermediate **186**; (2) a high rate of conversion of azo-diazo intermediate **186** into nitrile imine **187**; (3) nitrile-imine **187** formation does not require a skeleton rearrangement which is unavoidable in transformations involving nitrenes of the type **171** (Scheme 9, Section 6.07.5.2.1) <B-1996MI87>.

Table 23 Kinetic parameters of the thermal decomposition of 2,5-disubstituted tetrazoles <B-1996MI87>

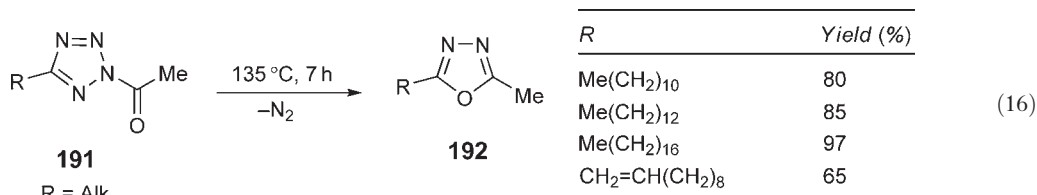
R^5	R^2	Gas phase or nitrobenzene solution	Decomposition interval ($^{\circ}\text{C}$)	E (kcal mol $^{-1}$)	$\lg A$ (s $^{-1}$)
Me	Me	Gas	190–260	42.2	15.01
Me	Me	Nitrobenzene	170–220	42.4	14.78
CH $_2$ =CH	Me	Gas	210–250	43.0	15.38
Ph	Me	Gas	190–240	42.4	15.29
Ph	Me	Nitrobenzene	180–230	42.0	14.85
Me	CH $_2$ COCH $_3$	Nitrobenzene	190–230	39.9	14.97
Me	CH $_2$ COCH $_3$	Gas	160–210	42.2	14.82
Ph	NH $_2$	Nitrobenzene	150–190	38.8	15.35
NO $_2$	CH $_2$ COCH $_3$	Gas	180–250	36.7	13.19

Further transformations of the nitrile imines **187** depend on a combination of factors: reaction temperature, solvent, and the character of the R^2 -substituent. Introduction of electron-withdrawing substituents into position 2 of the tetrazole ring decreases the energy barrier of the transition of **6** into **186** (Scheme 15), leading to destabilization of the tetrazole ring. For instance, for 2-picryl-5-nitrotetrazole ($E = 34.1$ kcal mol $^{-1}$), the decomposition interval is 75–95 $^{\circ}\text{C}$ <B-1996MI87>. This behavior provides the possibility of using the decomposition process of N^2 -substituted tetrazoles with electron-withdrawing substituents on nitrogen in synthesis. For instance, thermal decomposition of 2-acyl tetrazoles **188** is one of the most efficient procedures for the preparation of 2,5-disubstituted-1,3,4-oxadiazoles **190**. The latter arise from electrocyclization of the intermediate dipolar ions **189** (Scheme 16) <1999IJB188, 1999S999, 2001JMP1069, 2003S899>.

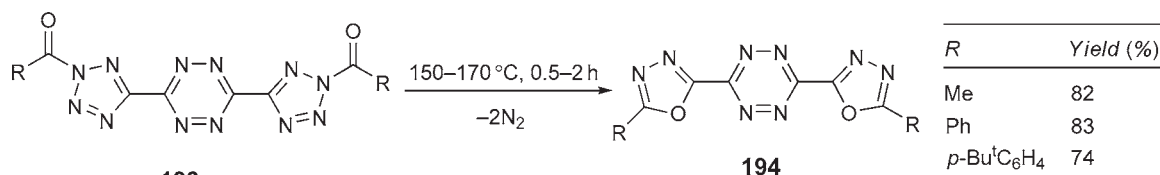


Scheme 16

This reaction has been widely applied to the synthesis of 1,3,4-oxadiazoles; for example, the conversion of 2-acetyltetrazoles **191** leads to the formation of 2,5-dialkyl-1,3,4-oxadiazoles **192** in good yield (Equation 16) <2003EJO885>.



Under similar conditions, bisacyltetrazolyl tetrazines **193** are converted into bisoxadiazolyl tetrazines **194** (Equation 17) <2001EJO697>.

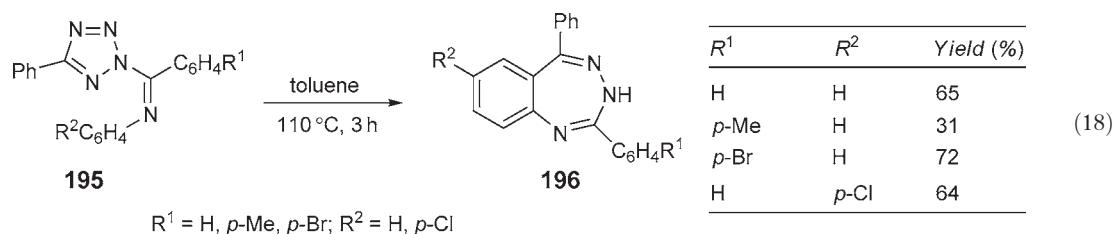


193
R = Alk, Ar

194

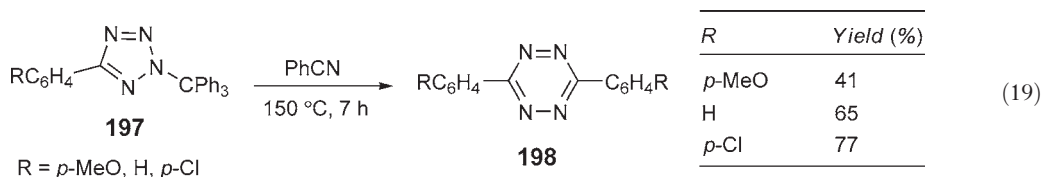
(17)

Systematic investigations of chemical behavior have been carried out on 2-imidoyltetrazoles, obtained *in situ* by acylation of N-unsubstituted 5-aryltetrazoles under PTC conditions. Thermal decomposition of 2-imidoyltetrazoles **195** afforded 3*H*-1,3,4-benzotriazepines **196** (Equation 18) in agreement with the mechanism shown in Scheme 15 <1994ACS596, 2003RJO611, 2003RJO1525, 2005RJO444>.



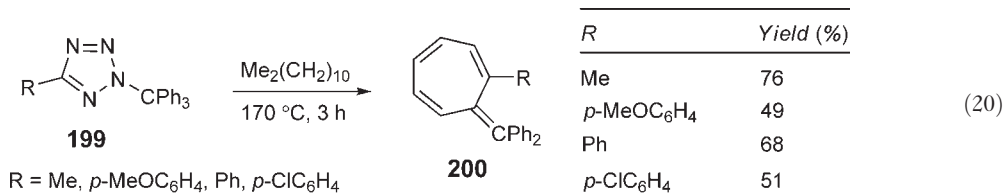
R¹ = H, *p*-Me, *p*-Br; R² = H, *p*-Cl

Although thermal decomposition of 2-trityl-5-aryltetrazoles **197** occurs specifically, the final result of the reaction may be ambiguous. For instance, these compounds on heating in benzonitrile give 3,6-diaryl-1,3,4,5-tetrazines **198**. Apparently the N₂ elimination in a polar solvent (benzonitrile) occurs with cleavage of triphenylmethane followed by dimerization of the intermediate aryl nitrile imine (Equation 19) <2002RJO1360>.



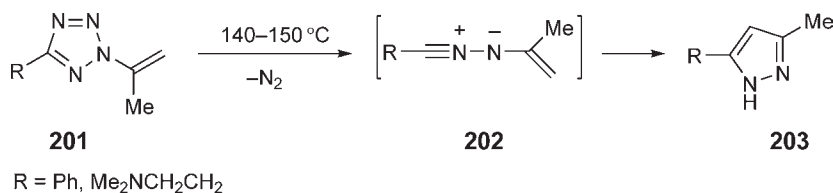
R = *p*-MeO, H, *p*-Cl

The heating in dodecane of 2-trityl-5-substituted tetrazoles **199** led to an unexpected result. Thermal decomposition of the tetrazoles **199** in nonpolar solvent is accompanied by a secondary process: a possible mechanism has been suggested <2002RJO1360>. It was established by X-ray diffraction analysis that the process results in formation in good yield of 1-substituted 8,8-diphenylheptafulvenes **200**, which lack any nitrogen atoms in their structure (Equation 20) <2002RJO1360>.



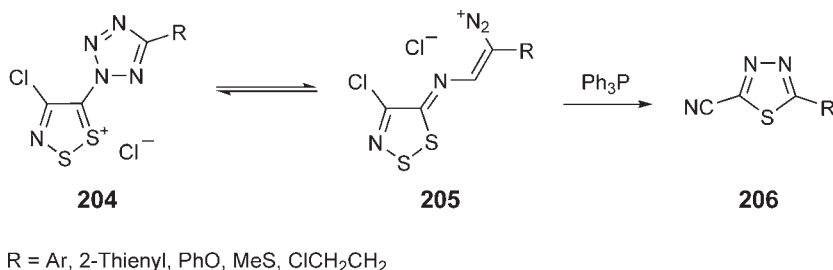
R = Me, *p*-MeOC₆H₄, Ph, *p*-ClC₆H₄

Thermal conversion of 5-R-2-isopropenyltetrazoles **201** to 5-R-3-methylpyrazoles **203** has been described <1997MC41>. The mechanism of the thermolysis apparently includes opening of the tetrazole ring with the elimination of nitrogen and formation of anitrile imine **202**, which is characteristic of 2,5-substituted tetrazoles (Scheme 17). The nitrile imine **202** then undergoes an intramolecular cyclization to give the pyrazole **203** (Scheme 17) <1997MC41, 2002CHE1422>.



Scheme 17

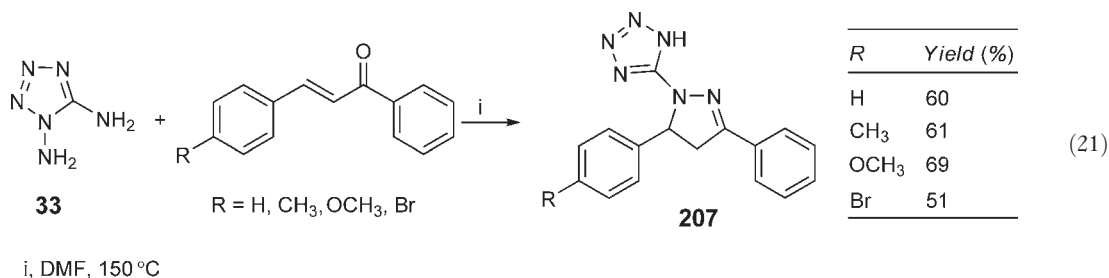
The opportunities inherent in ring transformations of the 2-substituted tetrazoles **6** are also demonstrated by the data in two publications <2000TL9407, 2002J(P1)1535>. Dithiazolium salts **204**, obtained by reacting 5-substituted tetrazoles **24** with 4,5-dichloro-1,2,3-dithiazolium chloride ('Appel salt'), give the hydrazonoyl chlorides **205**. Compound **205** is very reactive and is easily transformed into 2-cyanothiadiazoles **206** in high yield (Scheme 18) <2000TL9407, 2002J(P1)1535>.



Scheme 18

6.07.5.2.3 Rearrangements

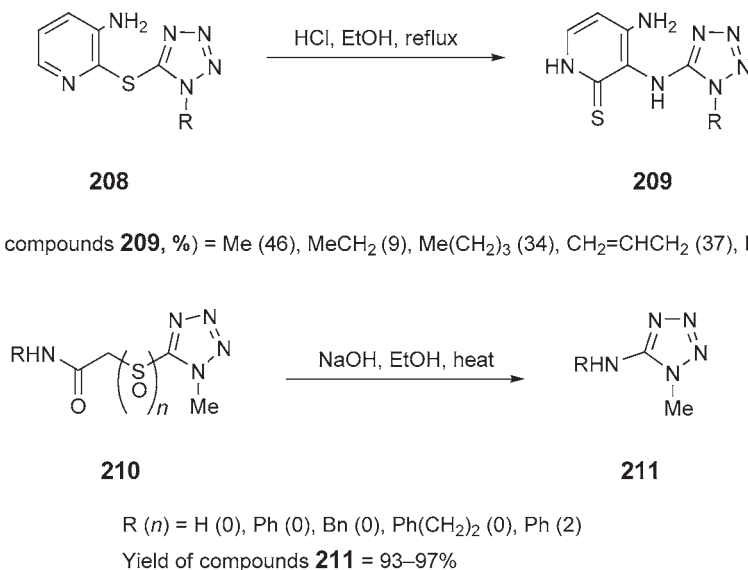
Examples of the Dimroth rearrangement involving substituted 5-aminotetrazoles, in particular, 5-hydrazinotetrazoles, have been reviewed <1996CHEC-II(4)621>, and a mechanism proposed. The attention of Brigas <2004SOS(13)861> was also focused on this process in the first part of his review where investigations on the isomerization of tetrazolamines by the Dimroth-type rearrangement were mentioned <1998AHC27, 1998JA4723>. An extension of the classical studies of the Dimroth rearrangement of aminotetrazoles has been published <2003CHE280, 2006JST(785)114, 2006S1307>. 1,5-Diaminotetrazole **33** upon reaction with chalcones (1,3-diphenylpropenones) in hot DMF undergoes Dimroth rearrangement to 5-tetrazolylhydrazine leading to formation of 1-(5-tetrazolyl)-3,5-diaryl-Δ²-pyrazolines **207** (Equation 21) <2006JST(785)114>.



This rearrangement proceeds via intermediate formation of 5-tetrazolylhydrazine, as confirmed by the synthesis of compounds **207** from 1,3-diphenylpropenones and the specially prepared 5-tetrazolylhydrazine <2006JST(785)114>.

A series of 5-aminoaryltetrazoles were obtained directly from the corresponding 1-aryl-5-aminotetrazoles by a one-pot sequential ring-opening, azidation, and intramolecular cyclization. 5-Alkylamino-1-aryltetrazoles are formed by a similar mechanism from 1,4-disubstituted tetrazolium salts. The influence of the aryl substituents and reaction conditions on the regioselectivity of the intramolecular cyclization of the intermediate guanyl azides was revealed <2006S1307>.

Publications on other types of rearrangements involving tetrazoles are cited at length in a review <2004SOS(13)861>; in particular, the Smiles rearrangement of 2-[(1-alkyl/aryl-1*H*-tetrazol-5-yl)sulfanyl]pyridine-3-amines **208** to 3-[(1-alkyl/aryl-1*H*-tetrazol-5-yl)amino]pyridine-2(1*H*)-thiones **209** under acidic conditions and Smiles rearrangement of 5-sulfanyl/sulfone-substituted tetrazoles **210** to tetrazol-5-amines **211** under basic conditions (Scheme 19) <2004SOS(13)861>.



Scheme 19

In the Brigas review <2004SOS(13)861>, examples of the Claisen-type rearrangement are also mentioned. On heating, 5-allyloxy- and 5-(allylsulfanyl)tetrazoles **212** undergo a concerted [3,3]-sigmatropic shift to give the 1-allyltetrazolone and the corresponding thiones **213** (Equation (22); Table 24).

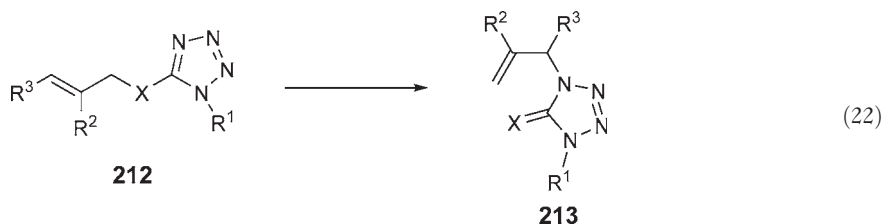


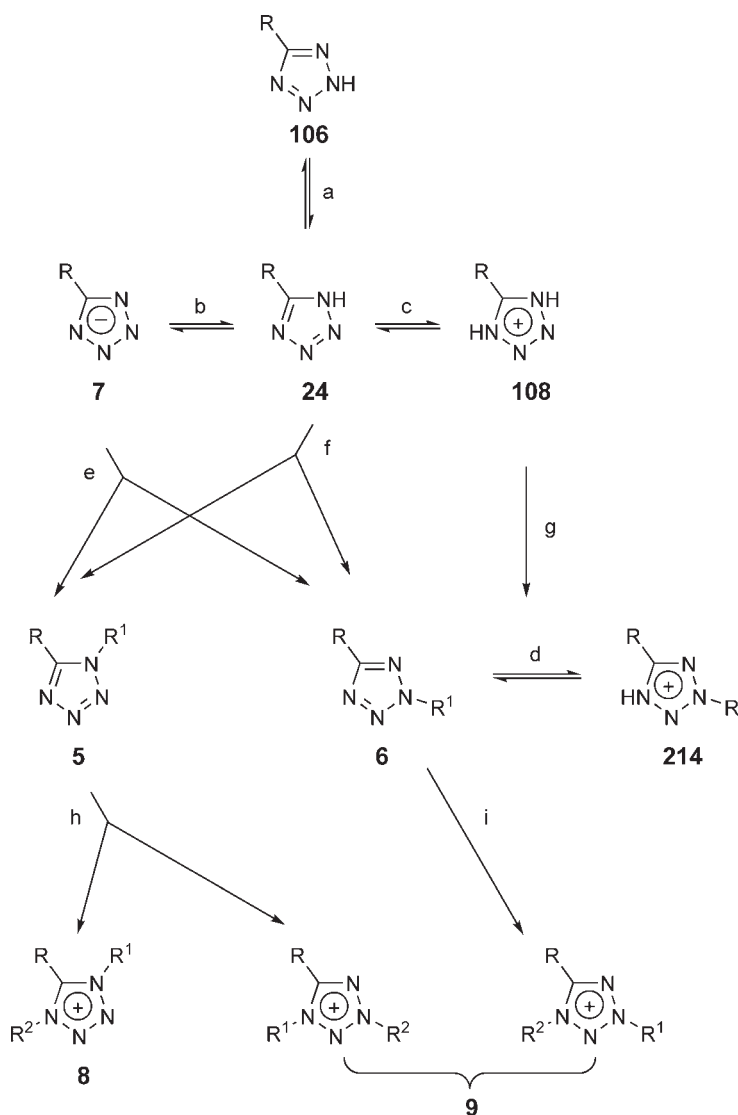
Table 24 Claisen-type rearrangement of tetrazoles (Equation 22) <2004SOS(13)861>

X	R ¹	R ²	R ³	Conditions	Yield (%)
S	Bu ^t	H	H	PdCl ₂ (NCPH) ₂ , benzene, 80 °C, 5 d	74
S	Me	H	H	PdCl ₂ (NCPH) ₂ , benzene, 80 °C, 8 d	82
O	Bu ^t	H	H	PdCl ₂ (NCPH) ₂ , benzene, 111 °C, 102 h	83

Thermal and photochemical conversion of 4-allyltetrazolones via concerted Claisen-type isomerisations have been studied in detail, including a series of works by Cristiano *et al.* <1997J(P2)489, 1997JCM164, 2002J(P1)1213, 2005TL6757>. Early <1990T633> and relatively recent <2003RJC275, 2001RJO1771, 2000JOC7284> publications on migrations from N-1 to N-2 in tetrazoles via an ionic dissociation–recombination mechanism are reported in a review <2004SOS(13)861>. An early article by Pleniewicz and Roszkiewicz on thermal rearrangement of 5-substituted-1-alkoxytetrazoles leading to 5-substituted-3-alkyltetrazole 1-oxides <1993PJC1767> should be noted. For more complete information, the reader should consult a review <2004SOS(13)861> and the cited original publications.

6.07.5.3 Electrophilic Attack at Endocyclic Nitrogen Atoms

Introduction of an appropriate N-substituent into an existing tetrazole ring is the most common and facile pathway to N-substituted tetrazoles **5**, **6**, and **31** and 1,4- and 1,3-substituted tetrazolium salts **8** and **9** <1996CHEC-II(4)621>. Some compounds, such as 2-alkyltetrazoles **6**, can still only be synthesized in practice by this approach <1976ZC90>. Apart from an enormous variety of alkyl substitutions, many other groups can be introduced by electrophilic reactions at nitrogen of the tetrazole ring, including acyl, imido, silyl, phosphoryl, sulfonyl, aryl, vinyl, and amino functions. A review <2000H(53)1421> summarizes studies on N-alkylation published before 2000, including addition to multiple bonds and other electrophilic reactions widely used in syntheses of N-substituted tetrazoles. As shown in **Scheme 20**,



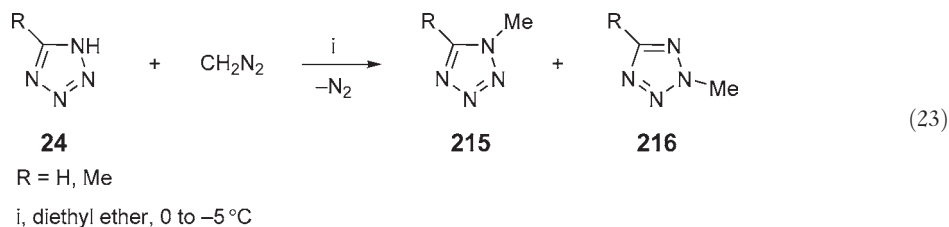
Scheme 20

all possible forms of existence of N-unsubstituted tetrazoles **24** and **106**, as well as N-substituted tetrazoles **5** and **6** (cf. Sections 6.07.1.3 and 6.07.4.4.1), are capable of reacting with electrophiles. Evidently, the efficient use of this reaction for the synthesis of target compounds can be attained only through an understanding of the regular trends, which govern reactivities of both tetrazole substrates and electrophilic reagents, and regioselectivity of the process (Scheme 20) <2000H(53)1421>.

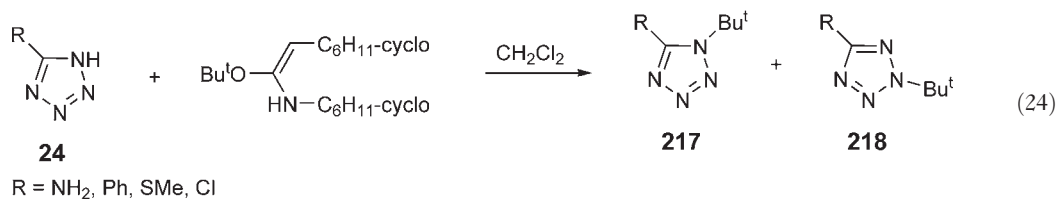
6.07.5.3.1 Reactivity of neutral tetrazoles

Reactions discussed below are represented in a generalized form by route f in Scheme 20. The exact nature of the tetrazole substrates undergoing electrophilic attack in these processes is as yet unknown. These reactions are grouped into this section based on the fact that under the conditions employed N-unsubstituted tetrazoles exist predominantly as nonionized species.

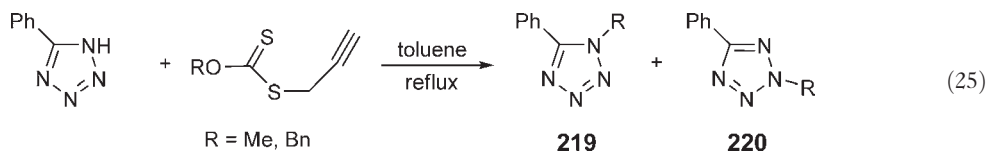
Alkylation of N-unsubstituted tetrazoles with diazomethane. N-Unsubstituted tetrazoles **24** react with diazomethane providing isomeric 1- and 2-methyltetrazoles **215** and **216** in a ratio close to that observed in alkylation of the respective tetrazolates with dimethyl sulfate or methyl iodide (Equation 23) <2000H(53)1421>. A possible reason for this similarity is that a (fast) proton transfer from the heterocyclic NH-acid (cf. Section 6.07.5.3.2) to diazomethane occurs in the first stage. Then, in the rate-limiting stage, the resulting tetrazolate anion reacts with the protonated diazomethane. Unfortunately, a detailed study of this reaction presents experimental difficulties since the determination of diazomethane concentration in solutions is always troublesome.



Alkylation of N-unsubstituted tetrazoles **24** with *O-tert*-butyl-*N,N'*-dicyclohexylisourea provides mixtures of isomeric 1- and 2-*tert*-butyltetrazoles **217** and **218** and seems to be the only practical method for synthesis of 1-*tert*-butyltetrazoles. The isourea is prepared by a preliminary reaction of *tert*-butyl alcohol with *N,N*-dicyclohexylcarbodiimide in the presence of a catalytic amount of copper(I) chloride (Equation 24) <1976JHC391>.

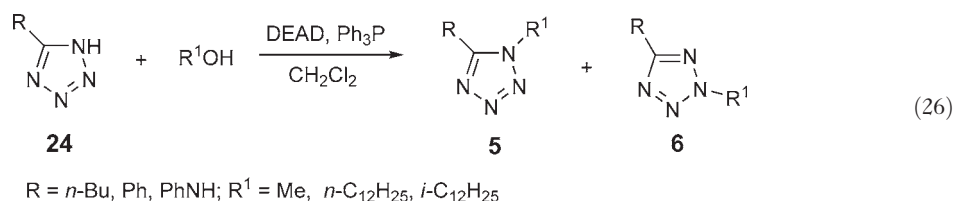


O-Alkyl-*S*-propargyl xanthates (dithiocarbonates) have been reported as useful esterification reagents capable of reacting with NH-acids <2000H(53)1421>. This was demonstrated by the methylation <1994JA9739> and benzylation <1998TL7301> of 5-phenyltetrazole. Methylation gave a 1:7 mixture of 1- and 2-substituted 5-phenyltetrazoles **219** and **220** (R = Me) <1994JA9739>, whereas the only reaction product detected on benzylation was the corresponding 2-alkyl derivative **220** (R = Bn) (Equation 25) <1998TL7301>.

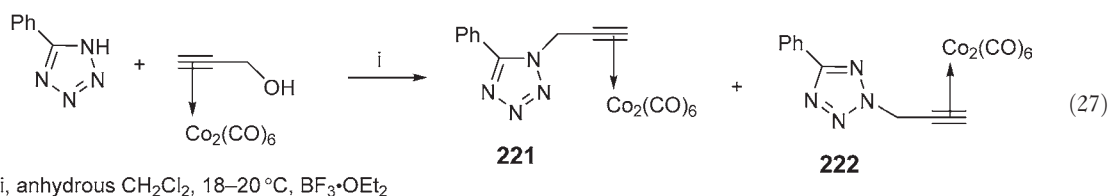


Alkylation of N-unsubstituted tetrazoles with alcohols can be performed under a variety of conditions. Alcohols that readily generate carbocations in the presence of acidic catalysts react with N-unsubstituted tetrazoles yielding mixtures of N¹- and N²-alkylated products. The reaction can be carried out in a neutral organic solvent (chloroform, dichloromethane, acetonitrile, nitromethane) in the presence of catalytic amounts of sulfuric, *p*-toluenesulfonic, or

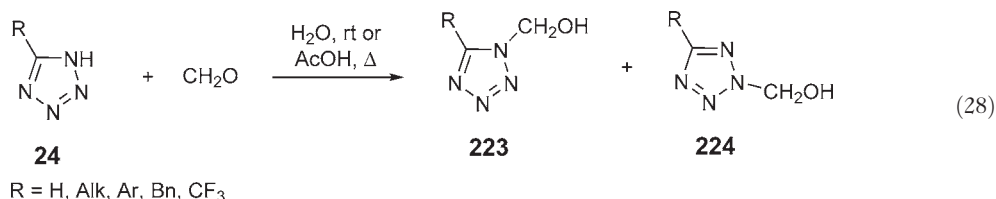
Lewis acids, such as boron trifluoride etherate, zinc triflate <2000H(53)1421>. N-Unsubstituted tetrazoles **24** can be alkylated with primary aliphatic alcohols using the Mitsunobu protocol (Equation 26) <1996SC2687>.



Direct comparison of preparative yields of products **5** and **6** from Mitsunobu alkylation and from reaction of triethylammonium salts of the same tetrazoles with the respective alkyl bromides showed that both processes gave the two isomeric products **5** and **6** in similar ratios. In the case of secondary alkyl groups, alkylation with alcohols provided notably higher overall yields <1996SC2687, 2000H(53)1421>. Metallopropargylation of tetrazole and 5-phenyltetrazole with hexacarbonyldicobalt-1-propynol in the presence of BF₃·OEt₂ has been studied <2001RJO1194>. The metallopropargylation of 5-phenyltetrazole led to compound **221** and the yield of isomer **222** did not exceed 10% (Equation 27) <2001RJO1194>.

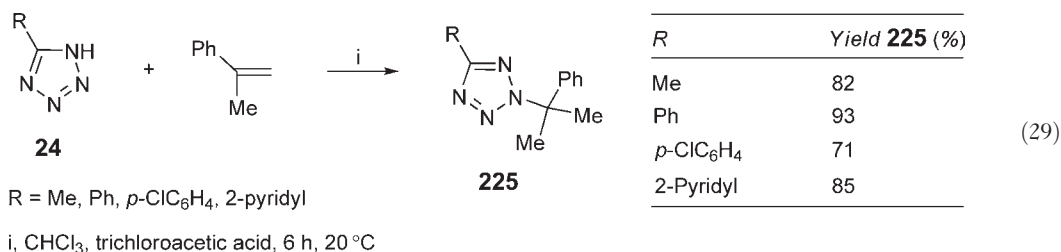


Hydroxymethylation of N-unsubstituted tetrazoles. N-Unsubstituted tetrazoles react slowly with formaldehyde in aqueous solution at pH 5 to produce mixtures of 1- and 2-hydroxymethyl derivatives **223** and **224** <2000H(53)1421>. The use of acetic acid as the reaction medium shortens the reaction time and relieves the problems of solubility (Equation 28) <1997RJO524>.

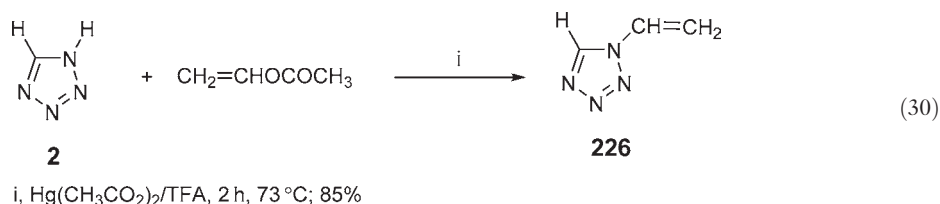


The true regioselectivity of the process could not be evaluated since individual isomers **223** and **224** are capable of interconversion and exist in solution in dynamic equilibrium <1997RJO524>. In contrast, the hydroxymethylation of 5-nitrotetrazole (37% formaldehyde, dilute H₂SO₄, 5–10 °C, 24 h) afforded a single isomer **224** (R = NO₂) in 67% yield <1997RJO1771>.

Reaction of N-unsubstituted tetrazoles with unsaturated reagents. Interaction of 5-substituted tetrazoles **24** with α-methylstyrene in the presence of trichloroacetic acid gives the corresponding 2-(α,α-dimethylbenzyl)tetrazoles **225** in high yield and high regioselectivity (Equation 29) <1999JOC9301, 2004RJO551>.



A regioselective synthesis of 1-vinyltetrazole **226** occurred by a vinyl exchange reaction. The process was promoted by mercury(II) acetate–TFA (Equation 30) <2002RJO1056>.



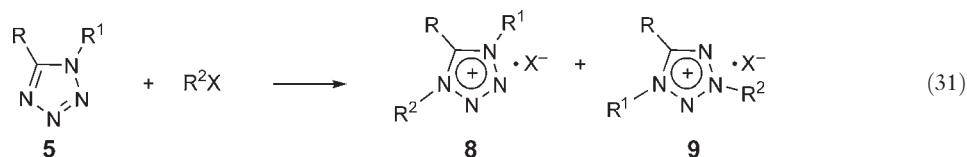
A regioselective synthesis of *N*¹-methyl tetrazole by alkylation of an unsubstituted tetrazole ruthenium complex with MeI has also been reported <2001JCD3154>.

Acylation with acetic anhydride. 5-Unsubstituted tetrazoles are converted into corresponding unstable 2-acyl tetrazoles by heating in acetic anhydride <2003EJO885> or acetic anhydride–pyridine <2003MI433>. As a result of *in situ* thermal decomposition of 2-acyl tetrazoles, the corresponding 1,3,4-oxadiazoles are obtained (cf. Section 6.07.5.2.2, Equation 16).

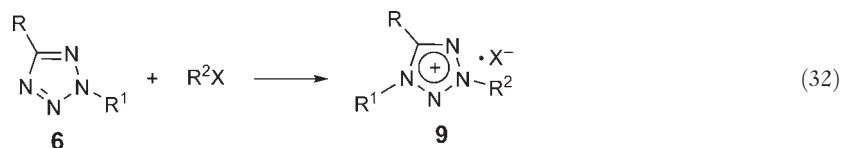
Acylation with the acylium ion in the gas phase. An unusual experiment was performed by Seldes *et al.* <2001OMS1069>. The *N*²-tautomeric form of a 5-substituted tetrazole was reacted in the gas phase with an acyl ion generated as the secondary reactive chemical by ionization plasma in a mass spectrometer. It was suggested that the mechanism of this process involved the formation of an acylated tetrazole intermediate, which could not be isolated in a condensed phase, and by rearrangement with nitrogen loss afforded an oxadiazole <2001OMS1069> (cf. Section 6.07.5.2.2, Equation 16). This experiment has no preparative value but provides important information on the interaction mechanism between the neutral N-unsubstituted tetrazoles and electrophilic agents in the gas phase.

*Acylation with the chloroacetyl chloride in *o*-xylene.* 5-Aryl- and 5-heteryltetrazoles react with chloroacetyl chloride in *o*-xylene (30–40 °C) to form 5-aryl-2-chloromethyl-1,3,4-oxadiazoles, 2-chloromethyl-5-(1,5-dimethyl-2-pyrrolyl)-1,3,4-oxadiazole, and 2-chloromethyl-5-(5-methyl-2-furyl)-1,3,4-oxadiazole in 80–93% yields (cf. Section 6.07.5.2.2, Equation 16) <2005RJA773>.

Alkylation of N-substituted tetrazoles. This reaction gives tetrazolium salts (routes h and i in Scheme 20) and hence is referred to as exhaustive alkylation. At present, an understanding of the mechanism(s) of this process is far from complete. However, one can find some parallels between exhaustive alkylation and protonation of N-substituted tetrazoles (cf. Section 6.07.4.5.2). The exhaustive alkylation of *N*¹-substituted tetrazoles **5** generally produces mixtures of isomeric 1,4-substituted **8** and 1,3-substituted **9** tetrazolium salts (Equation 31).



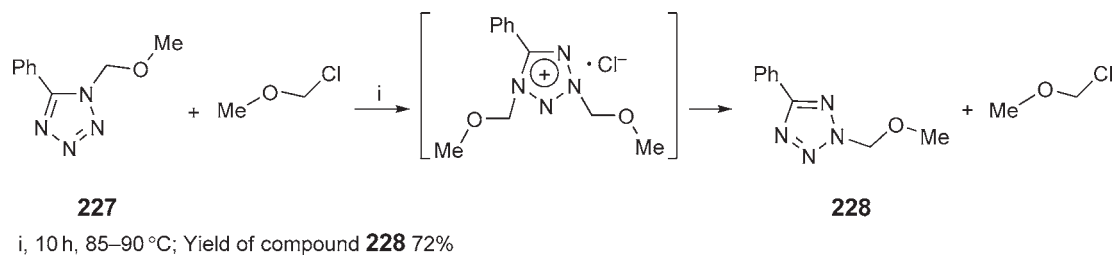
Unlike *N*²-substituted tetrazoles **6** can be alkylated only at position 4 of the ring to give 1,3-substituted tetrazolium salts **9** (Equation 32).



The research results on this subject published before 2001 (122 references) have been generalized in a review <2002RCR721>. We discuss below only studies demonstrating the use of the alkylation of N-substituted tetrazoles for the so-called ‘isomerization’. The procedure for interconversion of the N-substituted tetrazoles via intermediate 1,3-substituted tetrazolium salts **9** is based on the pioneering work of Isida *et al.* <1971JOC3807>. Myznikov *et al.* <2004RJO551> revealed that heating 1-methoxymethyltetrazoles **227** in methyl chloromethyl ether for 8–10 h at 85–90 °C resulted in their ‘isomerization’ into 2-methoxymethyltetrazoles **228**. This may be rationalized by the mechanism shown in Scheme 21 <2004RJO551>.

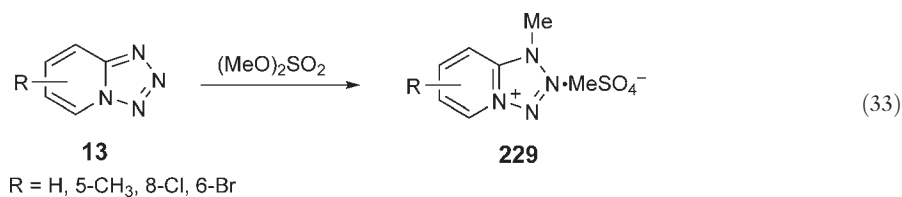
The reaction of α -hydroxyferrocenylalkyl derivatives and vinylferrocene with 1,5-disubstituted tetrazoles in two-phase systems methylene chloride–aqueous HX (X = BF₄, ClO₄) gives a mixture of 1,3,5- and 1,4,5-trisubstituted tetrazolium salts, with the 1,3,5-isomers prevailing. The synthesized salts are readily dealkylated under the action of

bases to give the starting compounds <2002RJO912, 2003RJC1468>. Versions of this approach based on reactions between carbocations and tetrazolium cations are considered in Section 6.07.5.3.3.



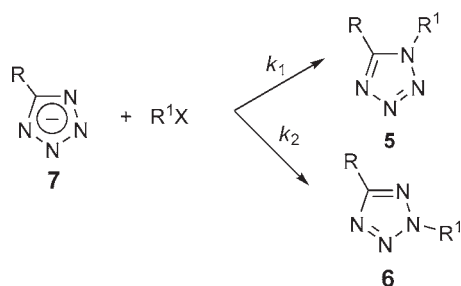
Scheme 21

Studies on reactions of fused tetrazoles with electrophilic agents are few, presumably due to the capability of these compounds to enter into various transformations <1998JPR687>. It was found <1999JST(477)119> that tetrazolo[1,5-*a*]pyridine **13** and its substituted derivatives undergo alkylation with dimethyl sulfate to give the *N*¹-methyl compounds **229** as the prevailing isomer. Only when R=H is a small amount of the *N*²-methyltetrazolo[1,5-*a*]pyridinium salt obtained (Equation 33) <1999JST(477)119>.



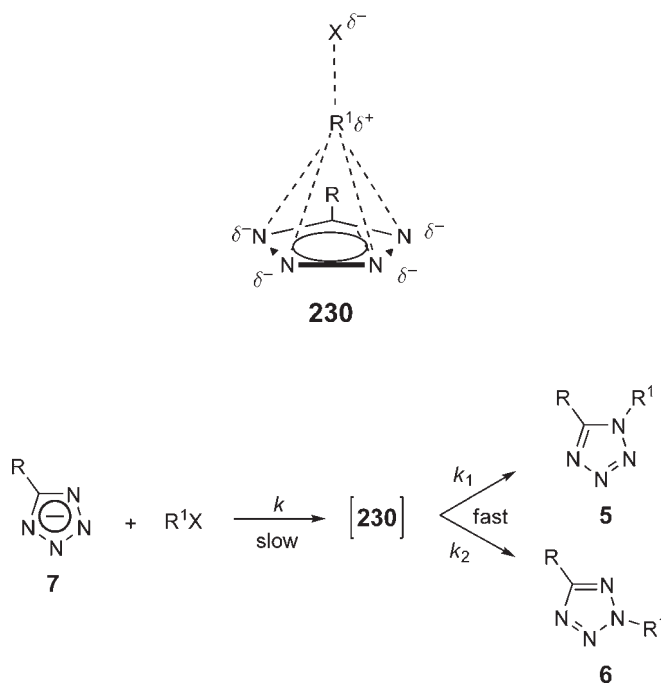
6.07.5.3.2 Reactivity of tetrazolate anions

Free tetrazolate anion. The central point in considering mechanisms of interaction of free tetrazolate anions **7** with electrophilic agents (route e in Scheme 20) is the regioselectivity of the process. The interpretation of the concurrent formation of isomers **5** and **6** has long been the subject of discussion. Authors of early publications believed that isomers **5** and **6** were formed by the substitution of a hydrogen atom in tautomers **24** and **106** (Scheme 20), respectively. This explanation collapsed when it was recognized that both tautomers dissociate in the presence of basic agents to form tetrazolate anions **7** that acted as the substrate for alkylation <2000H(53)1421>. It was suggested in CHEC-II(1996) <1996CHEC-II(4)621> that the isomers **5** and **6** result from a one-stage reaction of the ambident tetrazolate anions with the electrophile. In keeping with this suggestion, the regioselectivity of the alkylation is governed by the ratio of the rate constants k_1/k_2 of tetrazolate anion **7** reactions with electrophilic agents R¹X (Scheme 22) <2000H(53)1421>.



Scheme 22

However, later an alternative mechanism was established based on theoretical and experimental data that took into account the enhanced aromaticity of anion **7** (cf. Section 6.07.4.1). According to this mechanism, the interaction between tetrazolate anion and electrophile is a slow reaction stage of the multistep process. This bimolecular slow stage conceivably results in the formation of a labile intermediate **230**, which fast and irreversibly transforms into isomeric tetrazoles **5** and **6** (Scheme 23) <2000H(53)1421>.

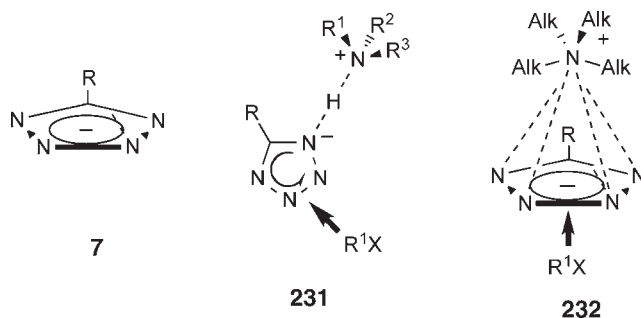


Scheme 23

In keeping with Scheme 23, the reaction rate is governed by the properties of the substituent R on tetrazolate anion **7**, by the reactivity of electrophilic agent R^1X , and by characteristics of the reaction medium. The formation of products, on the other hand, is controlled solely by the nature of intermediate **230**. The latter converts into isomeric N-substituted tetrazoles **5** and **6** via two parallel unimolecular processes (Scheme 23). The regioselectivity factor $\log F$ ($F = k_2/k_1$) was found to correlate linearly with $1/T$. The slope of this dependence was shown to be equal to $\Delta E = E_1 - E_2$, where E_1 and E_2 are activation energies of formation of isomers **5** and **6**, respectively <2000H(53)1421>. Structure of intermediate **230** was not elaborated in the publication cited, and Scheme 23 depicts a hypothetical structure proposed in a review <2000H(53)1421>.

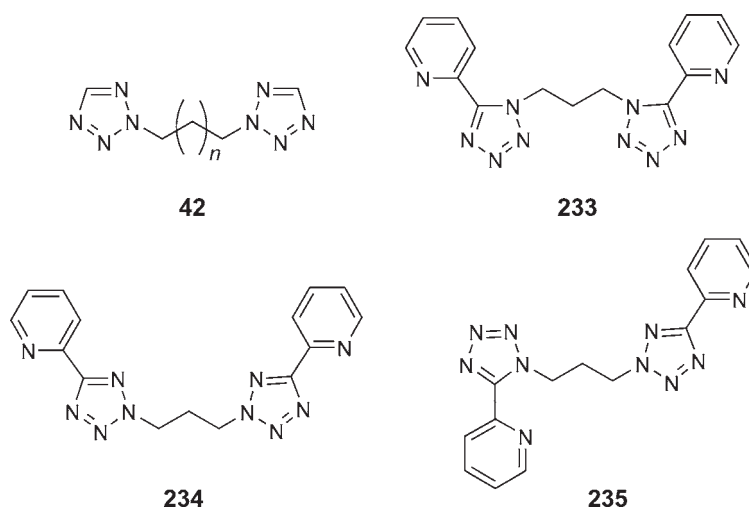
Within the framework of this mechanism of the electrophilic attack at endocyclic nitrogen atoms, it is possible to follow the effect of various factors on the rate and selectivity of the process. For instance, electron-withdrawing substituents on the carbon atom of the ring reduce the efficient charge on the endocyclic nitrogen atoms (cf. Section 6.07.2.1), leading to decrease in the reaction rate of anion **7** with R^1X . The electronic and steric effects of the R-substituents affect the ratio of isomers **5** and **6** during the fast transformation stage of intermediate **230** (Scheme 23). Electron-withdrawing substituents increase the relative yield of isomer **6** in the products. The yield of isomer **6** grows also with the bulk of the substituent at the carbon atom of the initial substrate. In contrast, higher temperature favors the greater yield of isomer **5** (Scheme 23) <2000H(53)1421>. In keeping with the discussed mechanism (Scheme 23), the specific solvation of anion **7** occurring in the reaction with electrophiles in water solution significantly decelerates the process but does not affect its regioselectivity <2000H(53)1421>.

Ion pairs and hydrogen-bonded species. Free tetrazolate anions **7** resulting from complete dissociation of salts of N-unsubstituted tetrazoles seldom exist under conditions of actual preparative experiments where ionic association must be taken into account, and the usual objects of an electrophilic attack are ion pairs of anion **7** and a metal cation, or ion pairs of the type **231** and **232** <2000H(53)1421>.

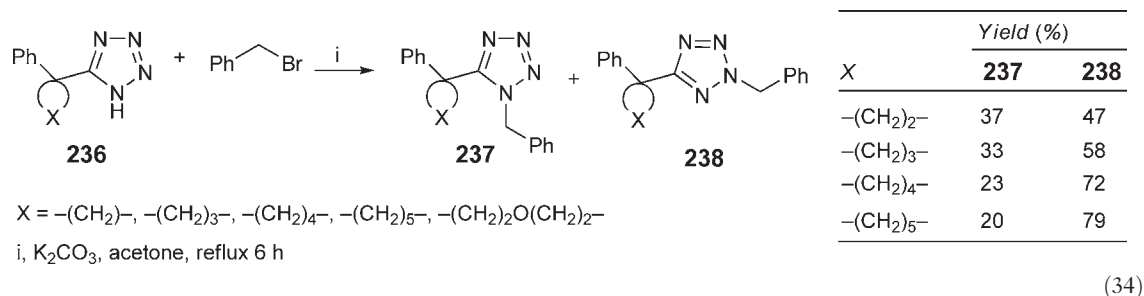


The change in the nature of the tetrazole substrate on going from tetrazolide **7** to contact ion pairs, solvent-separated ion pairs with a metal cation, to complexes of **231** and **232** type, etc., can result in deviations from the canonical mechanisms like those described above (Schemes 22 and 23). Also, the possibility cannot be excluded that the ion pairs formed by anion **7** react with the electrophile concurrently by several alternative pathways. We believe that just this versatility of reaction routes explains the difference between the predicted rate and selectivity of the electrophilic attack under 'ideal' conditions and the experimental result. In the light of these comments, new data on the application of ion pairs formed by anions of type **7** to the synthesis of N-substituted tetrazoles are discussed. As far as possible, attention is given to conclusions with respect to the regioselectivity of electrophile attack.

Reactions with sodium (potassium) salts, hydride, or hydroxide. Alkylation of tetrazole sodium salt with 1,3-dibromopropane <2004EJI3688> and 1,4-dibromobutane <2004ICA(357)396> in acetonitrile leads to formation of the corresponding bistetrazoles. Notwithstanding the prolonged (4 days) boiling of the reaction mixture, the yields of bistetrazoles **42** were 13% ($n=1$) and 10% ($n=2$). The low yields of compounds **42** and the prevailing formation of N²-isomers were caused apparently by the poor solubility of the tetrazole sodium salt in the organic solvent (the reaction rate was limited by diffusion), and also by the blocking of the N¹-atom by the metal cation within the tight ion pair 'tetrazolide **7**-Na⁺'. This assumption is supported by published data <2004JOC3212, 2004ICA(357)505> where the alkylation of the N-unsubstituted tetrazoles with an alkyl halide in an organic solvent was performed in the presence of potassium carbonate. Therewith the corresponding ion pairs are formed *in situ*, and electrophilic attack occurs under homogeneous conditions. The alkylation of the 5-(2-pyridyl)tetrazole with 1,3-dibromopropane in ethyl acetate in the presence of K₂CO₃ affords all three possible isomers of bistetrazoles **233–235** in a 1:1:1 ratio. All three regioisomers were isolated by column chromatography on silica gel <2004ICA(357)505>.

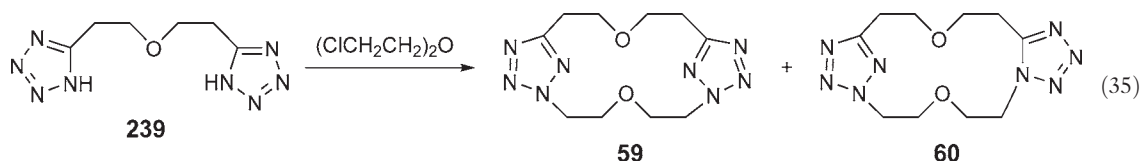


A systematic investigation has been published on the alkylation of 5-substituted tetrazoles **236** with benzyl bromide in acetone in the presence of K₂CO₃ <2006T1849>. It was established that the larger the ring in the substituent attached to the endocyclic carbon atom of the tetrazole, the higher was the yield of the N²-substituted tetrazole **238** (Equation 34).

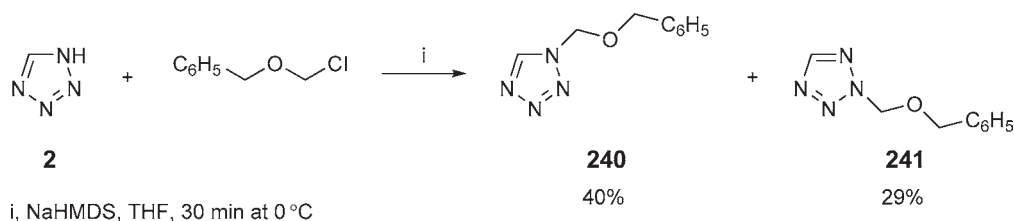


The alkylation of the [2-(1*H*-tetrazol-5-yl)benzyl]carbamic acid *tert*-butyl ester with MeI in DMF in the presence of K₂CO₃ has been studied [\[2004JME2995\]](#). A mixture of regioisomers was separated and purified by reverse-phase preparative HPLC. 2-(1-Methyl-1*H*-tetrazol-5-yl)benzylamine hydrochloride and 2-(2-methyl-2*H*-tetrazol-5-yl)benzylamine hydrochloride formed under these conditions in a ratio 1:1.5 [\[2004JME2995\]](#).

The alkylation of bistetrazole **239** with 2,2'-dichlorodiethyl ether under conditions of high dilution led to two isomeric crown-like macrocycles: 4,13-dioxo-1,7,8,9,17,18,19,20-octazatricyclo[14.2.1.1^{7,10}]icosa-8,10(20),16(19),17-tetraene **59** and 4,14-dioxo-1,7,8,9,10,18,19,20-octazatricyclo[15.2.1.1^{7,10}]icosa-8,10,17(20),18-tetraene **60** (Equation 35) [\[2001J\(P2\)417\]](#).



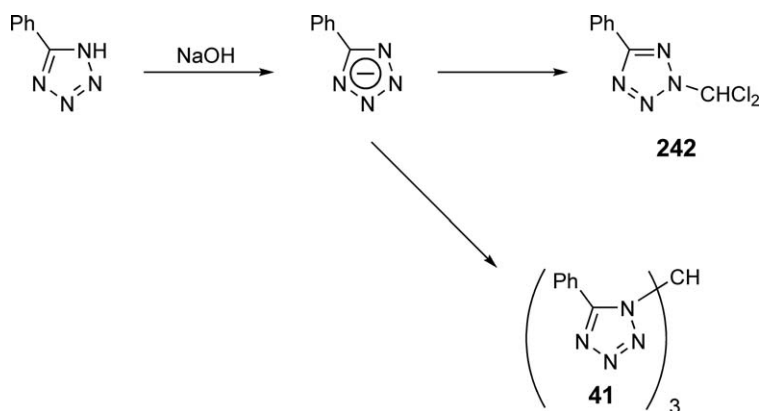
The generation of ion pairs from NH-unsubstituted tetrazoles has also been performed using sodium salts and sodium hydroxide. Tetrazole alkylation with benzyl chloromethyl ether in tetrahydrofuran (THF) in the presence of sodium hexamethyldisilazane (NaHMDS) has been reported [\[1995J\(P1\)1747, 1998SL528\]](#). Regioisomers **240** and **241** formed under these conditions in comparable amounts (Scheme 24) [\[1998SL528\]](#).



Scheme 24

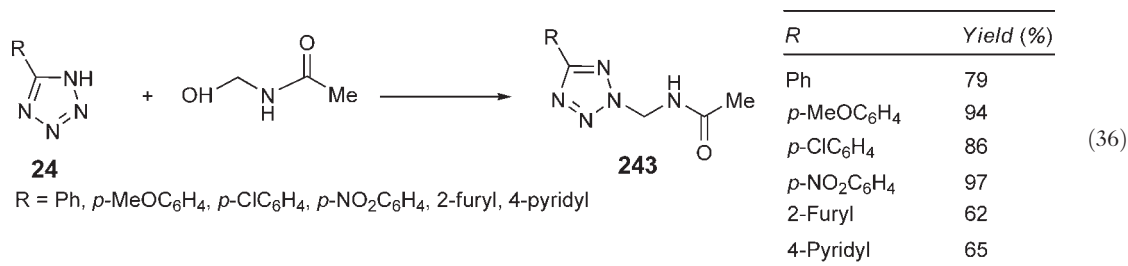
Apparently the tetrazole under the action of NaHMDS in THF formed *in situ* not a contact but a solvent-separated ion pair (tetrazolide **7**-Na⁺) that reacts with electrophilic reagents in conformity to the mechanism shown in Scheme 23.

Presumably the reactions involving NaH occur similarly. For instance, NH-unsubstituted tetrazoles react with 1-[2-(2,4-difluorophenyl)oxiranylmethyl]-1*H*-[1,2,4]-triazole in the presence of NaH in DMF for 4 h at 80 °C, with the opening of the oxirane ring giving a mixture of isomers with the N²-substituted tetrazole prevailing [\[2004EJM579, 2004BMC2225\]](#). Another example is the alkylation of 5-(3-phthalimido-4-pentenyl)-1*H*-tetrazole with MeI in THF in the presence of NaH (60% in mineral oil) to give 41% and 27% yields of N¹- and N²-methyl derivatives, respectively [\[2006BMC1331\]](#). 5-Phenyltetrazole in a two-phase system of aq. NaOH-CHCl₃ forms the 5-phenyltetrazolate anion, which reacts with chloroform to furnish two products, 2-dichloromethyl-5-phenyltetrazole **242** and tris(5-phenyltetrazole-1-yl)methane **41** (Scheme 25) [\[1997CHE364, 2007CHE320\]](#).



Scheme 25

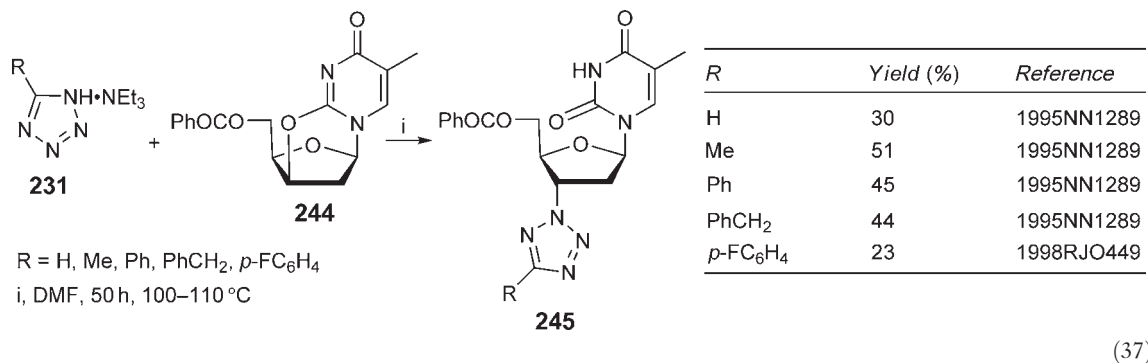
Amidoalkylation of 5-aryl(hetaryl)tetrazoles **24** with *N*-hydroxymethylamides of aliphatic and aromatic carboxylic acids occurs regioselectively and yields mainly 5-aryl(hetaryl)-2-acylaminoethyltetrazoles **243** (Equation 36) <2003RJO731>.



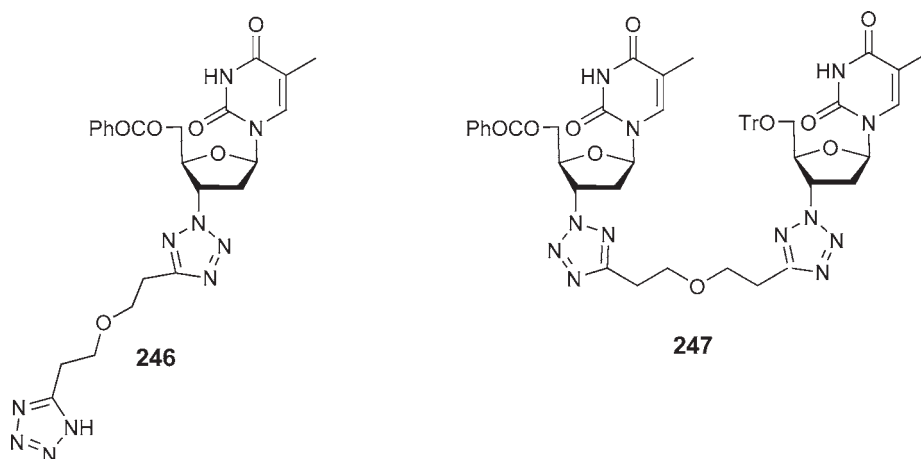
Taking into account the conditions of the process (heating of the reagents in the presence of NaOH and without solvent), it is presumed that amidoalkylation (Equation 36) involves an associated form (contact ion pair) of tetrazoles **24** sodium salts where the N¹-atom is blocked by the metal cation. The high regioselectivity of the electrophile attack is probably due to this circumstance. The reaction of 5-nitrotetrazole sodium salt tetrahydrate with *N*-hydroxymethylacetamide also led to the respective N²-isomer **243** (R = NO₂) as the major product. Here, however, the regioselectivity originated to a larger extent from the electron-withdrawing character of the substituent (nitro). Note that formation of the N²-isomers as the major products is characteristic of reactions with electrophilic reagents both of 5-nitrotetrazole and its salts and anion (alkylation and reactions such as Michael, Henry, Mannich, etc.) <1997RJO1771>.

Reactions with mono-, di-, and trialkylammonium salts 231. The association of ions in ion pairs, as well as specific solvation of tetrazolates, noticeably affects the rate and/or regioselectivity of the reactions under consideration. Unfortunately, reliable quantitative data on the rate and regioselectivity of reactions of ion pairs formed by tetrazolate anions and alkali metal cations are not available at present and generalizations drawn from the results of numerous preparative experiments may lead to misconceptions. This is especially true with regard to regioselectivity since the amounts and ratio of two isomeric products **5** and **6** isolated by distillation, fractional crystallization, or flash chromatography may not reflect the actual product ratio <2000H(53)1421>. Unlike the case of mono-, di-, and trialkylammonium salts **231**, reaction of tetraalkylammonium tetrazolate **232** yields isomeric products **5** and **6** in ratios analogous to those observed for the reactions of the same tetrazolates in the form of free anions. In the ion pair formed by tetraalkylammonium cation and tetrazolate anion, the cation is located over the plane of the ring <2000H(53)1421>. Mechanisms of electrophilic reactions involving ammonium or mono/di/trialkylammonium salts of *N*-unsubstituted tetrazoles seem to differ from those discussed above. In aprotic solvents, these salts exist as hydrogen-bonded complexes <2000H(53)1421> of the type **231** <2001RJO1767>. The electronic structure of

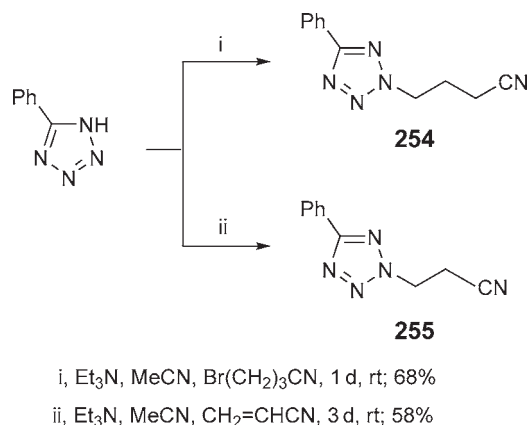
species **231** differs essentially from that of tetrazolates **7** either as free anions or in ion pairs because the aromaticity of the heterocycle is considerably disrupted due to the involvement of N-1 in the hydrogen bond <2001RJO1767>. It is quite possible that electrophilic attack of such substrates is directed frontally on the N(2)–N(3) bond rather than normally to the plane of the heterocycle, as it occurs in the case of highly aromatic tetrazolate anions **7** <2000H(53)1421, 2001RJO1767>. Research in recent years has frequently been directed to the application of reactions between substrates **231** and electrophilic reagents to give N-substituted tetrazoles. The regioselectivity of reactions involving mono/di/trialkylammonium salts of 5-monosubstituted tetrazoles **231** essentially depends on steric factors. More compact substituents at position 5 of the heterocycle afford both N¹- and N²-substituted tetrazoles **5** and **6** in comparable amounts <2000H(53)1421>. Unusually high regioselectivity was observed for the reaction of triethylammonium salts of tetrazole and 5-monosubstituted tetrazoles **231** with 5'-*O*-benzoyl-2,3'-anhydrothymidine **244**. The only products of these reactions were N²-substituted tetrazole derivatives **245** (Equation 37) <1995NN1289, 1998RJO449, 2000H(53)1421, 2001RJO759>.



The reaction of compounds **244** with triethylammonium tetrazolides **231** in DMF is described by a second-order kinetic equation, following first-order kinetics in each of the reactants. On the basis of experimental activation parameters ($\Delta H^\ddagger_{298} = 19 \text{ kcal mol}^{-1}$, $\Delta S^\ddagger = -28 \text{ cal mol}^{-1} \text{ K}^{-1}$), a mechanism was suggested where in the rate-determining stage triethylammonium tetrazolide **231** attacks the C-3 atom of 5'-*O*-benzoyl-2,3'-anhydrothymidine **244** with simultaneous loosening of the C(3)–O(2) anhydro bond (Equation 37) <2001RJO1767>. The above conditions (Equation 37) proved to be efficient also for the synthesis of mono- and bis-3'-substituted thymidine derivatives **246** and **247** with a polycyclic tetrazole linker (1,5-bis(tetrazol-5-yl)-3-oxapentane) <2002TL1901>.

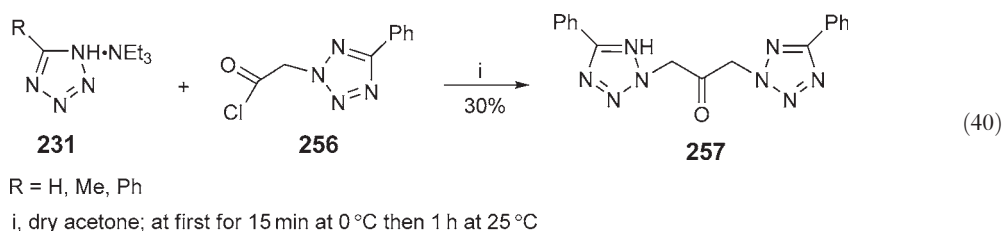


Reaction of triethylammonium tetrazolide **248**, obtained *in situ* from 1,3-deoxy-3'-(1*H*-tetrazol-5-yl)-5'-*O*-tritylthymidine and triethylamine, with 5'-deoxy-5'-iodothymidine led to 3'-deoxy-3'-[2-(5'-deoxythymidin-5'-yl)-2*H*-tetrazol-5-yl]-5'-*O*-tritylthymidine **249** (Equation 38) <2002HCA2847>.

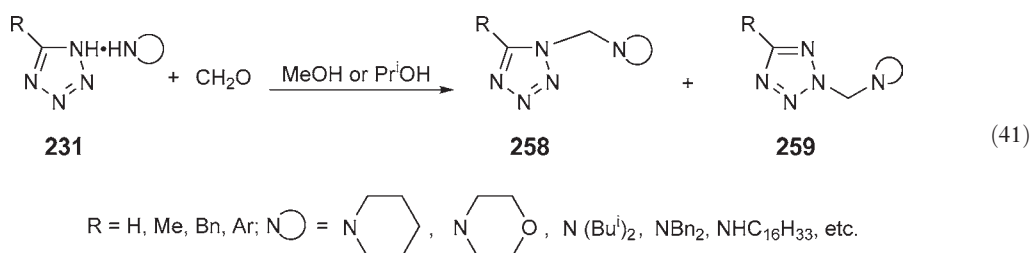


Scheme 26

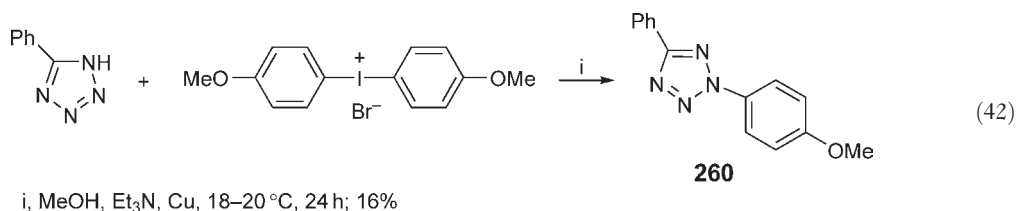
Ostrovskii *et al.* <1996MC24> described an unusual acylation reaction of tetrazole triethylammonium salts **231**: bis(5-phenyltetrazol-2-yl)acetone **257** was obtained by interaction of various tetrazole triethylammonium salts **231** with 5-phenyl-2-tetrazolylacetyl chloride **256**. The mechanism of the reaction is suggested to include a heterolysis of the *N*-acyl intermediate resulting in acyl cation formation followed by transacylation of the methylene group in the second molecule of the acyl halide (Equation 40) <1996MC24>.



A reaction specific for mono- and dialkylammonium salts of *N*-unsubstituted tetrazoles **231** is interaction with formaldehyde under mild conditions and leading to *N*-aminomethyltetrazoles **258** and **259** (Equation 41) <2000H(53)1421, 1997RJO524>.

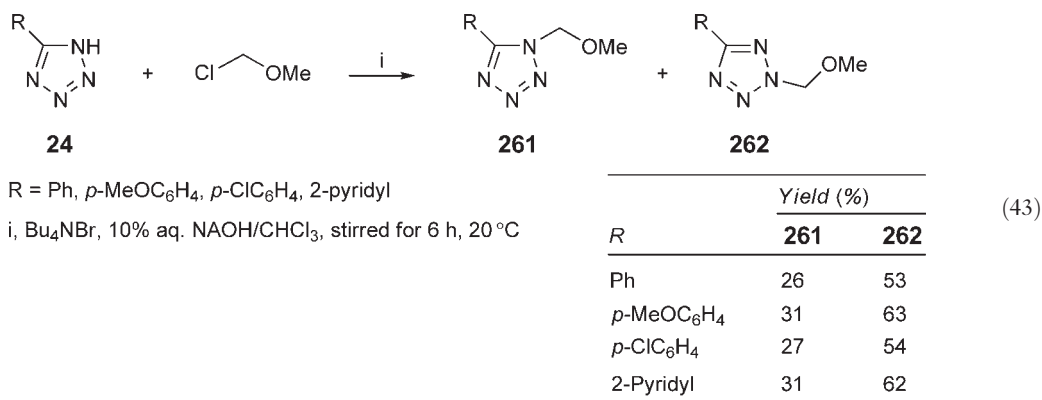


The *N*-arylation reactions are investigated more seldom than the *N*-alkylation ones. *N*-Arylation of 5-phenyltetrazole with bis-(4-methoxyphenyl)iodonium bromide in MeOH in the presence of Et₃N yielded only the *N*²-isomer **260** (Equation 42) <2001CHE372>.



The high regioselectivity of the N-arylation is due mostly to the specific features of hypervalent iodine compounds and not to the structure of triethylammonium tetrazolide **231**, etc. Thus the replacement of Et₃N–MeOH in the reaction (Equation 42) by K₂CO₃–DMF (room temperature) <2004JCR(S)404> and even by KOH–H₂O (100 °C) <2004CHE188> did not affect the regioselectivity of electrophilic attack. Similar results were obtained in the reaction of diaryliodonium salts with 5-aryltetrazoles in DMF in the presence of palladium and copper catalysts <2002TL6221>, and also in the arylation of 2-tributylstannyl-5-aryltetrazoles with diphenyliodonium chloride in CH₂Cl₂ in the presence of Cu(II) salts <2002TL6217>. An unusual N-arylation of tetrazole **2** with 1,4-dimethoxybenzene during undivided electrolysis has been described <2002RCB1523>. The procedure is claimed to be original but its applicability to the actual preparative synthesis of N-aryltetrazoles cannot be appreciated from the data published <2002RCB1523>.

Reactions with tetraalkylammonium salts 232. As already mentioned, the structure of tetraalkylammonium salts **232** does not sterically hinder the electrophilic attack, thus providing a possibility to form isomers **5** and **6** in agreement with the multistep mechanism through intermediate **230** (Scheme 23). Evidently this is the reason why the reactions of salts **232** commonly yield both isomers in a ratio depending on the electronic character and the bulk of the substituent attached to the carbon atom of the tetrazole ring <2000H(53)1421>. Salts **232** usually are formed *in situ* at the phase boundary or in the organic phase during alkylation and acylation of the N-unsubstituted 5R-tetrazoles **24** and 5-alkyl(aryl)sulfanyltetrazoles under conditions of PTC <1992ZOB3, 1994RCR797, 1994ACS596, 1997RJO1149, 2000H(53)1421, 2002RJO1360, 2003RJO611, 2003RJO1525, 2003RJO1679, 2004RJO447, 2004RJO551, 2005RJO444, 2006RJO494>. An example of such a process is the alkylation of 5-aryl(hetaryl)tetrazoles **24** with methyl chloromethyl ether in the presence of Bu₄NBr (Equation 43) <2004RJO551>.

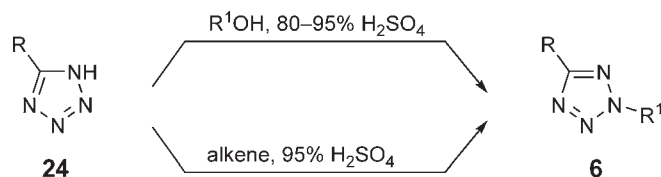


As seen from Equation (43), the yields of regioisomers in the alkylation of tetrabutylammonium tetrazolide **232** <2004RJO551> and those previously found in the reactions of free tetrazolide **7** with electrophilic reagents <2000H(53)1421> are in agreement. This result indirectly suggests the similarity of the mechanism of the electrophilic attack on both types of tetrazole substrates (Scheme 23). Only few examples of the arylation and hetarylation of tetrabutylammonium tetrazolide **232** have been reported. The hetarylation of tetrazole **2** with 2-cyano-3-fluoropyridine in DMF in the presence of tetrabutylammonium hydroxide (4 days, room temperature) has been described <2004JME2995>. As a result, the 3-tetrazol-1-yl-pyridine-2-carbonitrile was isolated in 12% yield <2004JME2995>. However, it is hard to appreciate from this experiment the efficiency and regioselectivity of the hetarylation of the tetrabutylammonium tetrazolide taking into account the difficulties in the separation and purification of the product <2004JME2995>.

6.07.5.3.3 Reactivity of tetrazolium cations

Formation of N²-alkyl derivatives as the only products from the reaction of N-unsubstituted tetrazoles with secondary and tertiary alcohols or the corresponding alkenes in sulfuric acid has been reported (Scheme 27) <2000H(53)1421>.

The reaction proceeded at room temperature to give 2-substituted tetrazoles **6** in nearly quantitative yield within a short time (≤1 h). No formation of N¹-alkylated products was detected regardless of electronic and spatial properties of the substituent at position 5 of the tetrazole ring. Conclusive evidence on the nature of N²-regioselective alkylation of tetrazoles was provided by subsequent kinetic studies <1993MI1043, 1995MI919> on the alkylation of 5-aryltetrazoles with isopropyl alcohol in sulfuric acid media. When considering possible mechanisms, it was taken into account that under the reaction conditions both N-substituted tetrazoles (TH) and alcohols are subject to protolytic equilibrium according to the equations shown in Scheme 28 <1993MI1043, 1995MI919, 2000H(53)1421>.

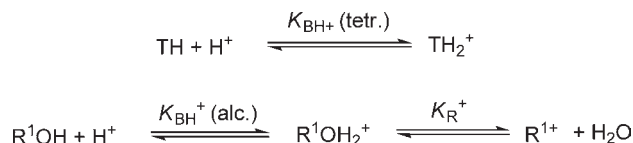


R = H, Alk, Ar, CF₃, etc.

R¹ = Prⁱ, Bu^t, *cyclo*-C₆H₁₁, etc.

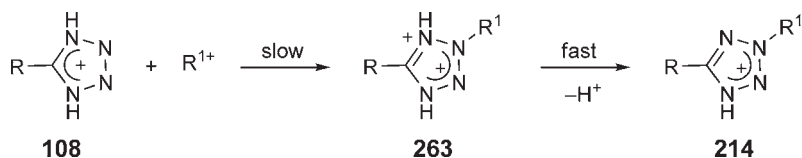
Alkene = CH₂=CHMe, CH₂=CMe₂, *cyclo*-C₆H₁₀, etc.

Scheme 27



Scheme 28

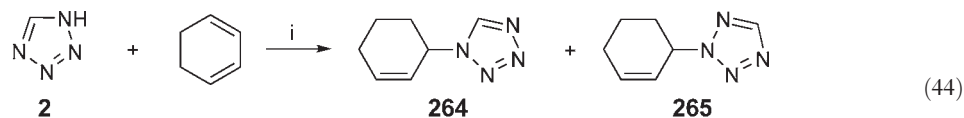
In these equations, TH is a nonionized tetrazole **24**, TH₂⁺ is a protonated tetrazole **108** (Scheme 20), R¹OH is an alcohol capable of forming a carbocation R¹⁺, K_{BH⁺}(tetr.) and K_{BH⁺}(alc.) are the basicity constants of TH and R¹OH, respectively, and K_R⁺ is the equilibrium constant for formation of the carbocation from the protonated alcohol R¹OH₂⁺. Since the reaction was found to be overall second order and first order with regard to either TH or R¹OH, the following assumptions on the interaction at the rate-limiting stage were tested: {TH + R¹OH}, {TH + R¹OH₂⁺}, {TH + R¹⁺}, {TH₂⁺ + R¹OH}, {TH₂⁺ + R¹OH₂⁺}, and {TH₂⁺ + R¹⁺}. Further analysis showed that the only assumption to fit the experimental kinetic data was {TH₂⁺ + R¹⁺}. It was therefore concluded that the two species interacting at the rate-limiting stage were protonated tetrazole and carbocation. Protonation of an N-unsubstituted tetrazole **24** is known to occur at position 4 of the heterocycle (cf. Sections 6.07.4.4.1 and 6.07.4.5.2) to give a symmetrical 1*H*,4*H*⁺-tetrazolium cation **108** (Scheme 20). In the latter atoms, N² and N³ are identical, and this distinctive feature results in the exceptional regioselectivity of the reaction (Scheme 29) <1993MI1043, 1995MI919, 2000H(53)1421>.



Scheme 29

Interaction of two positively charged entities seems rather unusual at the first sight; however, as revealed by quantum-chemical calculations for a series of 5-substituted 1*H*,4*H*-tetrazolium cations (cf. Section 6.07.2.1), these structures were characterized by a substantial electron density localized on atoms N-2 and N-3. Hence, it seems plausible that one of these atoms is attacked by the carbocation, which evidently is an extremely potent electrophile. The attack results in the formation of an unstable intermediate **263**. As follows from the analysis of the kinetic isotope effect observed in experiments employing the D₂SO₄-D₂O system <1993MI1043>, the process ends with a fast elimination of a proton from the intermediate to give protonated 2-substituted tetrazole **214** <2000H(53)1421>. Properties of N-substituted tetrazoles as weak bases were discussed previously (cf. Section 6.07.4.5.2). In terms of protolytic equilibrium (c, Scheme 20), this means that N-unsubstituted tetrazoles entering the reaction are completely protonated. Practically, this condition is achieved in the media of a sufficiently high acidity, like concentrated sulfuric or perchloric acids <1998RJO746>, where the ionization ratio $I = [\text{TH}_2^+]/[\text{TH}]$ is of the order of magnitude 10³ or higher. On the other hand, the same mechanism implies that should the medium acidity fail to provide the complete protonation of the tetrazole ring while still being sufficient for the generation of a carbocation, the reaction would have occurred at both the N¹- and N²-position (cf. Section 6.07.5.3.1). This inference was substantiated

experimentally by the results of alkylation of tetrazole with *tert*-butyl alcohol in phosphoric acid media where formation of both 1- and 2-*tert*-butyltetrazoles was detected. Moreover, it was shown that, in full agreement with the proposed mechanism, the fraction of the 1-isomer steadily grew with decreasing concentration of the phosphoric acid, that is, with decreasing extent of the tetrazole ring protonation <2000H(53)1421>. The alkylation of unsubstituted tetrazole in phosphoric acid with 1,3-cyclohexadiene also gives a mixture of 1- and 2-(2-cyclohexenyl) tetrazoles **264** and **265** in an overall 75% yield (isomer ratio ~1:2) (Equation 44) <2004RJO598>.

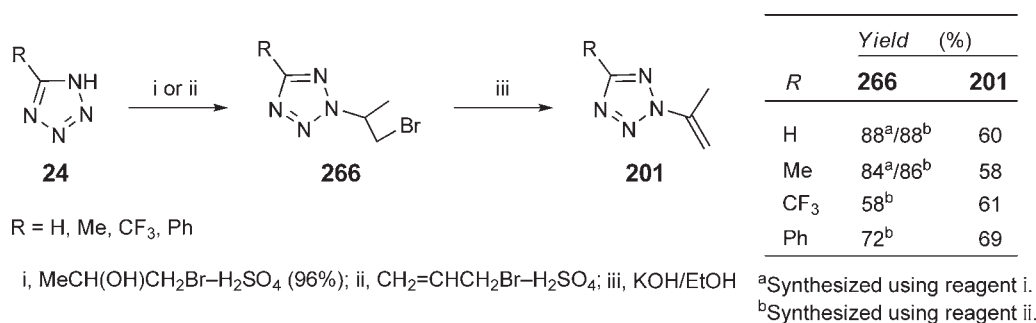


i, in 87% H₃PO₄, under stirring at rt, 30–40 min

The lack of selectivity in the reaction of unsubstituted tetrazole with 1,3-cyclohexadiene may be due to incomplete protonation of the substrate <2000H(53)1421>, as well as to the isomerization of the initially formed 2-substituted tetrazole **265** to the 1-substituted compound **264**. Analogous isomerizations were reported for 2-*tert*-butyltetrazole <1998RJO746> and 2-(1-adamantyl)tetrazole <1997RJO571>. It was shown that pure tetrazole **265** in 87% phosphoric acid was slowly converted into isomer **264**. After 4 days at room temperature, the isomer ratio **265**: **264** was ~1:2.3 <2004RJO598>.

It should be noted that when the reaction of 1,3-cyclohexadiene was carried out not with unsubstituted tetrazole but with 5R-tetrazoles **24** (R = Me, Ph, CN₄HCH₂CH₂), only the corresponding 2,5-disubstituted tetrazoles were isolated from the reaction mixture <2004RJO598>.

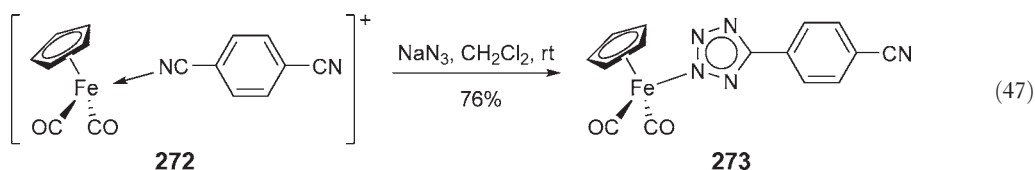
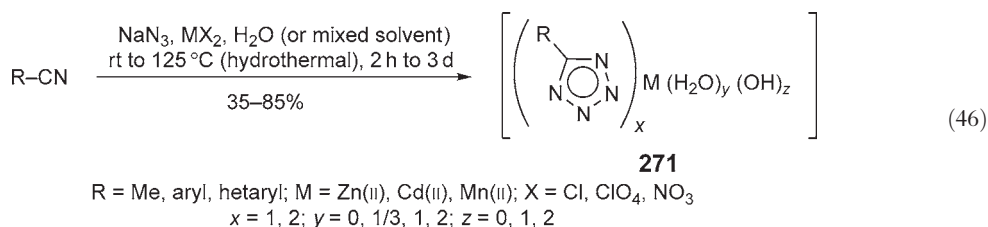
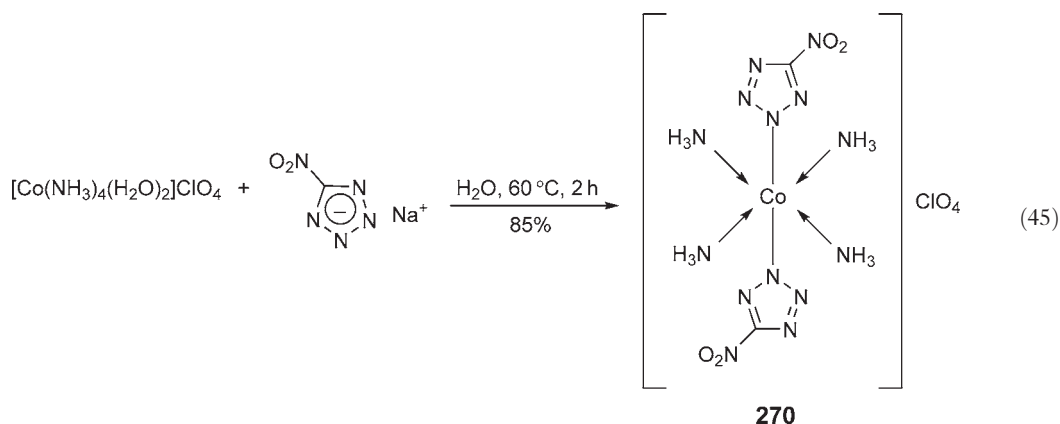
A wide set of alcohols and alkenes used for the N²-regioselective alkylation of tetrazoles in sulfuric and perchloric acid media have been extended to include *tert*-butanol <1998CHE579, 2001CHE949>, diacetone alcohol, <1999CHE1078>, dimethyl-2,5-hexandiol <2000CHE326>, 1-adamantanol <1997RJO571, 1999RJO1069, 2004RJC752>, and triphenylmethanol <2001RJO1670>. The reaction path g (Scheme 20) provides ample possibility to introduce selectively certain specific alkyl substituents at position 2 of the tetrazole ring. The subsequent functionalization of these substituents opens new opportunities for the synthesis of previously inaccessible tetrazole derivatives. For instance, 2-(1-methylvinyl)tetrazoles **201** have been obtained by regioselective alkylation of tetrazole and 5R-tetrazoles with 1-halopropan-2-ols and 3-bromopropene followed by dehydrohalogenation of the intermediate products **266** (Scheme 30) <1997MC41>.



Scheme 30

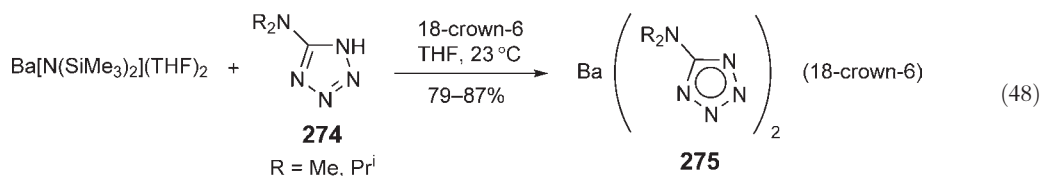
Use of the Bu^tOH/H₂SO₄ system permits a selective preparation of several tetrazolium salts. Hence, starting from tetrazoles **24**, Gaponik *et al.* <1998CHE579> obtained single picrates of 1,3-di-*tert*-butyltetrazoles **269**. The mechanism of this reaction apparently includes a regioselective N²-alkylation (Scheme 29) of the starting tetrazoles by *tert*-butanol and a subsequent quaternization of the 2-*tert*-butyltetrazoles **267** producing the bisulfates **268** (Scheme 31) <1998CHE579>.

A similar method was developed for the synthesis of di- and trisubstituted tetrazolium salts through the quaternization of 1- and 2-monosubstituted tetrazoles, including functionally substituted compounds, with diacetone alcohol <1999CHE1078> and *tert*-butanol <2001CHE949> in perchloric acid, and 2,5-dimethyl-2,5-hexandiol in sulfuric and perchloric acids <2000CHE326>. In the latter study <2000CHE326>, this method was used for a selective synthesis of binuclear N-substituted tetrazoles and tetrazolium salts.



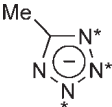
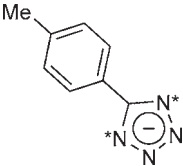
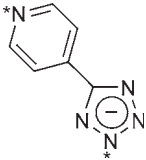
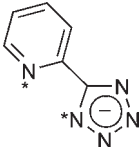
Depending on the ratio of the reagents in the reaction, the complexes obtained may have different composition and structural type. Also the acidity of the reaction solution can cause drastic changes in the structure of the products. The complexes formed as a rule are polymeric, poorly soluble, and sometimes unfit for X-ray diffraction study. Apart from the conditions of the synthesis, the structure of the complexes is significantly affected by the type of the substituent attached to the endocyclic carbon, and by the acidity and basicity of the ligand [\[2002RJC1457\]](#).

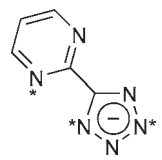
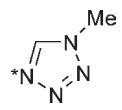
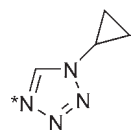
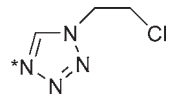
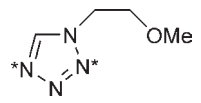
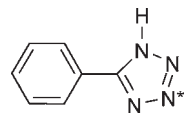
The best documented coordination mode for tetrazolato ligands is η^1 , although the formation of η^2 -coordinated complexes is also observed. For instance, Winter and co-workers demonstrated that 5-dialkylaminotetrazolates **274** form intricate complex compounds **275**, including in their structure 1,2- η^2 - and 2,3- η^2 -bonding modes of the tetrazolate anions ([Equation 48](#)) [\[2005IC4894\]](#). It should be stated, however, that according to calculations by the B3LYP method for the complexes of 5-methyltetrazolate with Ti(IV), the η^2 -coordination mode is predicted to be more stable than η^1 [\[2001IC6451\]](#).



As shown in [Table 25](#), the tetrazolate anions can coordinate in μ_1 -tetrazolyl, μ_2 -tetrazolyl, as well as μ_3 -tetrazolyl coordination modes. The first two coordination modes are the most typical for these compounds. Information on the μ_4 -coordination mode of tetrazolate ligands is rather poor [\[2006JCD3170\]](#). The bond lengths between the metal atoms and the endocyclic nitrogens in most cases indicate quite strong coordination interactions in these structures. Therewith the bonds change negligibly with the temperature. The geometry of the tetrazole hetero-ring also does not significantly alter in going from the free ligand to the complex.

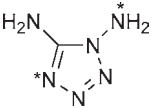
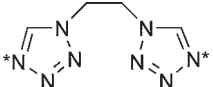
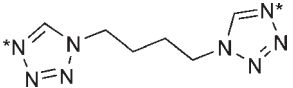
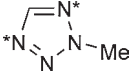
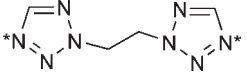
Table 25 Structural data on selected metal complexes of tetrazole derivatives

<i>Ligand (T)^a</i>	<i>Metal (M)</i>	<i>Molecular formula</i>	<i>X-Ray analysis data</i>				<i>Reference</i>
			<i>Structural type</i>	<i>Crystal system</i>	<i>Space group</i>	<i>M–N bond length (Å)</i>	
	Zn(II)	[MT ₂]	3-D polymeric highly distorted diamond-like network	Orthorhombic	<i>Pbca</i>	1.971–1.987	2005IC5278
	Zn(II)	[MT ₂] ₃ (H ₂ O)	3-D super-diamond-like topological network	Cubic	<i>Fd3m</i>	2.163–2.166	
	Zn(II)	[MT ₂]	2-D network containing hexagonal net	Orthorhombic	<i>Pbcn</i>	1.972–2.014	
	Zn(II)	[M ₂ (OH)T ₃]	Two identical and independent rectangular grid sheets	Triclinic	<i>P1</i>	1.991–2.048	2004EJI3662
	Mn(II)	[MT ₂ (H ₂ O) ₂]	Hydrogen-bonded 2-D and 3-D structures	Monoclinic	<i>P2₁/c</i>	2.212 (Mn–N _{tetr.}) 2.255 (Mn–N _{pyr.})	2005JCD2388

	Co(II) Fe(II)	[MT ₂]	2-D square-grid-like structure	Orthorhombic	<i>Pbca</i>	2.090–2.149 (Co–N) 1.958–1.995 (Fe–N)	2005CC5228
	Ni(II)	[MT ₆](CF ₃ SO ₃) ₂	Octahedral	Triclinic	<i>R1</i>	2.087 2.103 2.114	2001POL1699
	Ni(II) Cu(II)	[MT ₆](BF ₄) ₂	Octahedral	Trigonal	<i>R3</i>	2.100 (Ni–N) 2.134 (Cu–N)	2005JCR421
	Cu(II) Fe(II)	[MT ₂ Cl ₂] [MT ₂ Br ₂] [MT ₂ (NO ₃) ₂] [MT ₆](BF ₄) ₂	2-D distorted square grid planes Octahedral	Monoclinic Monoclinic	<i>P2₁/c</i> <i>C2/c</i> <i>P2₁/c</i>	1.994 (Cu–N) 1.975 (Cu–N) 1.976 (Cu–N) 2.187–2.205 (Fe–N)	2002IC6468 2003ICA(350)57 2002ICA(335)61
	Cu(II)	[MT ₂ Br ₂]	2-D centrosymmetrical square planar structures	Monoclinic	<i>P2₁/c</i>	2.781 (Cu–N ₂) 2.004 (Cu–N ₄)	2003JCD3628
	Ti(IV)	[MT ₂ Cl ₄]	2-D supramolecular arrays organized by N–H···H hydrogen bonds	Monoclinic	<i>P2₁/n</i>	2.265–2.271	2004POL801

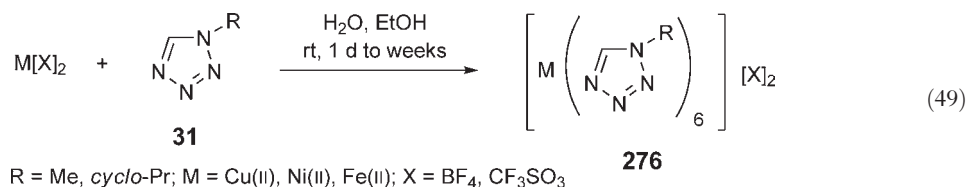
(Continued)

Table 25 (Continued)

<i>Ligand (T)^a</i>	<i>Metal (M)</i>	<i>Molecular formula</i>	<i>X-Ray analysis data</i>				<i>Reference</i>
			<i>Structural type</i>	<i>Crystal system</i>	<i>Space group</i>	<i>M–N bond length (Å)</i>	
	Cu(II)	[MT ₂ Cl ₂]	2-D polymeric networks	Monoclinic	<i>P2₁/c</i>	1.983 (Cu–N _{tetr.}) 2.745 (Cu–N _{am.})	2005ICA(358)2549
	Cu(II)	[MT ₃](ClO ₄) ₂	1-D linear-chain polymer	Orthorhombic	<i>Pbcn</i>	2.034–2.391 (Cu–N)	2001ICA(326)101
	Fe(II)	[MT ₃](BF ₄) ₂		Trigonal	<i>P3c1</i>	2.182 (Fe–N, 296 K), 2.004 (Fe–N, 100 K)	2002ICA(339)297
	Fe(II)	[MT ₃](PF ₆) ₂	3-D octahedron coordination network	Trigonal	<i>P3</i>	2.193 (300 K) 1.993 (100 K)	2004IC155
	Cu(II)	[MT ₂ Cl ₂]	Layered coordination polymer	Monoclinic	<i>P1/n</i>	2.501 (Cu–N ₂) 2.037, 2.068 (Cu–N ₄)	2005ICA3949
	Zn(II)	[MT ₃](ClO ₄) ₂	1-D coordination polymer	Trigonal	<i>P3c1</i>	2.159, 2.163	2002ICA(340)215

^aCoordination centers are marked.

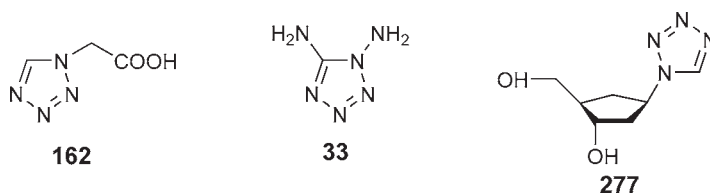
Complexes of metal ions with 1*H*-tetrazole ligands can also be obtained from the corresponding neutral tetrazoles and metal salts in water or organic solvents. These reactions commonly require longer time than the analogous processes with the tetrazolate anions. Thus 1-alkyltetrazoles **31** with Cu(II) and Ni(II) salts afford octahedral complexes **276** (Equation 49) <2001POL1699, 2005JCR421>. The coordination compounds of copper(II) and iron(II) with ditetrazol-1-ylalkanes were prepared in the similar way <2001ICA(326)101, 2002ICA(339)297, 2004IC155>. It was determined that the coordination environment in these complexes is comparable to that found in the mononuclear hexakis(1-alkyl-substituted tetrazole) metal(II) compounds in which six tetrazole ligands coordinate monodentately to the metal(II) ion by N-4.



Under similar conditions, 2-D coordinated polymers of some other 1-alkyltetrazoles **31** were synthesized using copper(II), iron(II), and nickel(II) halides and nitrates <2002IC6468, 2002ICA(335)61, 2003M255, 2003ICA(350)57, 2003JCD3628>. In these complexes, halide and nitrate anions are included in the inner coordination sphere.

Reactions of (tetrazol-1-yl)acetic acid **162** with copper(II) and lanthanide(III) (Ln = Gd(III) or Nd(III)) salts gave binuclear [CuLn(**162**)₄(H₂O)₅Cl] complexes at low pH (3.5) and 2-D heterometallic coordination polymers at higher pH (6.6) <2005IC559>. The palladium(II) complex of tetrakis(tetrazol-1-yl)calix[4]arene was obtained from K₂PdCl₄ and the corresponding ligand <2005T12282>. The reaction of titanium tetrachloride with 5-phenyltetrazole in dichloromethane gave the corresponding titanium(IV) complex (Table 25) <2004POL801>. 1,5-Diaminotetrazole **33** reacting with copper chloride gave a coordination octahedron, where N-4 of the tetrazole ring and nitrogen atom of 1-amino group are coordinated <2005ICA(358)2549>.

Quantitative estimation of the stability constants for metal ion complexation with 1-substituted tetrazoles has been performed <2005CEJ6246>. It was demonstrated that tetrazole nucleoside **277** shows a low tendency to form stable complexes with ions Ag(I) and Hg(II) comparing with imidazoles and 1,2,4-triazoles. Only Ag⁺ is able to form a 1:1 complex with compound **277** (log β₁ 0.86), and no coordination of Hg²⁺ to **277** can be detected.

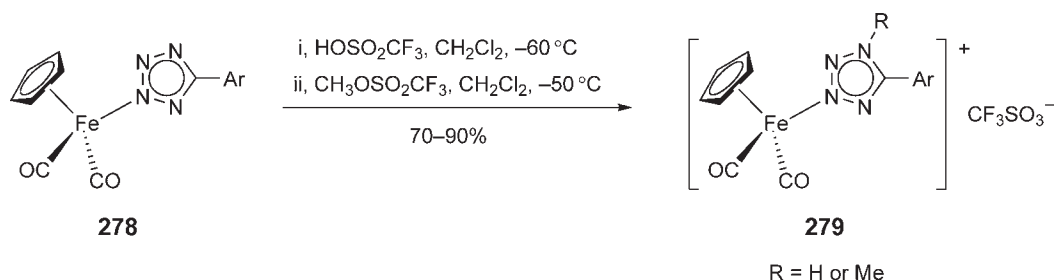


Recently, the structure was established for a whole series of copper(II) complexes with 1-alkyl- and 1-aryltetrazoles: 1-(2-azidoethyl)tetrazole <2001AXEm335>, 1-*tert*-butyltetrazole <2002AXCm288>, 1-(2,4,6-trimethylphenyl)tetrazole <2003AXEm14>, 1-phenyltetrazole <2004AXCm368>, 1-ethyl- and 1-hexyltetrazoles <2005EJI1678>.

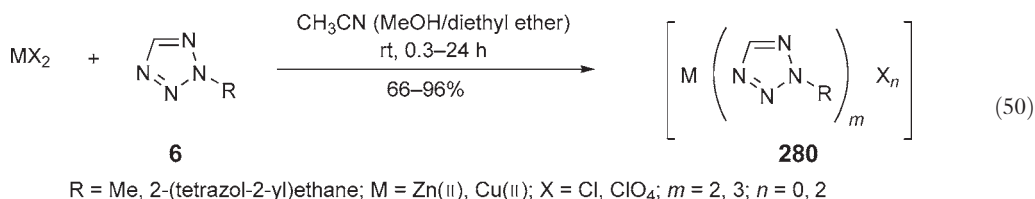
Yet another unusual synthetic procedure was developed for preparation of complexes of 1*H*-tetrazoles with metal ions. Thus iron(II) complexes with 1-unsubstituted and 1-methyltetrazole ligands **279** can be obtained by protonation or alkylation of the corresponding tetrazolate complexes **278** (Scheme 32) <2003JOM(669)135, 2005JOM(690)2052>. As shown in the cited studies by the X-ray diffraction analysis and NMR spectroscopy in going from complex **278** to complex **279**, the changes in the molecular structure are insignificant, and only a large variation of the torsion angle between tetrazole and benzene ring planes was observed.

Mono- and binuclear ruthenium(II) polypyridyl complexes containing 5-aryl-1*H*-tetrazole ligands were analogously prepared <2006IC695>.

Until recently, the information on the coordination compounds of 2-substituted tetrazoles **6** was very poor. It has been shown that reaction of mono- and binuclear 2-substituted tetrazoles with zinc(II) perchlorate and copper(II) chloride in organic solvents gives coordination polymers **280** containing as a ligand 2*H*-monosubstituted tetrazole ring (Equation 50) <2002ICA(340)215, 2005ICA3949>.



Scheme 32



Also the coordination compounds of copper(II) with different 2-alkylmonosubstituted tetrazoles have been synthesized and structurally characterized: 2-propyl- and 2-allyltetrazoles <2005AXCm158>, 2-hexyltetrazole <2005AXEm183>, 2-ethyltetrazole <2003AXCm204>, 2-*tert*-butyltetrazole <2003AXEm38>.

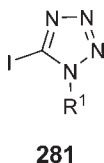
As seen from Table 25, neutral 1*H*- and 2*H*-tetrazoles typically form complexes with μ_1 and μ_2 coordination modes for the ligands.

6.07.5.4 Electrophilic Attack at Endocyclic Carbon

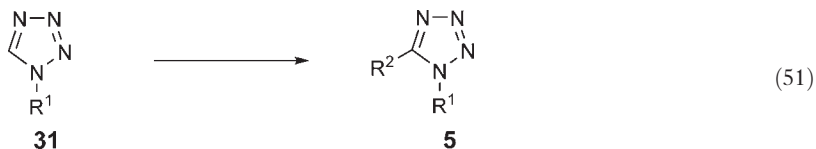
N¹-Substituted tetrazoles are potential substrates for an electrophilic attack at carbon. There are only few publications on this topic, which indirectly indicate the low reactivity of these substrates. One of the reasons for relatively slow development of this line of research is an insufficient level of theoretical understanding of the mechanism of the relevant processes. Examples of these reactions and the description of the corresponding products of hydrogen replacement at C-5 are cited in reviews (Table 26) <1996CHEC-II(4)621, 2004SOS(13)861, 2005RJO1565>. Thus, 1*R*-tetrazoles **31** (R = alkyl, vinyl, aryl) undergo electrophilic iodination at C-5 (I₂, KMnO₄, H₂SO₄) to give 5-iodo-derivatives **281** in 55–75% yield <1996CHEC-II(4)621, 2005RJO1565>.

Table 26 Electrophilic reaction at C-5 of the N¹-tetrazoles (Equation 51) <2004SOS(13)861>

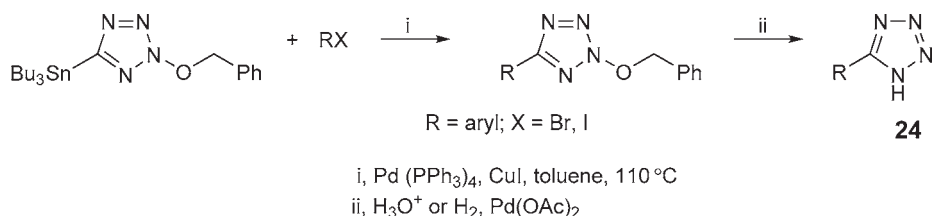
<i>R</i> ¹	<i>R</i> ²	Reagents	Yield (%)	Reference
H	Me ₂ NCH ₂	H ₂ CO, Me ₂ NH, HCl, benzene, nitrobenzene, heating	78	2004SOS(13)861
Me	Me ₂ NCH ₂	H ₂ CO, Me ₂ NH, HCl, benzene, nitrobenzene, heating	96	2004SOS(13)861
<i>p</i> -MeOC ₆ H ₄	PhCH ₂ CH ₂ CH(OH)	PhCH ₂ CH ₂ CHO, BuLi, THF, hexane, –98 °C	73	1998SL528



The other examples useful for understanding of the problem are listed in the Brigas review <2004SOS(13)861> (Table 26). According to Butler <1996CHEC-II(4)621>, these reactions involve protonation at N-4 followed by deprotonation at C-5 giving a reactive ylide that is subjected to electrophilic attack (Equation 51).



2-Benzyloxymethyl-5-(tributylstannyl)tetrazole is a useful reagent for conversion of aryl and heteroaryl bromides and iodides to 5-aryl- and 5-heteroaryl-1*H*-tetrazoles **24**. The reaction involves a Stille palladium-catalyzed, copper(I) iodide cocatalyzed cross-coupling and an *N*-benzyloxymethyl deprotection step. The coupling was possible with electron-neutral and electron-poor substrates in yields ranging from 35% to 93% (Scheme 33) <2000TL2805>.

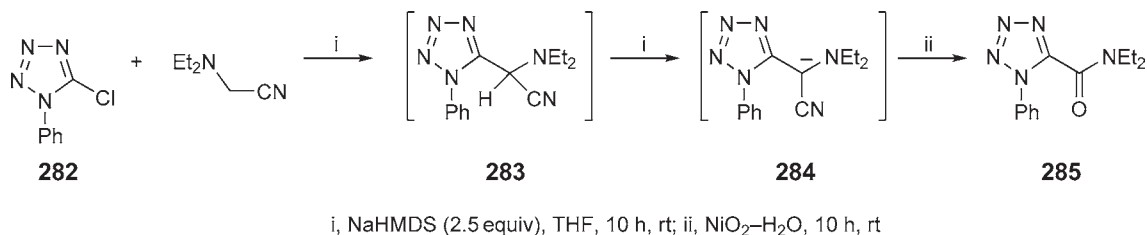


Scheme 33

These processes were extended to preparation procedures and application to the organic synthesis of organometallic tetrazole derivatives, including 5-metallated tetrazoles and tetrazoles with a metal–carbon bond in a substituent, and also of organotin tetrazoles <2005RJO1565>.

6.07.5.5 Nucleophilic Attack at Endocyclic Carbon

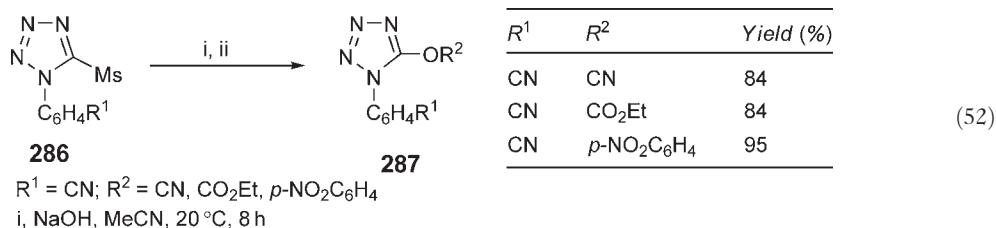
This section summarizes the results of studies on nucleophilic reactions at the carbon atom of the tetrazole ring published since 1994 <1994RCR797, 1994OPP499, 1996CHEC-II(4)621, 2004SOS(13)861>. The substitution of halogen and some other leaving groups located at position 5 of the ring under the action of C- and N-nucleophiles is an attractive way to the functionalization of tetrazoles. An interesting example was published of a halogen atom replacement in 1-phenyl-5-chlorotetrazole **282** via an S_NAr substitution process <2004JOC1360>. The nucleophilic reagent here was apparently a carbanion generated *in situ* from *N,N*-diethylaminoacetonitrile with NaHMDS in THF. The nucleophilic substitution of the halogen atom by this reagent resulted in adduct **283** whose deprotonation afforded carbanion **284**. The oxidation of carbanion **284** with NiO₂–H₂O gave 1-phenyl-5-tetrazolecarboxamide **285** (Scheme 34) <2004JOC1360>.



Scheme 34

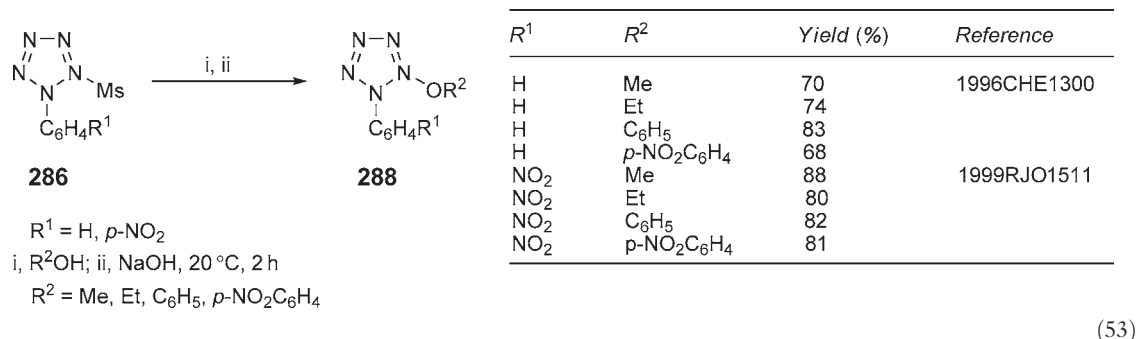
The same team reported recently on a similar reaction of **282** aiming at a one-pot preparation of heteroaryl amide **285** <2004TL5909>. However, in this case, the malononitrile was successfully used as a carbonyl synthon instead of *N,N*-diethylaminoacetonitrile <2004TL5909>.

The chlorine at the endocyclic carbon atom was replaced by an azide group on prolonged heating of 1-phenyl-5-chlorotetrazole **282** with sodium azide in DMF (60 °C, 18 h) <2005MI17>. Methanesulfonyl group at the carbon atom of the tetrazole ring is a better leaving group for the attack of various C-nucleophiles. For instance, 1-phenyl-5-methanesulfonyltetrazole **286** reacted under relatively mild conditions with malonic acid derivatives or with a *p*-nitrophenylacetonitrile affording the corresponding 1-phenyl-5-substituted tetrazoles **287** (Equation 52) <1996CHE1300>.



Under similar conditions (NaOH, 20 °C, 13 h), 1-phenyl-5-methanesulfonyltetrazole **286** reacts with 1-imidazole, 1-benzimidazole, or 1-benzopyrazole to give the corresponding 1-phenyl-5-azolyl derivatives in 68–78% yield <1996CHE1300>.

Methanesulfonyl groups at the endocyclic carbon atom of tetrazoles are easily substituted on treating with O-nucleophilic reagents, such as alcohols. The corresponding O-linked derivatives **288** can be obtained in 68–88% yields. Reactions of 1-phenyl-5-methanesulfonyltetrazole **286** with MeOH or EtOH are carried out in excess alcohol. In reactions with phenol or *p*-nitrophenol, ethanol was used as solvent (Equation 53) <1996CHE1300, 1999RJO1511>. Note that *N*-aryl-5-methanesulfonyltetrazoles **286** react similarly with both monohydric and polyhydric alcohols <2002RJO1356, 2004RJO1318>. Also 1-aryl-5-methanesulfonyltetrazoles **286** are more reactive with respect to N- and O-nucleophiles than the isomeric 2-aryl-5-methanesulfonyltetrazoles <2001CHE1493, 2002RJO1356>.



It was shown recently that the phenoxy group in the 1-aryl-5-phenoxytetrazoles is relatively easily (NaOH, 60 °C, 0.5 h) replaced by alkoxy groups upon treatment with primarily or secondary aliphatic alcohols. The corresponding 1-aryl-5-alkoxytetrazoles are formed in 59–78% yields <2000RJO1698>.

6.07.5.6 Nucleophilic Attack at Hydrogen Attached to Endocyclic Carbon

The CH-acidity of 5-unsubstituted tetrazoles was estimated based on rate of H/D-exchange <2006RJO1585>. Note that the fully deuterated parent tetrazole (CD₂N₄) is a very volatile crystalline solid with a low temperature of sublimation <2006UP3>.

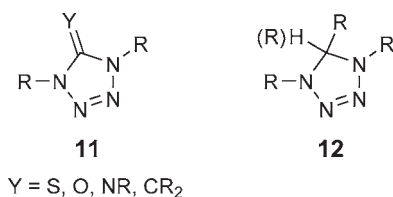
6.07.5.7 Reactions with Radicals and Electron-Deficient Species, Reaction at Surfaces, and Reduction

Reactions of fully conjugated rings with carbene species constitute an exotic part of tetrazole chemistry. A systematic analysis of information regarding these reactions is now impossible because of lack of data. Individual publications touching on these problems are discussed in this chapter, for example, the reaction of 5-phenyltetrazole with dichlorocarbene <1997CHE364, 2007CHE320> (cf. Section 6.07.5.3.2). More information is available on the reactions of tetrazole substrates with carbocations (cf. Section 6.07.5.3.3). These reactions are now the main method for carrying out regioselective reactions between tetrazoles and electrophilic reagents (cf. Section 6.07.5.3.3). After publication of the fundamental kinetic investigations on the acid-catalyzed reactions of tetrazoles with carbocations <1993MI1043, 1995MI919>, the number of experimental studies on this topic constantly grows <1997RJO571, 1998RJO746, 1998CHE579, 1999CHE1078, 1999CHE1078, 1999RJO1069, 2000CHE326, 2001CHE949, 2001RJO1670, 2004RJO598, 2004RJC752>. The reactions of tetrazole substrates with carbocations are discussed in reviews <2000H(53)1421, 2006RJO494, 2006RJO1585>.

PTC has come to the forefront as an efficient method for alkylation and acylation of tetrazoles (cf. Section 6.07.5.3.2) <1992ZOB3>. A new and promising direction is synthesis of tetrazoles and transformation of the tetrazole ring in the solid phase. We consider these reactions in Sections 6.07.5.3, 6.07.7.2, 6.07.9.1, and 6.07.9.4.1. Here we enumerate the recently published studies on this topic <2000JCO19, 2004OL1143, 2004BML317, 2005TL3107>. Concerning reactions of fully conjugated rings under the conditions of an electrochemical reduction, we found a single publication <2002RCB1523> where the N-arylation of tetrazoles by 1,4-dimethoxybenzene in the course of an undivided electrolysis was described (cf. Section 6.07.5.3.1). Apparently the processes of the electrochemical reduction are more characteristic of tetrazolium salt conversion to corresponding formazanes <2002RCR721>.

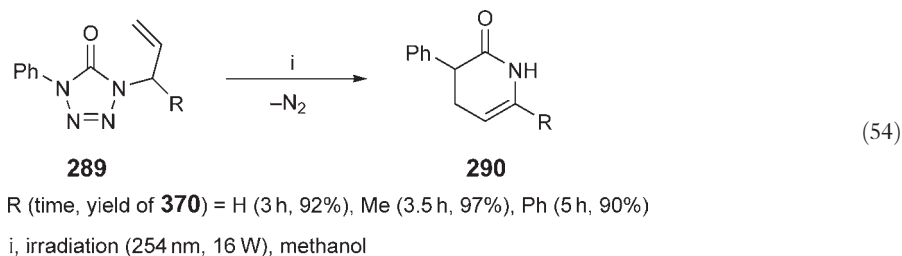
6.07.6 Reactivity of Nonconjugated Rings

The first classification of reactivity of 1,4-dihydropyrazoles was described by Butler <1996CHEC-II(4)621>. According to this classification, the main types of nonconjugated tetrazoline compounds are the 1,5- and 1,4-dihydroderivatives with general structures **11** and **12**.

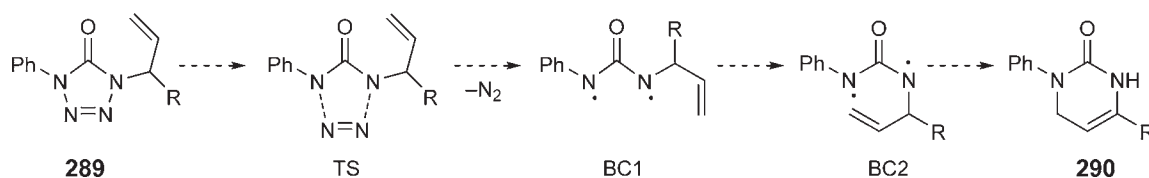


The fundamental difference in the electronic structure of the 1,4-dihydropyrazole ring and that of the fully conjugated tetrazole ring is apparent (cf. Section 6.07.2.1). Therefore, the reactivity of 1,4-dihydropyrazoles **12** is a poorly understood problem. It is clear <1996CHEC-II(4)621> (cf. Section 4.17.6.1) that the known reactions of 1,4-dihydropyrazoles **12** cannot be easily classified for they are prone to numerous reversible equilibria and nonreversible rearrangements, thermolysis, photolysis, etc. The task is still more difficult due to the small number of publications, which commonly treat special cases. No major change in the situation has occurred since the publication of CHEC-II(1996) <1996CHEC-II(4)621>. In Section 6.07.6, recent publications on this topic (that we regard as the most important) are discussed.

We have already referred to the studies of Cristiano *et al.* on thermal and photochemical conversions of 4-allyltetrazolones via a concerted Claisen-type isomerization (Section 6.07.5.2.3) <1996J(P1)1453, 1997J(P2)489, 1997JCM164, 2002J(P1)1213, 2005TL6757>. In the last paper of this series <2005TL6757>, a new strategy for the synthesis of 3,4-dihydro-6-substituted-3-phenylpyrimidin-2(1*H*)-ones is exploited. Photolysis ($\lambda = 254$ nm) of 4-allyl-tetrazolones **289** in alcoholic solutions produced the corresponding pyrimidinones **290** as the only product in nearly quantitative yield, with simultaneous extrusion of molecular nitrogen (Equation 54) <2005TL6757>.



The mechanism probably involves a transition structure TS. Rotation of the allylic chain in TS and N-2 extrusion leads to a biradicalar complex BC1 with the terminal carbon of the allylic chain (C-1) very distant from N-1. Subsequent reaction coordinate calculations consider that C-1 approaches N-1 to give a biradicalar complex, BC2, thermodynamically more stable by 19.1 kcal mol⁻¹. The formation of pyrimidinone **290** from BC2 ensues through 1,2-migration of hydrogen and exothermic formation of a new C(1)–N(1) single bond (Scheme 35) <2005TL6757>.



Scheme 35

Results <1999BML1251> confirming the possibility of a directional synthesis of complex molecules through successive transformations of 1-phenyl-tetrazolone **291** involving both the endocyclic nitrogen and phenyl group require more detailed consideration. The process includes an alkyl group introduction at position 4 of the tetrazolone ring, and then aromatic nitration of the alkylated product **292** with nitronium hexafluoroborate. In the next step, palladium-catalyzed hydrogenation of the nitro group of *p*-nitrophenyltetrazolone **293** gives aniline **296** in quantitative yield. Subsequent diazotization and reaction with sulfur dioxide–copper(I) chloride at –20°C to room temperature gives the requisite sulfonyl chloride **295**. Standard sulfonamide formation with aniline **296** concludes by treatment with acid to remove the *t*-butoxycarbonyl (BOC) protecting group to give the desired final compounds **297** (Scheme 36) <1999BML1251>.

The first step of the multistep synthesis shown in Scheme 36 was later studied in detail by Poplavskaya *et al.* <2000RJO1793>.

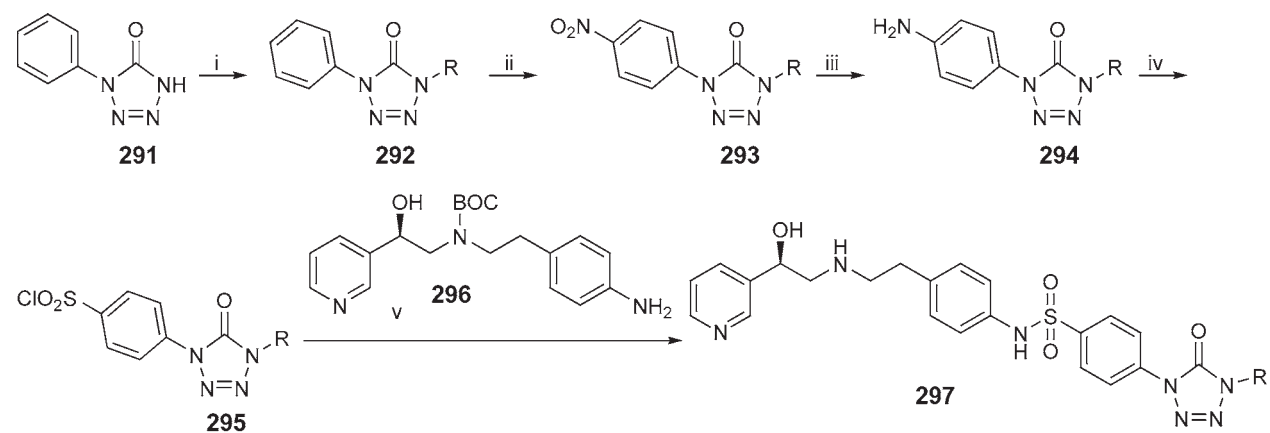
The formation of structures of type **300** as intermediate in the synthesis of 5-alkylamino-1*H*-1,2,3-triazoles has been discussed (Scheme 37) <2006S1943>. Deprotonation of tetrazolium cation **298** with potassium hydride and treatment of the resulting solution of tetrazoline compound **299** with methyl azide afforded the spirocyclic 1,3-dipolar cycloadduct **300**. The treatment of the intermediate product **300** with a small excess of strong base effected the opening of the tetrazole ring to yield the elusive tetrazenide ion **301** that eliminated methyl azide and afforded methylaminotriazole **302** after protonation. The ring cleavage is facilitated by the strain inherent in the spiro structure and by formation of an aromatic system. A good yield (88%) of alkylaminotriazole **302** was obtained without isolation of intermediates (Scheme 37) <2006S1943>.

It was shown earlier <1998J(P1)1755> that heteroallene salts with *N,N'*-dialkylcarbodiimides undergo cycloaddition to furnish 1,3,4,5-tetrasubstituted-4,5-dihydro-tetrazolium salts (cf. Section 6.07.9.3), which on heating in acetonitrile eliminate an alkene to afford 1,3,5-trisubstituted tetrazolium salts.

The synthesis and reactivity of tetrazole-5-thiones are considered in Section 6.07.7.5. A preparation of sulfone **304** in two steps from the corresponding tetrazole-5-thione **303** by alkylation and subsequent oxidation has been described (Scheme 38) <2006JOC360>.

The formulas of 1-aryl-4-difluoromethyltetrazole-5-thiones **305**, whose preparation and properties have been reported, are shown <2004RJO601>. These compounds are of interest as useful substrates for functionalization (e.g., by replacing the halogen of the difluoromethyl group in the position 4).

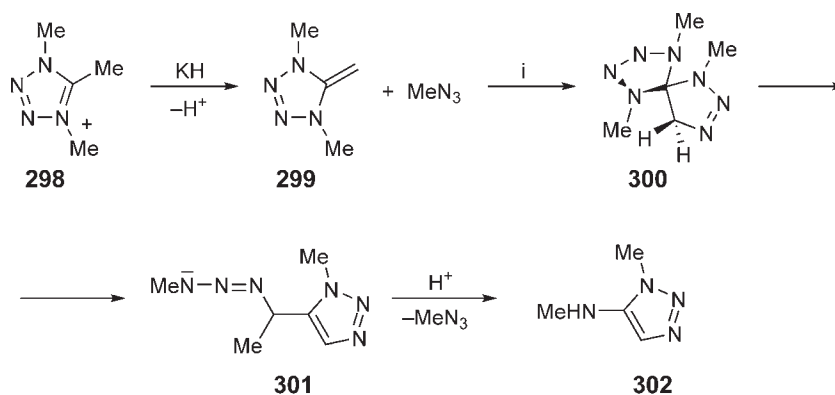
It should be noted in conclusion that 1-amino-4-methyl-5-imino-4,5-dihydro-1*H*-tetrazole **306** obtained by elimination of HN₃ from 1,5-diamino-4-methyltetrazolium salt (X=N₃) **172** (cf. Section 6.07.5.2.1) at 160–185°C decomposes giving HCN, 1,2,4-triazole, and cross-linked products <2005THE168>.



R = cyclopentylpropyl

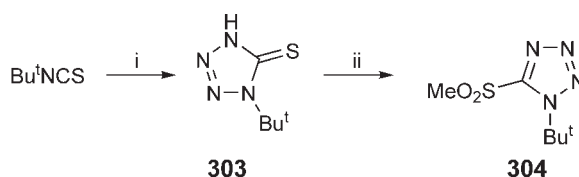
i, RI, KOH, DMF; ii, NO_2BF_4 , MeCN; iii, H_2 , 10% Pd/C, EtOH; iv, (a) NaNO_2 , conc. HCl; (b) AcOH, SO_2 , CuCl, AcOH; v, 9 N aq. HCl

Scheme 36



i, THF, -40°C in a Schlenk tube; 10°C , 15 h; yield of compound **302** = 88%

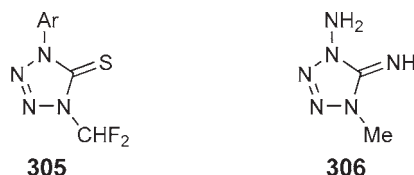
Scheme 37



i, NaN₃, PrⁱOH/H₂O, reflux; yield of compound **303** = 77%

ii, NaH, MeI, THF; Mo₇O₂₄(NH₄)₆, H₂O₂, EtOH; yield of compound **304** = 91%

Scheme 38



Ar = C₆H₅, *o*-MeC₆H₄, *p*-MeC₆H₅, 2,4-Me₂C₆H₃, 2,5-Me₂C₆H₃

6.07.7 Reactivity of Substituents Attached to Ring Carbon Atom

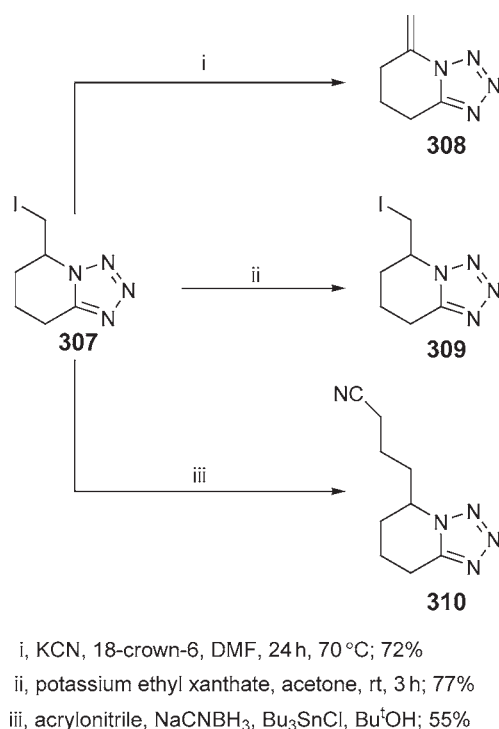
6.07.7.1 General Survey

Unlike the other azoles, the tetrazole ring contains a single carbon atom. This structural feature somewhat limits the possibility of tetrazole functionalization. The procedures for introduction of C-substituents and their subsequent functionalization was treated at length by Butler [<1996CHEC-II\(4\)621>](#) and was also discussed, yet not so fully, in recent reviews on the tetrazole chemistry [<2004SOS\(13\)861, 2006RJO494>](#). In this section, the most important studies in this area of tetrazole chemistry are summarized.

6.07.7.2 C-Linked Substituents

6.07.7.2.1 Fused ring

Reactions involving a fused ring occur either with opening of one of the rings or proceeding at the functional groups or atoms in the side chain without ring opening. The halogen substitution in 5-iodomethyl-5,6,7,8-tetrahydrotetrazolo[1,5-*a*]-pyridine **307** effected by hard and soft nucleophiles and also by radical species occurs with retention of the fused ring ([Scheme 39](#)) [<2003T6759>](#).



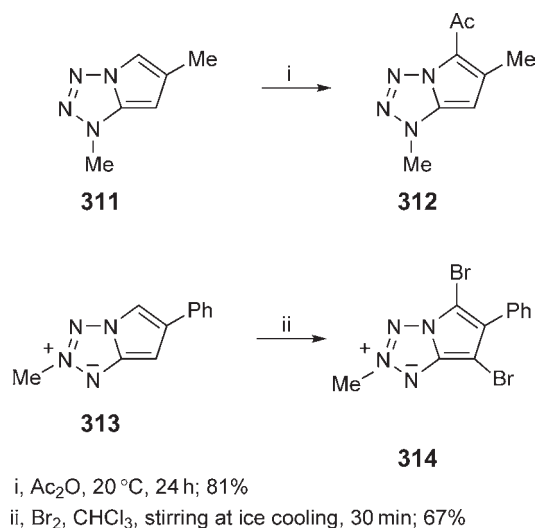
Scheme 39

Pyrido[2,3-*d*]pyrimidines are synthesized in a two-step procedure from amides and tetrazolo[1,5-*a*]pyridine-8-carbonyl chloride. Crude imides with triphenylphosphine underwent an intramolecular aza-Wittig reaction to afford a variety of substituted pyrido[2,3-*d*]pyrimidines in good to moderate yields (30–76%) [<2006TL3361>](#). Protonation, acetylation, benzoylation, carbamoylation, formylation, bromination, azo coupling, nitrosation, and addition to DMAD of 1*H*- and mesoionic 2*H*-pyrrolotetrazoles have been studied [<2001J\(P1\)720, 2001J\(P1\)729>](#). Early studies of ring opening induced by nucleophilic attack have been cited [<2005ARK131>](#). Two examples are: acylation of pyrrolotetrazole **311** with acetic anhydride and bromination of mesoionic analog **313** to afford the corresponding products **312** and **314** in good yields (Scheme 40) [<2001J\(P1\)720, 2001J\(P1\)729>](#).

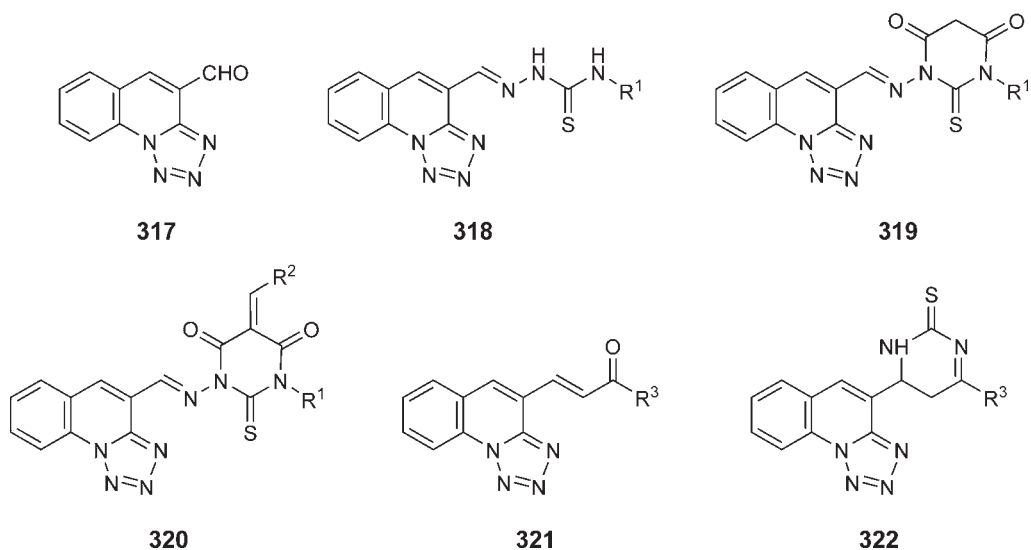
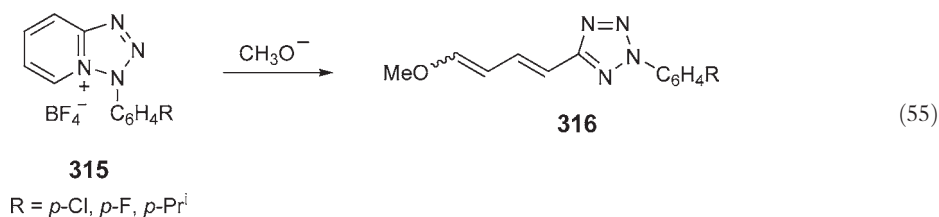
Similarly, the acylation of 1-methyltetrazolo[5,1-*a*]isoindole with acyl chlorides led to 5-acyl-1-methyltetrazolo[5,1-*a*]isoindoles. This reaction permits introduction of various alkyl, aryl, or heteroaryl substituents to the central methine carbon of the isoindole ring [<2004T195, 2003JST\(658\)171>](#). It has been shown [<2003T7485>](#) that tetrazolopyridinium salt **315** with nucleophile (CH₃O[−]) suffered an opening of the pyridine ring giving 1-methoxy-4-(2-aryltetrazol-5-yl)butadienes **316** (Equation 55).

Further reactions of compounds **316** by the action of oxygen and under UV irradiation led to the 2-(4-aryl)-5-[(1*E*)-3-oxoprop-1-en-1-yl]-2*H*-tetrazoles (cf. Section 6.07.7.2.7).

Three series of tetrazolo[1,5-*a*]quinoline derivatives have been synthesized. The first series was synthesized starting by condensation of tetrazolo[1,5-*a*]quinoline-4-carboxaldehyde **317** with substituted thiosemicarbazides followed by cyclization of the resulting thiosemicarbazones **318** with malonic acid in the presence of acetyl chloride to give pyrimidyl derivatives **319** (R¹ = C₆H₅, *p*-CH₃C₆H₄, *p*-ClC₆H₄). The second series was prepared by condensation of **319** with selected aromatic aldehydes to afford arylidene derivatives **320** (R² = C₆H₅, *p*-(CH₃)₂NC₆H₄). The third series **321** was synthesized by condensation of tetrazolo[1,5-*a*]quinoline-4-carboxaldehyde **317** with the appropriate acetophenone R³COCH₃ (R³ = C₆H₅, *p*-BrC₆H₄, *p*-ClC₆H₄), followed by cyclocondensation of the resulting α,β-unsaturated ketones with thiourea. As a result of cyclocondensation, the series of 4-(3-aryl-5-arylidene-4,6-dioxo-2-thioxohexahydropyrimidin-1-yl)-iminomethyl-tetrazolo[1,5-*a*]quinolines **322** was obtained [<2004EJM249>](#).



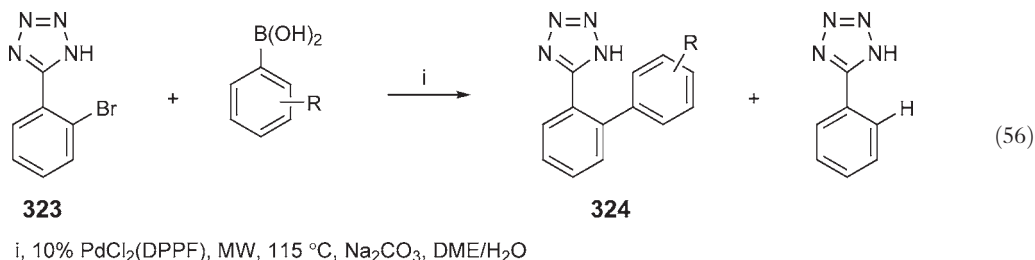
Scheme 40



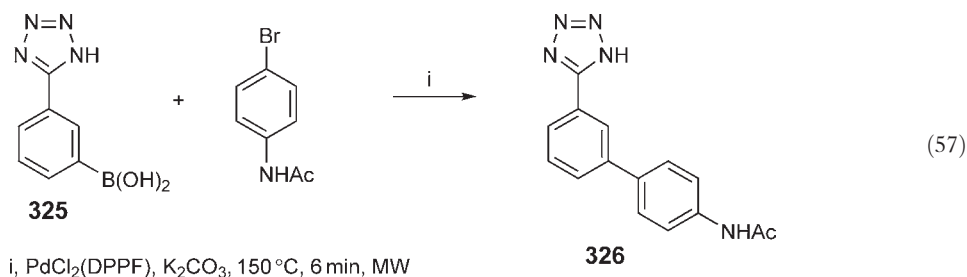
6.07.7.2.2 Aryl and hetaryl groups

Successful studies were carried out on the reactivity of substituents attached to the ring carbon of tetrazole. This direction of research is of interest because of the need of regioselective introduction of new groups into the carbocyclic substituent as, for example, in the synthesis of *ortho*-biphenyltetrazoles, basic compounds for the preparation of active pharmaceutical ingredients of AII receptor antagonist, losartan **29**, and its analogs <2001CRV2727, 2002BMC3379>. This aim is achieved by using Suzuki coupling with tetrazole-containing boronic acid. The protection of N-2 of the tetrazole ring

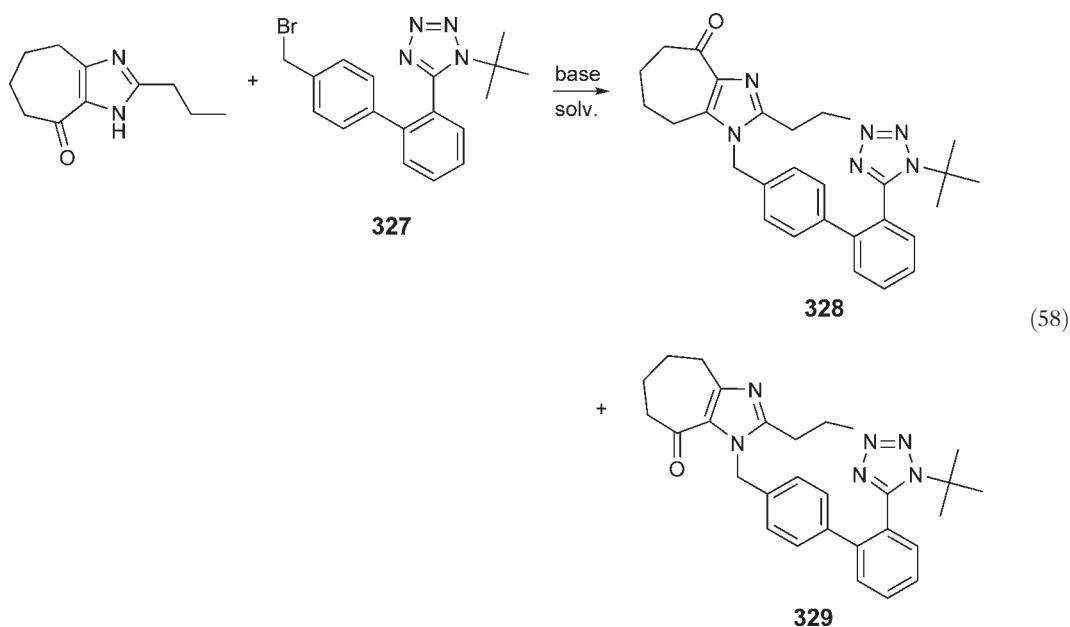
was necessary in earlier works because the free tetrazole (cf. Section 6.07.4.5.2) acted as poison on palladium catalysts <1994JOC6391, 2000TL2265>. An efficient protocol for the Suzuki–Miyaura synthesis of *ortho*-biphenyltetrazoles **324** from nonprotected 2-bromophenyltetrazole **323** and arylboronic acids has been described <2005TL6529>. The optimized conditions were achieved using 1,10-bis(diphenylphosphino)ferrocene dichloropalladium(II) (PdCl₂(DPPF)) as catalyst and Na₂CO₃ as base. A set of structurally diverse arylboronic acids were used to demonstrate the scope of the coupling procedure (Equation 56) <2005TL6529>.



Unprotected 3-tetrazolephenylboronic acid **325** was coupled with 4-bromoacetanilide in the presence of PdCl₂(DPPF) to afford product **326** in 74% unoptimized yield (Equation 57) <2004OL3265>.



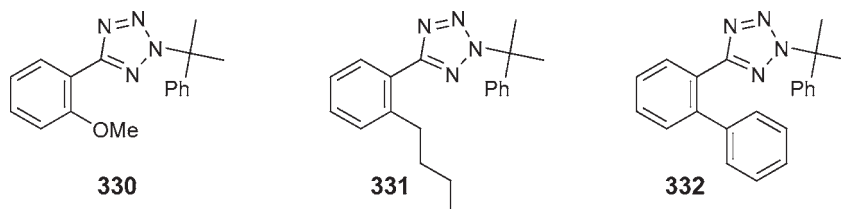
Reaction of 2-propyl-5,6,7,8-tetrahydro-3*H*-cycloheptimidazol-4-one with 5-(4-bromomethyl-biphenyl-2-yl)-1-*tert*-butyl-1*H*-tetrazole **327** led to the corresponding 1*H*-isomers **328** and 3*H*-isomers **329** (Equation (58); Table 27) <2006CPB706>.



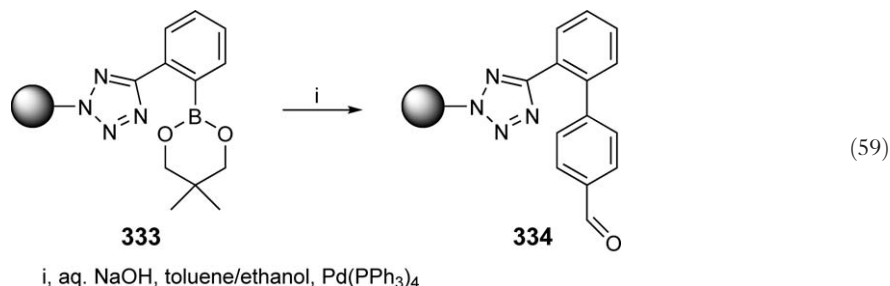
Other unconventional methods were also developed for introducing substituents into the phenyl ring of the 5-aryltetrazoles. Reaction of organolithium compounds (BuLi, PhLi, *p*-tolyllithium, 1-naphthyllithium, etc.) with 2-cumyl-5-(2-methoxyphenyl)tetrazole **330** (in hexane, 23 °C, 4.5 h) led to corresponding products of nucleophilic aromatic substitution such as **331** and **332** in 47–90% yields <1999JOC9301>.

Table 27 Reaction of 2-propyl-5,6,7,8-tetrahydro-3*H*-cycloheptimidazol-4-one with 5-(4-bromomethyl-biphenyl-2-yl)-1-*tert*-butyl-1*H*-tetrazole **327** (Equation 58) <2006CPB706>

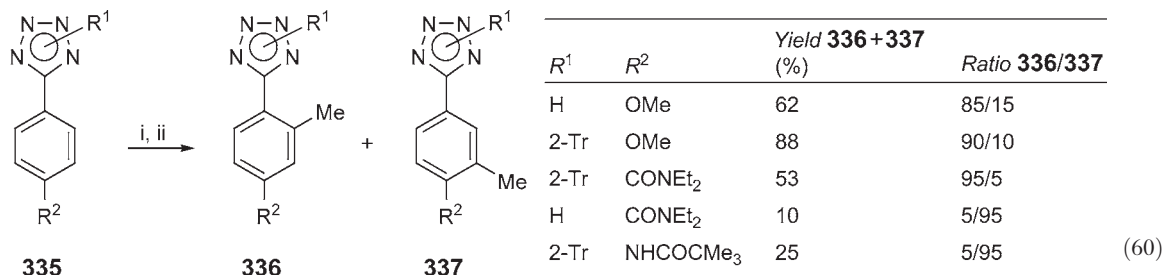
Base	Solvent	Reaction time (h)	Yield ^a (%)	Selectivity ^b
NaH	DMF	1	98	72/28
NaH	THF	2	97	76/24
K ₂ CO ₃	DMF	6	97	24/76
K ₂ CO ₃ , 18-crown-6	THF	16	95	29/71
Bu ^t OK	DMF	1.5	95	26/74
10% NaOH, Bu ₄ NBr	DMF	1	85	44/56

^aTotal isolated yield of compound **328** and compound **329** is shown.^bCalculated ratio based on isolated yields of compound **328** and compound **329**.

An efficient solid-phase protocol for the synthesis of substituted (5-biphenyltetrazolyl)-hydantoins and -thiohydantoins has been developed. Suzuki cross-coupling between resin-bound 2-(tetrazol-5-yl)-phenylborinane **333** and 4-bromobenzaldehyde gave the corresponding tetrazolylbiphenyl aldehyde **334** (Equation 59) <2004BML317>.



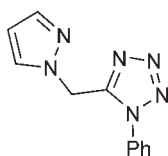
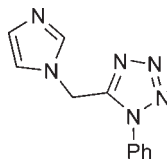
ortho-Lithiation followed by electrophilic trapping of *N*-unsubstituted and *N*²-triphenylmethyl-substituted 5-aryl-tetrazoles **335**, simultaneously substituted with another *ortho*-director in the *para*-position of the aryl ring, resulted in the formation of regioisomers **336** and **337**, whose ratio depended on the competing *para*-substituents. By such intramolecular competition experiments, the *ortho*-directing strength of these tetrazol-5-yl groups in comparison to some commonly employed *ortho*-directors was found to be: OMe < 1*H*-tetrazol-5-yl < CONEt₂ < 2-(triphenylmethyl)-2*H*-tetrazol-5-yl < NHCOCMe₃, OCONEt₂ (Equation 60) <2002TL3137>.

R¹ = H, R² = OMe; R¹ = 2-Tr, R² = OMe; R¹ = 2-Tr,R² = CONEt₂; R¹ = H, R² = CONEt₂;R¹ = 2-Tr, R² = NHCOCMe₃; etc.i, TMEDA, dry THF, -78 °C, Bu^sLi, 1 h

ii, MeI, -78 °C → rt

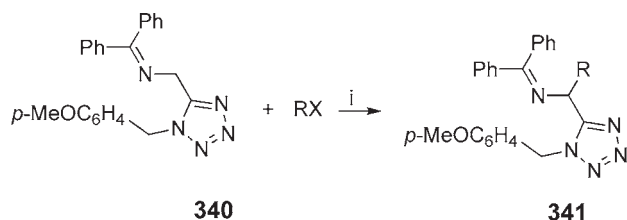
6.07.7.2.3 Alkyl group

Nucleophilic substitution of the terminal halogen in the alkyl groups at C-5 atom is a simple but efficient approach to modification of tetrazole derivatives. Treatment of 1-phenyl-5-chloromethyltetrazole with imidazole or pyrazole (DMSO, NaOH) gave the corresponding products of the halogen β -substitution **338** and **339** <2002JOC8230>.

**338****339**

A series of tetrazole amide derivatives of ($\pm$)-2-dodecylphenyl-*N*-(2,4,6-trimethoxyphenyl)-2*H*-tetrazole-5-acetamide were prepared by action of amines and *N,N*-dicyclohexylcarbodiimide (DCC) in dichloromethane at -15°C on the corresponding acetic acid <1996JME2354>.

Attention has been directed to the development of selective procedures for electrophilic alkylation of 5-alkyltetrazole derivatives with an active methylene group in the α -position at C-5. Alkylation of Schiff base **340** was effected by treating an equimolar mixture of compound **340** and an alkyl halide in THF with 1 equiv of NaHMDS (-78°C to room temperature). The highly versatile nature of this procedure allowed a facile synthesis of monoalkylated products **341** with alkyl, allyl, and benzyl halides in good yields (Equation 61) <1998TL3367>.

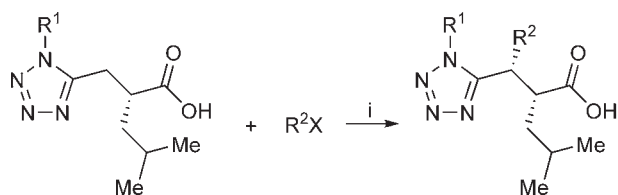


i, RX, THF, NaHMDS, -78°C , 15 min, rt, 1 h

<i>RX</i>	Yield (%)
CH_3I	82
	79
	88
	90
	94
	92
	67
	75

(61)

A new procedure for diastereoselective alkylation of β -tetrazolyl propionic acids **342** in the presence of lithium diisopropylamide was described (Equation 62) <2004TL111>.

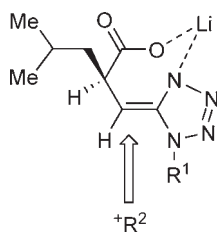


R^1	R^2X	<i>syn:anti</i>	Yield (%)
Pr	allylBr	30:1	92
Pr	Mel	11:1	95
Pr	Pr ⁱ Br	30:1	45
Me	allylBr	20:1	40
Me	Pr ⁱ Br	20:1	42

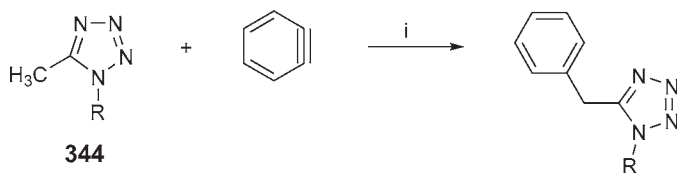
(62)

342 $R^1 = \text{Pr}; R^2X = \text{allylBr, Mel, EtBr, BuBr, Pr}^i\text{Br}$ $R^1 = \text{Me}; R^2X = \text{BnBr, allylBr, Pr}^i\text{Br}$ i , THF, LDA, -78°C to rt for 20 h

A seven-membered chelate model **343** was suggested to rationalize the observed high level of *syn*-selectivity.

**343**

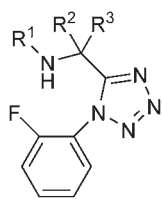
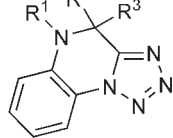
Interest in α -hydrogen substitution in an alkyl attached to C-5 is also demonstrated by reaction of 1-aryl-5-methyltetrazoles **344** with the generated 1,2-dehydrobenzene [<2005TL2679>](#). This reaction afforded 1-aryl-5-benzyltetrazoles **345** in 60–78% yields (Equation 63) [<2005TL2679>](#).



(63)

 $R = \text{Ph, } p\text{-MeOC}_6\text{H}_4, p\text{-ClC}_6\text{H}_4, \text{etc.}$ i , boiling in MeCN, 12–18 h; 60–78%**345**

Growing attention is directed to intramolecular reactions involving alkyls attached to position 5 of the tetrazole ring. The synthesis of 4,5-dihydro-1,2,4-triazolo[1,5-*a*]quinoxalines **347** from 5-substituted tetrazoles **346** via the intramolecular $S_N\text{Ar}$ substitution of the halogen in the *ortho*-position of the N^1 -aryl substituent is an example of such a reaction (Equation 64) [<2006TL2041>](#).

**346****347**

R^1	R^2	R^3	Yield (%)
	C_6H_5	H	96
	$p\text{-NO}_2\text{C}_6\text{H}_4$	H	95
	$p\text{-MeOC}_6\text{H}_4$	H	92
	Me	Me	57

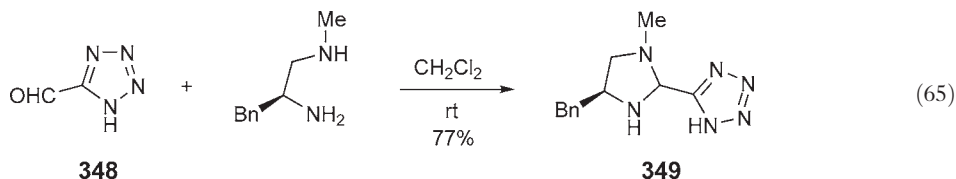
 i , DMF, Cs_2CO_3 , 100°C , 3–48 h $R^1 = \text{Alk, } cyclo\text{-Alk};$ $R^2 = \text{A, Alk}; R^3 = \text{H, Alk}$

(64)

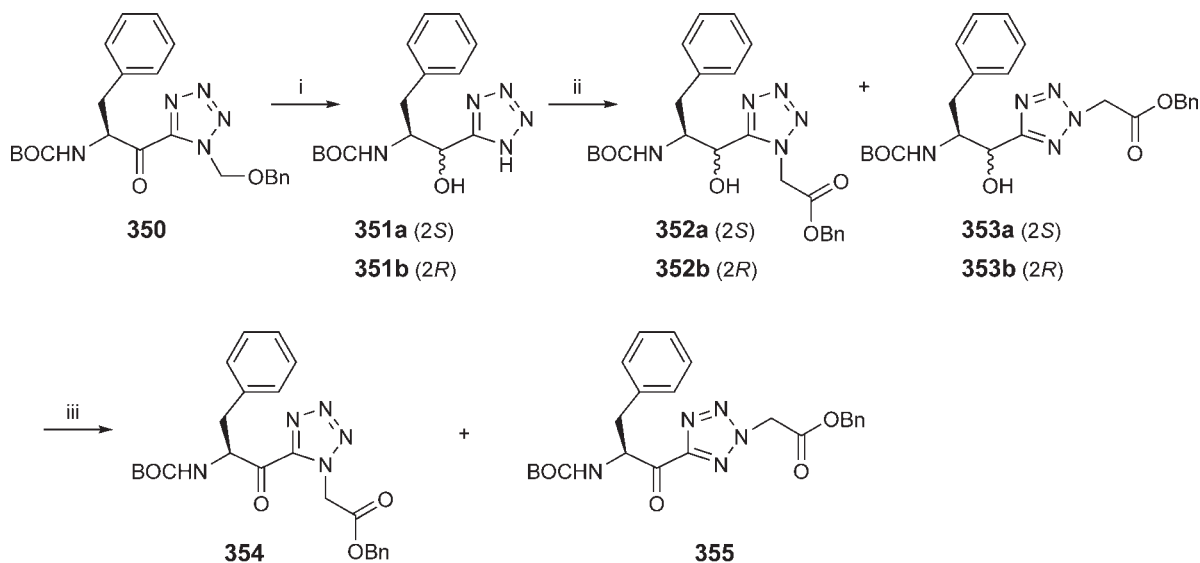
Reactions of alkyl substituents of the tetrazole ring relevant to the formation and transformations of vinyl groups at C-5 are considered in a review <2003RCR143> (cf. Section 6.07.7.2.7).

6.07.7.2.4 Aldehydes and ketones

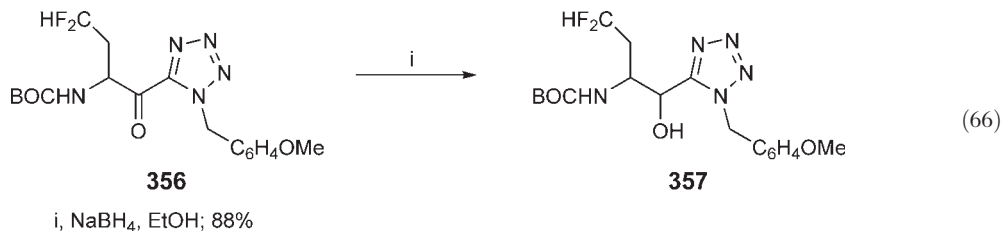
Reactions of tetrazole-5-carbaldehyde are relatively seldom employed in functionalization of tetrazoles due to poor accessibility and low stability of the compound. Therefore, a study in which 1*H*-tetrazole-5-carbaldehyde **348** (prepared using a slight modification of the original Moderhack protocol <1981ZNB656>) is used as a reagent in the synthesis of imidazolidine-2-yl-tetrazole derivative **349** is worth mentioning (Equation 65) <2005OL3897>.



In contrast to tetrazole-5-carbaldehyde, tetrazole-5-keto analogs are relatively accessible and are attractive reagents for synthesis. 5-(α -Diazoethyl)tetrazoles were efficiently prepared from 5-acetyltetrazoles via hydrazone dehydrogenation with Ag₂O in the presence of NaOH <1996ZNB1815>. Reactivity of α -keto tetrazoles is efficiently used in the stereoselective synthesis of α -keto tetrazole-based dipeptide mimetics <1997J(P1)2475, 2001TL5641> (cf. Section 6.07.12.1.1). A catalytic hydrogenation of the *N*-BOC-protected tetrazole **350** resulted in removal of the benzyl methyl ether tetrazole protecting group, as required, and also in reduction of the α -carbonyl group <2001TL5641>. The reaction gave a mixture of epimeric α -hydroxy-1*H*-tetrazoles **351a** and **351b** in 90% yield. The product was used without further purification. Alkylation of the α -hydroxy-1*H*-tetrazoles **351a** and **351b** with benzyl bromoacetate in the presence of *N,N*-diisopropylethylamine (DIPEA) gave epimeric 1,5-disubstituted tetrazolyl products **352a** and **352b** and also 2,5-disubstituted tetrazolyl products **353a** and **353b**. The products were purified, but not separated, by flash column chromatography to give the regiomeric tetrazoles **352** and **353** as a mixture in 60% yield. The α -hydroxy tetrazoles **352** and **353** were then oxidized as a mixture with a solution of 2,2,6,6-tetramethyl-piperidine-1-oxyl (TEMPO) <1994JME2918> to give the regiomeric α -keto tetrazoles **354** and **355**, respectively (Scheme 41) <2001TL5641>.



In another example [<2002BML705>](#), the reduction of the keto group of intermediate α -keto tetrazoles **356** to an α -hydroxy group of tetrazole **357** (Equation 66) is an important stage in the directional synthesis of potent tripeptide α -ketoacid inhibitors of the hepatitis C virus NS3/NS4A serine protease (cf. [Section 6.07.12.1.1](#)).



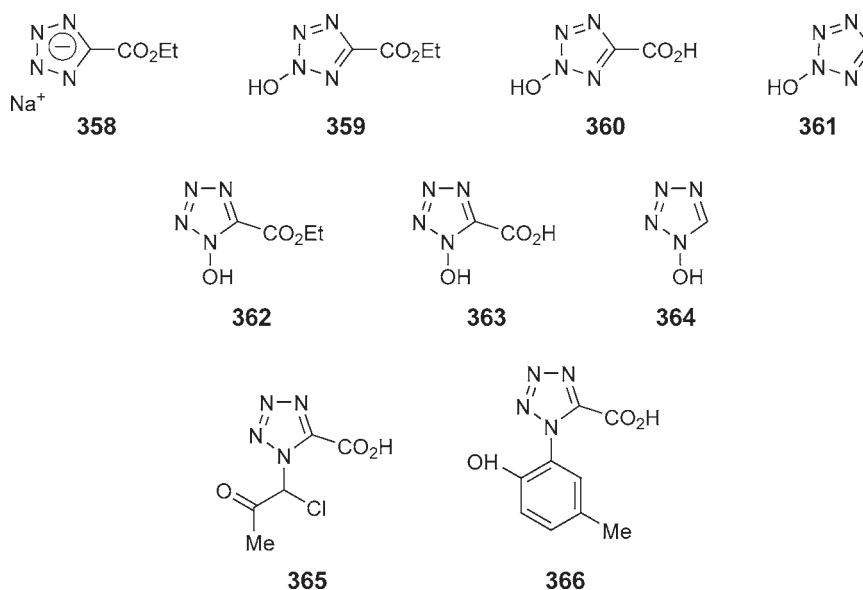
6.07.7.2.5 Carboxylic acids and their derivatives

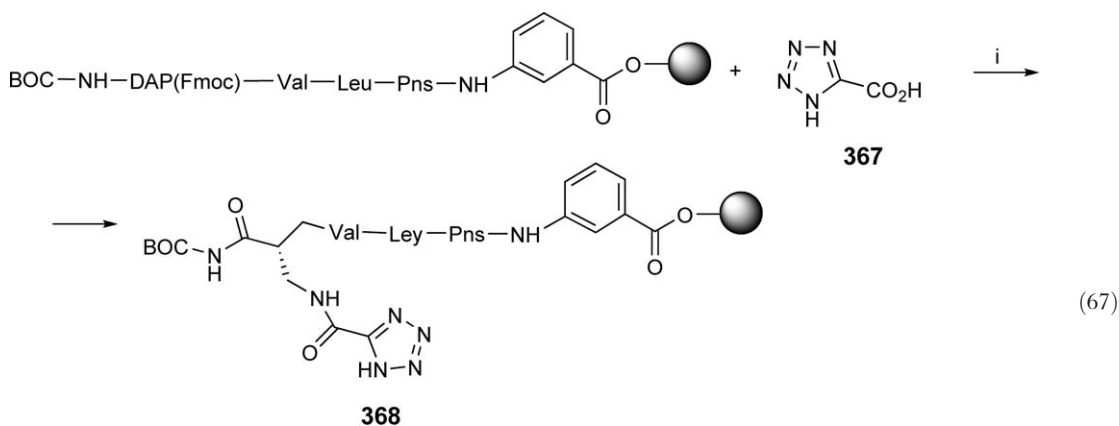
Oxidation of the sodium salt of ethyl tetrazole-5-carboxylate **358** using Oxone™ (potassium peroxymonosulfate, 2KHSO₅, KHSO₄, K₂SO₄) in aqueous acetone at pH 7.5 results in almost exclusive formation of ethyl *N*²-hydroxytetrazole-5-carboxylate **359** (*N*²:*N*¹ ~ 70:1) that can be isolated in pure form in 80% yield. Treatment of compound **359** with sodium hydroxide in ethanol at reflux for 2 h followed by acidification results in isolation of 2-hydroxytetrazole-5-carboxylic acid **360** in 81% yield [<1999TL6093>](#). Decarboxylation of carboxylic acid **360** requires severe conditions (HCl/reflux/90 h), and after workup affords 2-hydroxytetrazole **361** in 40% yield [<1999TL6093>](#). 1-Hydroxytetrazole-5-carboxylate **362** was also used as a precursor to 1-hydroxytetrazole-5-carboxylic acid **363**. Treatment of tetrazole **362** with sodium hydroxide in ethanol at reflux, followed by acidification at room temperature, results in spontaneous decarboxylation of intermediate 1-hydroxytetrazole-5-carboxylic acid **363** to give 1-hydroxytetrazole **364** in 81% yield [<1999TL6093>](#).

It was reported that the decarboxylation rate of 1-hydroxytetrazole-5-carboxylic acid **363** is considerably higher than that of isomeric 2-hydroxytetrazole-5-carboxylic acid **360** [<1999TL6093>](#).

Caution: Giles *et al.* [<1999TL6093>](#) confirm the observations of Begtrup's group [<1995J\(P1\)243>](#) regarding the explosive nature of *N*-hydroxytetrazoles.

The decarboxylation rate is affected not only by the regioisomeric nature of *N*-substituted 5-carboxylic acid but also by the character of the substituent at the endocyclic nitrogen. This is confirmed by additional data [<1996T8813>](#) where the spontaneous decarboxylation of *N*¹-substituted 5-carboxylic acids **365** and **366** is described. Apart from the unimolecular decarboxylation, the bimolecular reactions involving 5-carboxylic acids are of great interest. Among the rare examples of such reactions, a process involving 1*H*-tetrazole-5-carboxylic acid **367** yielding amides of complex structure **368** has been described (Equation 67) [<2005BML211>](#).



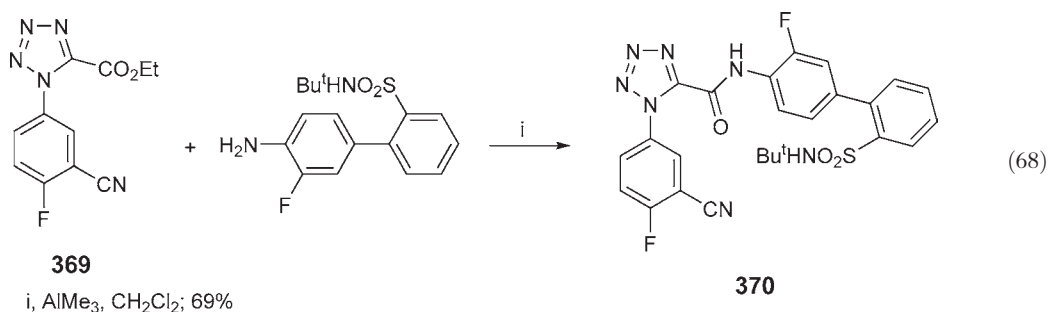


= 2-chlorotrityl resin

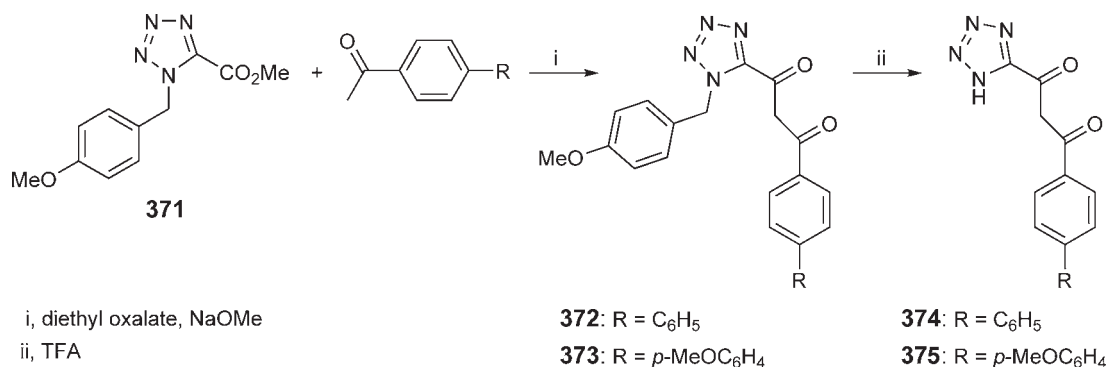
DAP = L- α,β -diaminopropionic acid

i, 20% piperidine/DMF

Esters of tetrazole-5-carboxylic acids are attractive substrates for aminolysis with various amines. These reactions are frequently involved in the synthesis of complex biologically active substances containing a tetrazole ring (cf. Section 6.07.12.1). Reactions of ethyl tetrazole-5-carboxylate **369** with anilines may be cited as an example that results in products of type **370** (Equation 68) <2003BML369>.

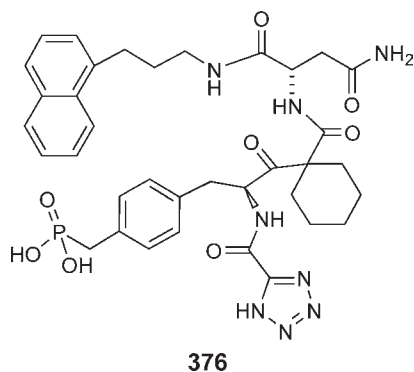


Methyl 1-(*p*-methoxybenzyl)tetrazole-5-carboxylate **371** under conditions of base catalysis reacted with substituted acetophenones giving diketones **372** and **373**. On removing the protecting group (*p*-methoxybenzyl, PMB) at position 1 of the tetrazole ring, the corresponding unsubstituted tetrazoles **374** and **375** were isolated (Scheme 42) <2004BML4915>.



Scheme 42

Coupling of aryl methyl ketones and also of indolyl methyl ketones with ethyl 1-(*p*-methoxybenzyl)tetrazole-5-carboxylate was performed by Pais *et al.* <2002JME3184>. Most of the condensation products were obtained in high yields (70–88%). However, the process in this case required considerably more severe and complex conditions (lithium hexamethyldisilazide (LHMDS), THF, -20°C , -78°C to room temperature, 1 h, room temperature, 2 h) <2002JME3184>. Burke Jr. *et al.* also reported the synthesis of complex N-terminal tetrazole-containing amides, such as **376** (cf. Section 6.07.12.1), by acylation of the corresponding amines with 1-(*p*-methoxybenzyl)tetrazole-5-carbonyl chloride, and finally carrying out the deprotection procedure <2001BMC1439>.



6.07.7.2.6 Other substituted alkyl groups

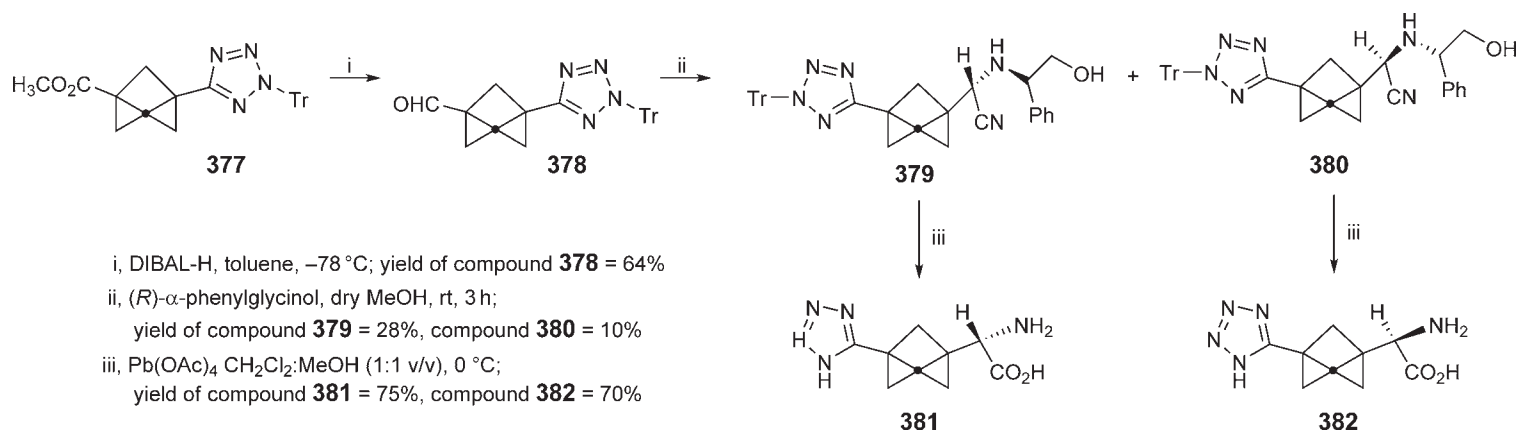
Here we restrict our survey to two arbitrarily chosen studies from a great number of publications on this topic. Note the uncommon molecular design of C-linked tetrazole derivatives in Scheme 43 <2001BMC221>. We present the multistage reaction route developed and carried out in this study: methyl 3-(2-trityltetrazol-5-yl)bicyclo[1.1.1]pentane-1-carboxylate **377**, the corresponding aldehyde **378**, (2*S*)- **379** and (2*R*)-*N*-[(*R*)- α -phenylglycinyl]-2-[3'-(2-trityl-2*H*-tetrazol-5-yl)bicyclo[1.1.1]pent-1-yl]glycinonitrile **380**, (*S*)- **381** and (*R*)-2-[3-(1*H*-tetrazole-5-yl)bicyclo[1.1.1]pent-1-yl]glycine **382** (Scheme 43) <2001BMC221>.

The results of an investigation of tetrazolylmethyl radical **385** as an intermediate in the synthesis of a variety of tetrazole derivatives <1998TL19> are interesting but subject to discussion. By treating 5-chloromethyltetrazole **383** with potassium *O*-ethyl xanthate, the tetrazolyl xanthate **384** was prepared. Upon addition of a small quantity of lauroyl peroxide to a refluxing solution of tetrazolyl xanthate **384**, and then addition of allyl acetate in benzene, a smooth reaction occurred to give the expected adduct **386** in 72% yield (Scheme 44). A variety of tetrazole derivatives are easily accessible by simply modifying the alkene trap (Scheme 44) <1998TL19>.

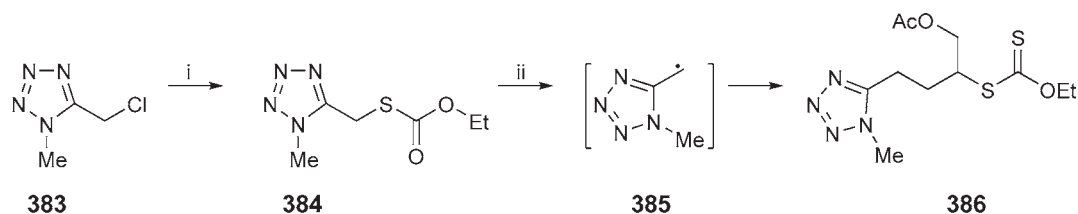
6.07.7.2.7 Vinyl group

The first representatives of *C*-vinyltetrazoles were obtained by Henry and Finnegan over 40 years ago. They proposed to apply polymers from these compounds as binders for explosives and inflammable materials. The homo- and copolymerization of NH-unsubstituted *C*-vinyltetrazole **387** and isomeric N-substituted *C*-vinyltetrazoles **388** and **389** were later studied in detail <1997MI84, 1999THS(3)467, 2003RCR143>.

Radical polymerization of *C*-vinyltetrazoles initiated by azobisisobutyronitrile, benzoyl peroxide, ammonium persulfate, transition metal acetylacetonates, and redox systems (H_2O_2 – FeSO_4 , FeSO_4 – $(\text{NH}_4)_2\text{S}_2\text{O}_8$ – $\text{K}_2\text{S}_2\text{O}_5$) are of particular interest. The NH-unsubstituted tetrazole **387** is prone to a spontaneous block polymerization without initiators at room temperature. The spontaneous polymerization of vinyltetrazole **387** was also observed on dissolving the monomer in water, ethanol, formamide, DFA, and DMSO, but in solvents like acetone, acetonitrile, etc., the monomer **387** did not undergo spontaneous polymerization. The polymerization of *C*-vinyltetrazoles proceeds in high conversion affording products of high molecular weight <2003RCR143>. The reactions of the vinyl group of *C*-vinyltetrazoles not resulting in polymerization have been less studied. Below, we give recently described examples of these reactions.



Scheme 43

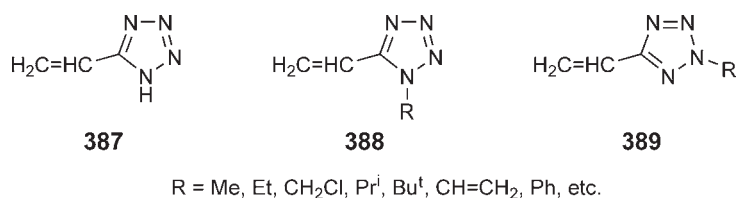


i, EtOCSSK, acetone

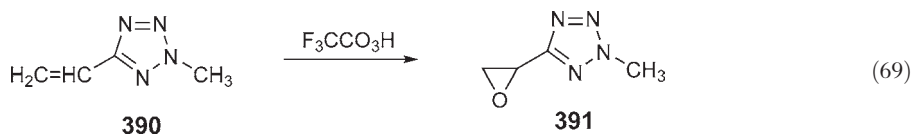
ii, degassed 1,2-dichloroethane, allyl acetate, lauroyl peroxide, reflux under argon;

yield of compound **386** = 72%

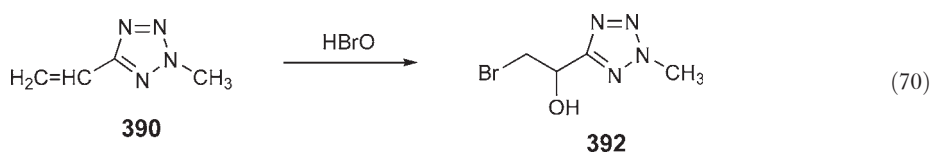
Scheme 44



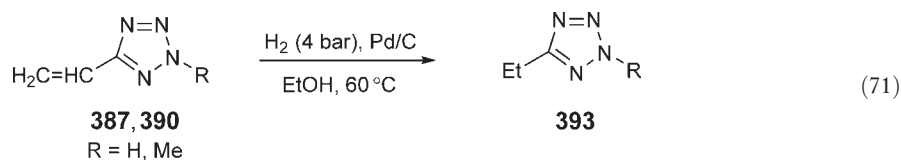
The vinyl group of the 2-methyl-5-vinyltetrazole **390** is stable on treating with hydrogen peroxide and *tert*-butyl hydroperoxide. However, 2-methyl-5-vinyltetrazole **390** with trifluoroperacetic acid gave epoxide **391** in 30% yield <1997MI98> (Equation 69).



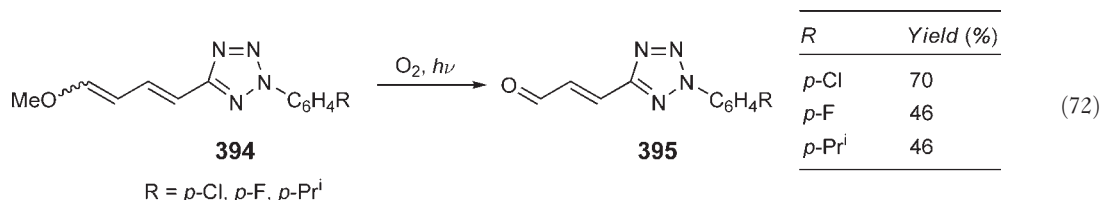
Petrov *et al.* <1997MI98> found that 2-methyl-5-vinyltetrazole **390** reacted stereospecifically with hydrobromic acid providing 2-methyl-5-(1-hydroxy-2-bromoethyl)tetrazole **392** in a quantitative yield (Equation 70).



The vinyl groups of 5-vinyltetrazole **387** and 2-methyl-5-vinyltetrazole **390** underwent hydrogenation at an excessive pressure; the tetrazole ring remained intact (Equation 71) <B-2003MI41>.



The corresponding tetrazolyldienes are even less investigated than the *C*-vinyltetrazoles. Recently, Nagy *et al.* <2003T7485> reported on the oxidative degradation of 1-methoxy-4-(2-aryltetrazol-5-yl)diene **394** yielding tetrazolyl acroleins **395** (Equation 72).

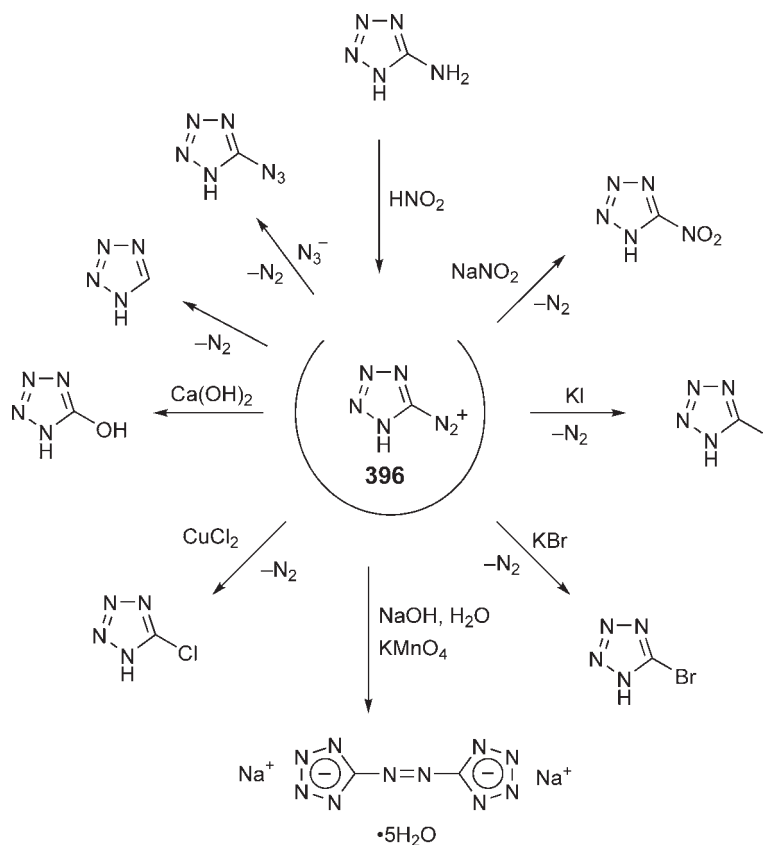


6.07.7.3 N-Linked Substituents

The analysis of recent publications shows a growing interest in the reactivity of N-linked substituents attached to the ring carbon of tetrazoles. This trend is especially evident for 5-aminotetrazole and its derivatives. The reactivity of the amino group at position 5 has for a long time been used for tetrazole functionalization <B-1967MI(8)8>. New developments encompass salts and complexes of 5-aminotetrazoles (cf. Section 6.07.5.3.4). Finally, there have been important developments in the synthesis of 5-aminotetrazole derivatives that are potentially useful for application as energetic substances (cf. Section 6.07.12.2) and biologically active compounds (cf. Section 6.07.12.1). It is important that concurrent with the above advancements 5-aminotetrazole and its derivatives become industrially available <B-1998MI536>.

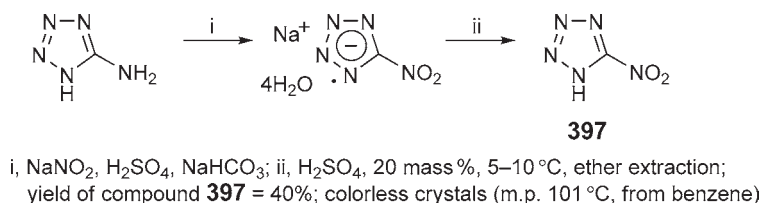
6.07.7.3.1 5-Aminotetrazole and its derivatives

Diazotization of 5-aminotetrazole leads to the formation of 5-tetrazolediazonium **396**. Further transformations of this very reactive intermediate are controlled by the reaction conditions and afford a wide range of 5-substituted tetrazoles (Scheme 45) <B-1967MI(8)8, 1975CRV241, 2005CM3784, 2005MI17, 2006AGE3584>.



Scheme 45

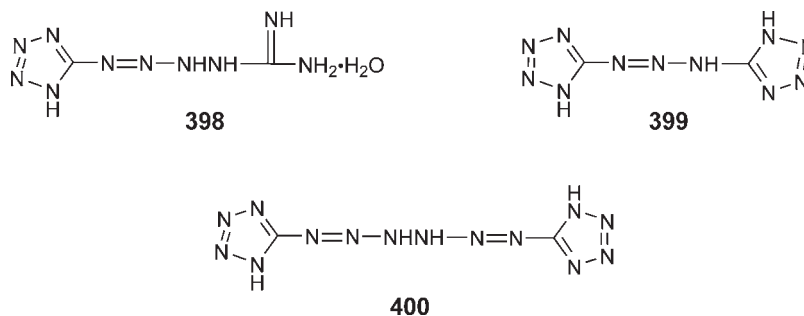
The diazotization of 5-aminotetrazole as a general preparative method for 5-substituted tetrazoles with versatile simple substituents is still important. For instance, the preparation of *N*-unsubstituted 5-nitrotetrazole **397** through 5-nitrotetrazole sodium salt tetrahydrate [<1997RJO1771>](#) is a significant achievement of the last decade and demonstrates new features of the amino group reactivity in 5-aminotetrazole derivatives (**Scheme 46**).



Scheme 46

Caution: 5-Nitrotetrazole sodium salt (tetrahydrate) when heated to temperatures higher than 50 °C loses water molecules. The anhydrous salt has high sensitivity to impact and friction.

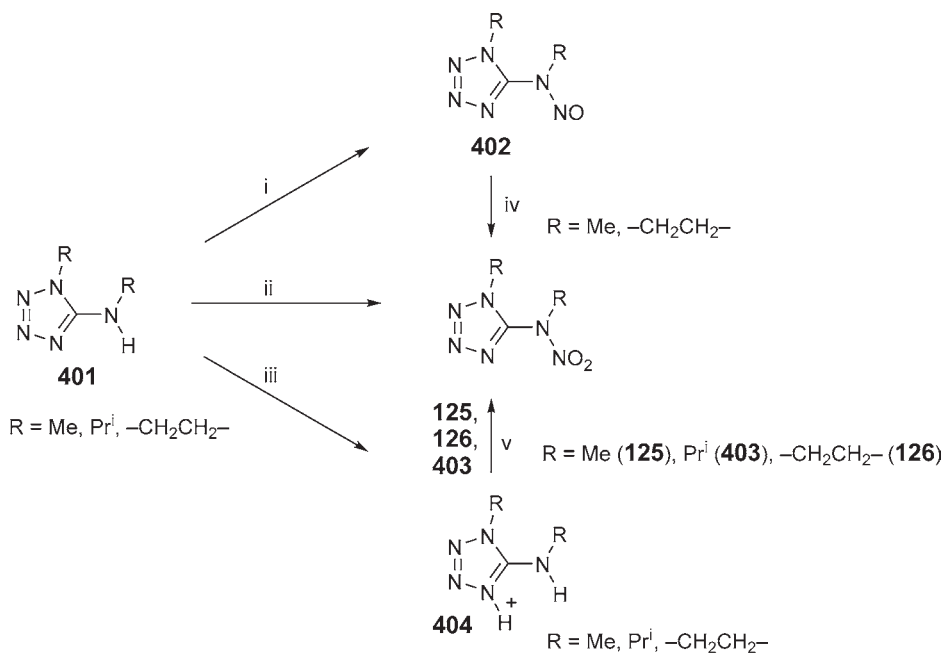
Enthalpy of formation and other thermochemical and detonation parameters of 5-nitrotetrazole are considered in [Section 6.07.4.3](#). The functionalization of 5-nitrotetrazole by reactions on endocyclic nitrogen atoms has been described [<1997RJO1771>](#) and discussed in a review [<1999THS\(3\)467>](#). Coupling of 5-tetrazoldiazonium **396** with aminoguanidine affords tetrazene **398** as a primary explosive used in ammunitions; with 5-aminotetrazole, it gives 1,3-di(tetrazole-5-yl)triazene **399** [<2006JST\(785\)114>](#). Finally, coupling of 5-tetrazoldiazonium **396** with hydrazine results in the formation of bis-5,5'-diazotetrazolyldiazene **400**, a compound which contains 87.5% of nitrogen and is extremely sensitive to impact, friction, and heating [<1999THS\(3\)467>](#).



Apart from diazotization and oxidation of the amino group of 5-aminotetrazole, other nitration processes are of great importance. Nitration of 5-aminotetrazole in sulfuric acid affords 5-nitraminotetrazole, a high-nitrogen representative of the *N*-nitramine series, and interaction of 5-aminotetrazole with tetranitromethane, hexanitroethane, and pentaerythritol tetranitrate (PETN) in alkaline media gives the corresponding 5-nitraminotetrazole salts [<1999THS\(3\)467>](#). In its turn, nitration of 5-aminoalkyltetrazoles **401** with HNO₃/Ac₂O and interaction of these substances with HNO₂ led to the corresponding 5-*N*-nitroso derivative **402** and 5-*N*-nitroalkyl derivatives **125**, **126**, and **403** (**Scheme 47**) [<2006JOC1295>](#).

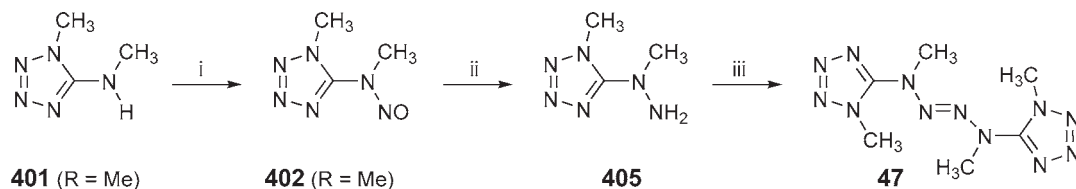
1-Methyl-5-(methylamino)-1*H*-tetrazole (**401**; R = CH₃) was used as initial reagent in the synthesis of 1,4-bis-[1-methyltetrazol-5-yl]-1,4-dimethyl-2-tetrazene **47**, a formal hexamer of diazomethane. The synthetic pathway presumably involves intermediate formation of the corresponding nitrosotetrazole **402** and hydrazinotetrazole **405** (**Scheme 48**) [<2004MI325>](#).

The exocyclic amino group of 5-aminotetrazole is reactive in nucleophilic substitution of halogen atoms in halonitrobenzenes. For example, the synthesis of 5-picrylamminotetrazole **406** is based on this process [<1999THS\(3\)467>](#). Finally, 5-aminotetrazole and 1-methyl-5-aminotetrazole **407** undergo a Mannich reaction with formaldehyde and trinitromethane with formation of products **408** (R = H, Me) [<B-1967MI\(8\)8, 1999THS\(3\)467>](#).



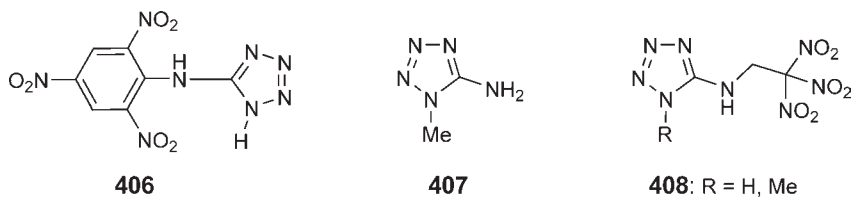
i, 2 M HCl, H₂O, NaNO₂, during mixing at 0–5 °C; stirred 5–10 °C, 30 min; pH 8; 94%;
 ii, to cooled Ac₂O 100% HNO₃ was added dropwise over 10 min; after 20 min respective tetrazole **401** was added in small portions over 10 min; iii, -8 °C, conc. H₂SO₄; iv, 90% H₂O₂, cooled CH₂Cl₂, trifluoroacetic anhydride; v, HNO₃

Scheme 47

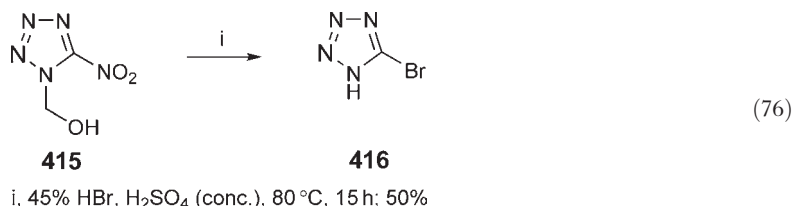


i, cold 2 M HCl, NaNO₂, H₂O, 0–5 °C;
 ii, AcOH, Zn, H₂O, 0–5 °C;
 iii, Br₂ was added dropwise, standing overnight, 10 °C; yield of compound **47** = 23%

Scheme 48



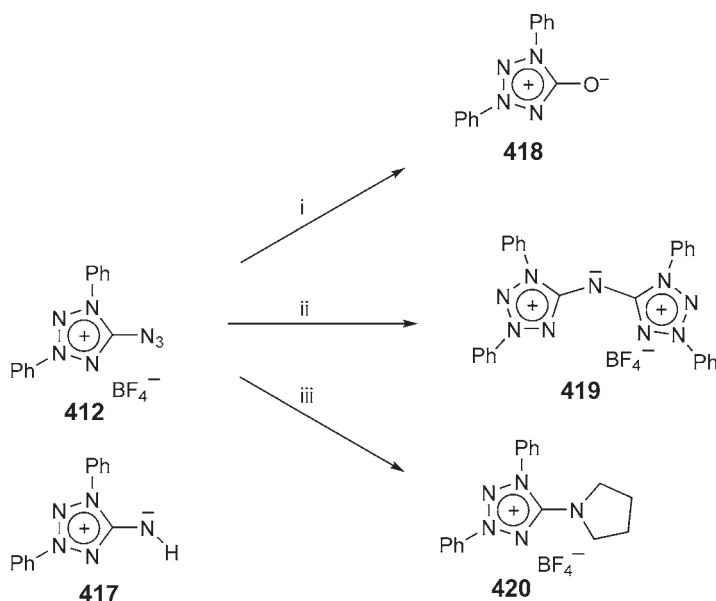
Reactions of the amino group at position 5 of 5-aminotetrazole have recently found extensive application in the syntheses of biologically active compounds. For example, at the beginning of a multistep synthesis of L-N⁶-(1-iminoethyl)lysine 5-tetrazole amide **410**, which is a prodrug of a selective inducible NO synthase (iNOS) inhibitor (cf. Section 6.07.12.1), a condensation was carried out between N^α-BOC-N⁶-Z-L-Lys-OH with 5-aminotetrazole affording phenylmethyl (5*S*)-5-[[[1,1-dimethylethoxy)carbonylamino]-6-oxo-6-(1*H*-tetrazol-5-ylamino)hexyl]carbamate **409** (Scheme 49) <2002JME1686>.



Caution: We have observed that on treating 2-methyl-5-nitrotetrazole with NaN₃ in H₂O solution a product is formed that is prone to spontaneous explosive decomposition. Apparently, under similar conditions, the nitro group is replaced by the azido group giving the corresponding 5-azidotetrazole derivative.

6.07.7.3.3 5-Azidotetrazole

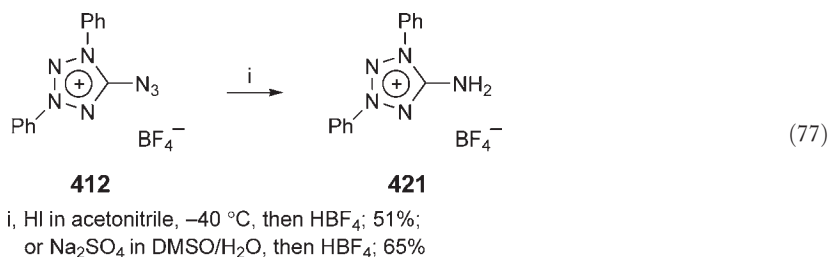
The synthesis and decomposition mechanisms of 5-azidotetrazole **3** and 1-phenyl-5-azidotetrazole have been discussed by Klapötke and co-workers <2005MI17>. However, we could not find any publications on studies of typical chemical reactions of the azido group in high-nitrogen tetrazole derivative **3** (88.3 weight percent of nitrogen), except data on some thermal reactions <2003MI65, 2005MI17>. Theoretical investigations suggest that reactions involving the azido group of compound **3** are not forbidden <1999JST(458)249, 2003MI65> (cf. Section 6.07.2.1). The poor information on the reactivity of the azido group evidently originates from the fact that compound **3** “is extremely sensitive towards friction, shock and electrostatic impact” <2005MI17>. The danger of handling 5-azidotetrazole and its salts was reported by Thiele (1895), Rathsburg (1928), Friederich (1937), and was also pointed out in a review <1999THS(3)467>. However, transformations of the azido group at position 5 of the tetrazole ring in 1,3-diaryl-5-azidotetrazolium salts **412** have been described <1998EJO121>; the reaction between 1-phenyl-5-aminotetrazole **33** and tetrazolium salt **412** is shown in Equation (74). In this study <1998EJO121>, other substitution reactions of the azido group in compound **412** were also performed by treating with nucleophilic reagents, such as OH[−], 1,3-diphenyltetrazolio-5-amide **417**, and pyrrolidine, to obtain products **418–420** in high yields (Scheme 50) <1998EJO121>.



- i, 1 N NaOH, DMF, stirred for 1 h; yield of compound **418** = 87%
 ii, a mixture of reagents **412** and **417** in acetonitrile was stirred at rt for 10 min;
 yield of compound **419** = 82%
 to a solution of **412** in dichloromethane were added
 iii, a few drops of pyrrolidine; the mixture was stirred for 10 min; yield of compound **420** = 86%

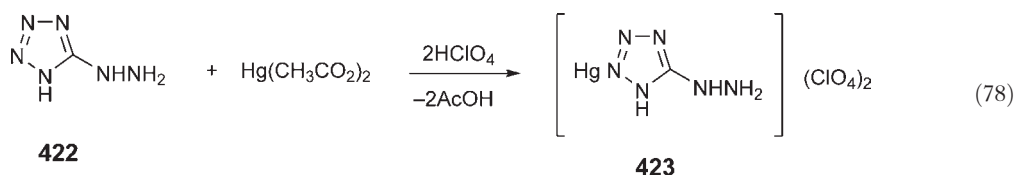
Scheme 50

It has also been reported that the azido group of azidotetrazolium salt **412** is readily reduced by hydroiodic acid or sodium sulfite to give the aminotetrazolium salt **421** (Equation 77) <1998EJO121>.



6.07.7.3.4 Other N-linked substituents

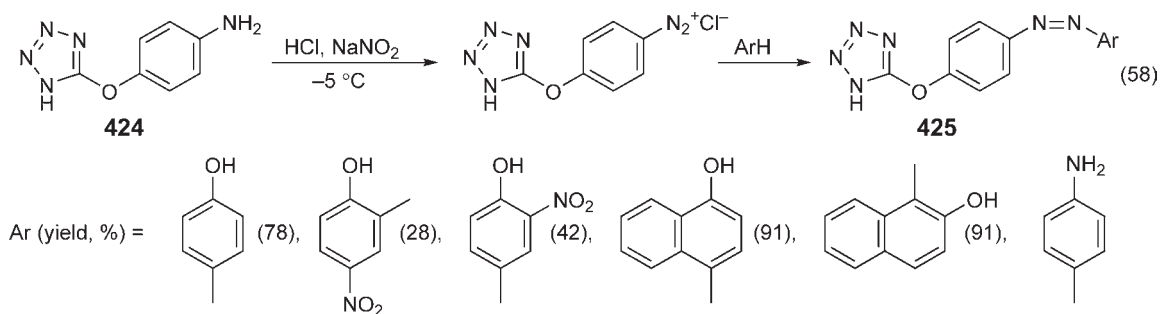
The 5-hydrazinotetrazole **422** is known to be used in the preparation of energetic coordination metal complex systems, for example, the perchlorate complex of mercury(II) with 5-hydrazinotetrazole **423** (cf. Section 6.07.12.2) (Equation 78) <2005MI21>.



However, the reactivity of 5-hydrazinotetrazole **422** in reactions typical of a hydrazine is poorly documented. An example of the reactivity of some derivatives of 5-hydrazinotetrazole (e.g., **405**) in the synthesis of high-nitrogen tetrazole derivatives, such as 1,4-bis-[1-methyltetrazol-5-yl]-1,4-dimethyl-2-tetrazene **47**, is shown in Scheme 48 <2004MI325>.

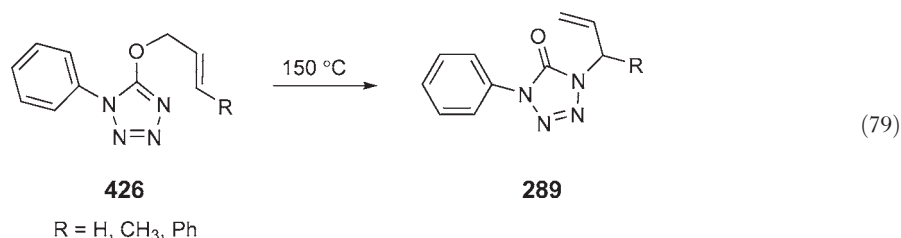
6.07.7.4 O-Linked Substituents

The reactivity of 5-tetrazolones as examples of isomers of fully conjugated rings is discussed in Section 6.07.6. The number of available studies on the reactivity of O-linked substituents attached to ring carbon is relatively small. The synthesis of new azo-dyes **425** containing the aryloxytetrazole functional group was reported. The 5-(4'-aminophenoxy)tetrazole **424** was diazotized and coupled with electron-rich aromatic rings (Scheme 51) <2002DP(54)37>.



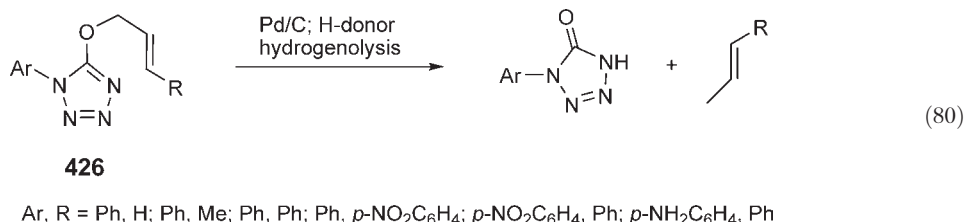
Scheme 51

We have already (cf. Section 6.07.6) referred to research carried out by Cristiano and co-workers, where a new strategy was developed for the synthesis of 3,4-dihydro-6-substituted-3-phenylpyrimidin-2(1*H*)-ones based on photolysis of 4-allyltetrazolones **289** <2005TL6757>. One of the elements of this strategy includes the conversion of 5-allyloxytetrazoles **426** into tetrazolone **289** (Equation 79) <2005TL6757>.



(79)

It should be mentioned that in the publications of Cristiano *et al.* [<1996J\(P1\)1453, 1997J\(P2\)489, 1997JCM164, 2006JOC3583>](#), apart from the thermal process, an alternative reaction pathway was considered which is Pd/C, H-donor hydrogenolysis (Equation 80).

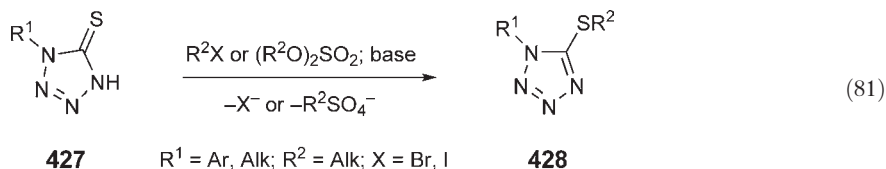


(80)

6.07.7.5 S-Linked Substituents

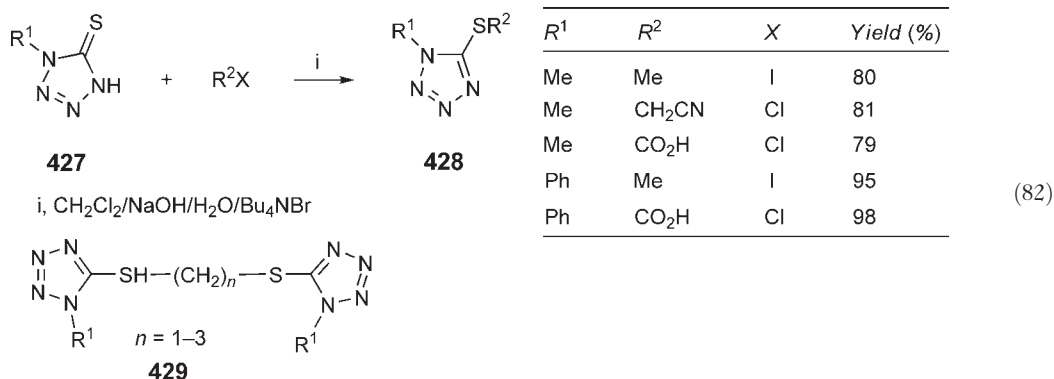
Preparative methods and chemical properties of tetrazole-5-thiones (tetrazole-5-thiols) have been summarized in a review [<2004RJO447>](#). The most significant results in this field were obtained in the last decade while studying the alkylation of tetrazole-5-ylthiones (tetrazole-5-ylthiols), and the oxidation of 1-substituted 5-alkylsulfatetrazoles to the corresponding sulfinyl and sulfonyl derivatives. Special attention should be paid to the Kocienski-modified Julia olefination based on the application of 5-alkylsulfonyltetrazoles to the activation of chemical reactions.

It was shown in early publications [<2004RJO447>](#) that the direction of the alkylation of 1-substituted-1*H*-tetrazol-5-ylthions **427** with alkyl halides and alkyl sulfates in the presence of bases does not depend on the structure of the substituent at position 1 and occurs selectively at the sulfur atom [<2004RJO447>](#), affording 1-substituted 1*H*-(tetrazol-5-yl)alkylsulfa derivatives **428** (Equation 81).

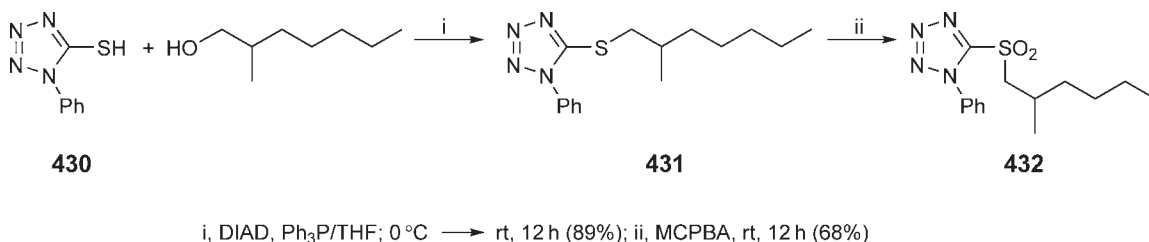


(81)

The high selectivity of alkylation of 1-substituted-1*H*-tetrazol-5-ylthions **427** with alkyl halides and alkyl sulfates under homogeneous conditions was confirmed in a series of studies published since 1996 [<1996CCC791, 2000SL365, 2002J\(P1\)2563, 2002T4425, 2002JA12420>](#). The same conclusion followed from the alkylation of 1*H*-tetrazol-5-ylthions **427** under PTC conditions [<1996RJO1194, 1996RJO1367, 1999RJO1820>](#). The alkylation of 1*H*-tetrazol-5-ylthions **427** with dibromoalkanes under the PTC conditions also gave ditetrazoles **429** (Equation 82) [<1996RJO1194>](#).



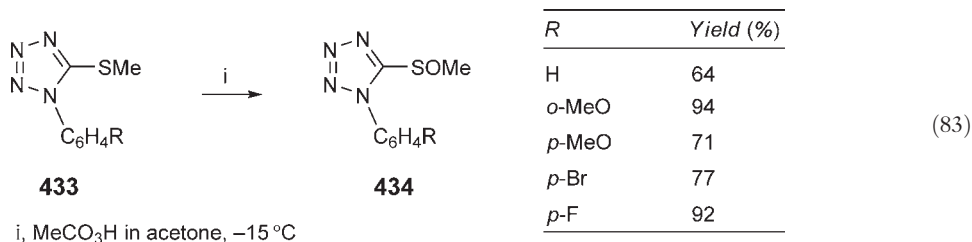
Recently, an alternative synthesis of 1-alkyl(aryl)-1*H*-substituted 5-alkylsulfatetrazoles by alkylation of the corresponding 1*H*-tetrazole-5-ylthions (thiols) with aliphatic alcohols according to the Mitsunobu protocol has found an extensive application. Under these conditions, the S-linked derivatives formed exclusively, as for the already-considered alkylation with alkyl halides and alkyl sulfates <1998SL26, 1999OL1491, 1999JOC9632, 2002JA9328>. For example, the alkylation of 1-phenyl-1*H*-tetrazole-5-thiol **430** with 2-methyl-1-heptanol furnished the product of S-alkylation, **431**, whose oxidation with *m*-chloroperoxybenzoic acid (MCPBA) provided sulfonyltetrazole **432** (Scheme 52) <1998SL26>.



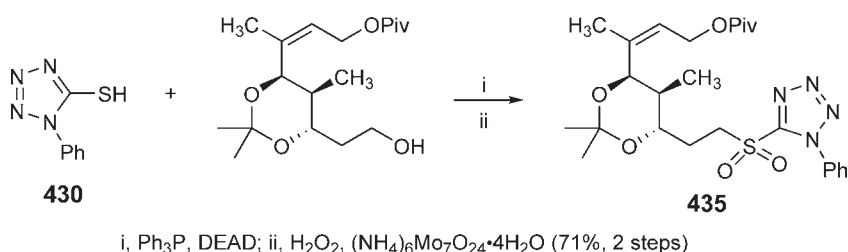
Scheme 52

The oxidation of sulfanyltetrazoles presents a special problem in that treating with oxidants can provide both the sulfinyl (SO) and sulfonyl (SO₂) derivatives. Different oxidants are employed in order to obtain various target products. Apart from the already-mentioned (Scheme 52) MCPBA <1998SL26, 2000SL365>, peroxyacetic acid <2004TL7955>, H₂O₂ <2000JOC3738, 2001T681, 2004RJO447>, the system H₂O₂-(NH₄)₆Mo₇O₂₄·4H₂O <1999OL1491, 2000JOC3738, 2001OL1685>, KMnO₄ <1996RJO1194, 1999RJO1511, 2000RJO916, 2003RJO1679>, and also Oxone™ <2000SL365, 2002JA9328> are used. The selectivity of sulfinyl or sulfonyl formation is controlled by an appropriate choice of the oxidant and of the conditions of the process. The oxidation of 1-substituted-5-alkylsulfanyltetrazoles by MCPBA in CH₂Cl₂ or CHCl₃ at 0 °C led to 5-alkylsulfanyltetrazoles, whereas at 18–20 °C the corresponding sulfonyltetrazoles were obtained <1999JOC6730, 2004RJO447>. It has been shown that in the oxidation of sulfanyltetrazoles by MCPBA only the sulfanyl group is involved in the reaction leaving other functional groups intact <2001EJO503, 2002J(P1)2563, 2002AGE176>. Below are given some typical examples demonstrating the preparation of sulfinyltetrazoles from the respective sulfanyltetrazoles.

The oxidation of sulfanyltetrazoles **433** with peroxyacetic acid gives the corresponding sulfinyltetrazoles **434** in high yield (Equation 83) <2004TL7955>.

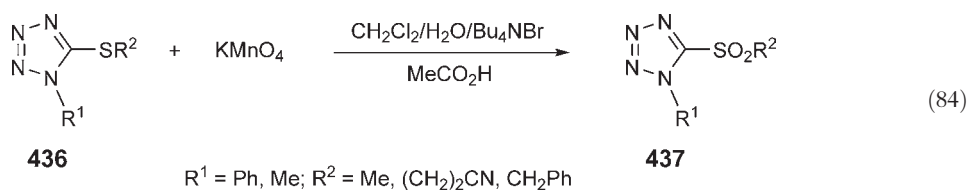


While oxidation of 5-alkylsulfanyl-1-substituted tetrazoles with 30% hydrogen peroxide afforded sulfinyl derivatives <2004RJO447>, the use of a catalytic oxidation system H₂O₂-(NH₄)₆Mo₇O₂₄·4H₂O led to sulfonyl derivatives in high yield <1999OL1491, 2000JOC3738, 2001OL1685>. This is illustrated by the synthesis of sulfone **435** (Scheme 53). Note that this procedure combining alkylation at sulfur with subsequent oxidation of the alkylsulfanyl group (Schemes 52 and 53) has found an application in the stereoselective synthesis of complex molecules containing optically active centers (Scheme 53) <1999OL1491>.



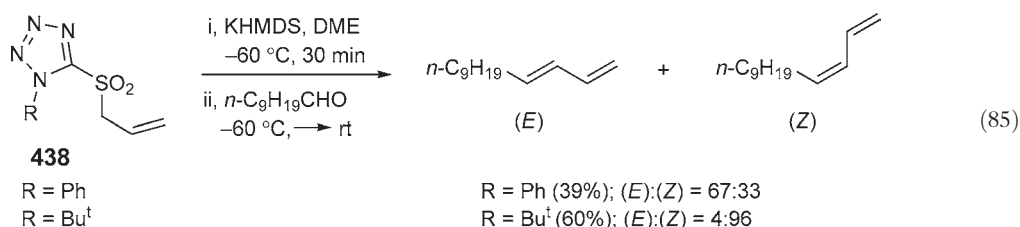
Scheme 53

Among the other oxidants, potassium permanganate and Oxone™ should be mentioned. Oxidation with potassium permanganate occurs most efficiently under PTC conditions (Equation 84) <1996RJO1194, 1999RJO1511, 2000RJO916, 2003RJO1679>.



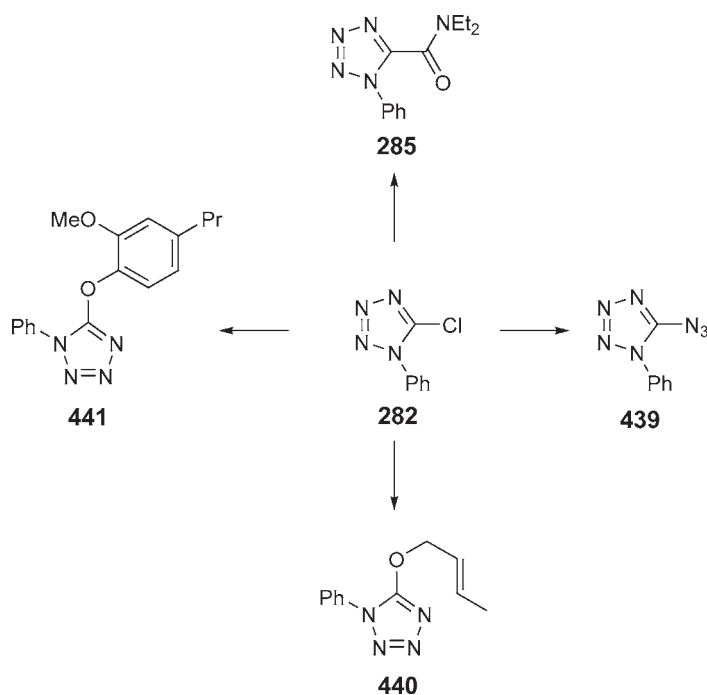
In the reaction of Oxone™ with 1-substituted-1*H*-5-alkylsulfanyltetrazoles **436**, the yield of the corresponding sulfone **437** depends on the structure of the substituent attached to sulfur. For instance, 5-(*n*-butyl)sulfanyl-1-(*t*-butyl)tetrazole with Oxone™ in methanol gave the corresponding sulfone in 81% yield, whereas the oxidation of 5-benzylsulfanyl-1-(*t*-butyl)tetrazole formed only 12% of the sulfone <2000SL365>.

Kocienski and co-workers demonstrated that the reaction of 1-substituted-5-alkylsulfonyltetrazoles **438** with aldehydes in the presence of sodium or potassium hexamethyldisilazides (NaHMDS or KHMDS) in dimethoxyethane (DME) at -60°C leads to stereoselective formation of *trans*-1,2-disubstituted alkenes in high yield <1998SL26, 2000SL365, 2002J(P1)2563>. This procedure is known as the Julia–Kocienski olefination. The advantage of the Kocienski-modified Julia method <1973TL4833, 1991TL1175> consists of the possibility of controlling the yield and the ratio of isomeric (*E*)- and (*Z*)-alkenes (Equation 85) <2002J(P1)2563>.



6.07.7.6 5-Halotetrazoles

Information on the reactivity of 5-halotetrazoles appears in several sections of this chapter (cf. Sections 6.07.5.4, 6.07.5.5, 6.07.7.3.3, and 6.07.7.4), although the topics treated in these sections are different. This demonstrates that 5-halotetrazoles are key reagents in the synthesis of substituted tetrazoles. Products **285**, **439**, and **440**, whose synthesis has been described <2004JOC1360, 2005MI17, 2005TL6757>, and compound **441** <2001CJC1201> are shown in Scheme 54. Taking into account that compounds **441**, **285**, **439**, and **440** were prepared from the same substrate (5-chloro-1-phenyl-1*H*-tetrazole **282**, Scheme 54), the reactivity of the halogen atom at position 5 undoubtedly provides the widest opportunities for the functionalization of tetrazoles (Scheme 54).



Scheme 54

6.07.8 Reactivity of Substituents at Ring Nitrogens

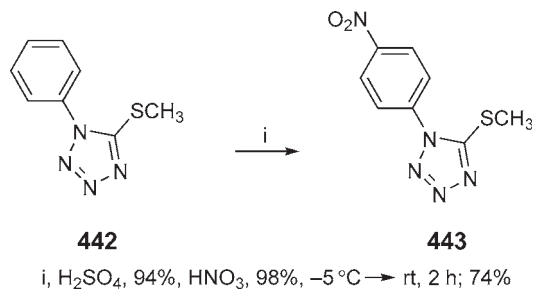
6.07.8.1 General Survey

Recent achievements in the synthesis of NH-unsubstituted tetrazoles [<2000CHE759>](#) and success in the development of methods by which substituents may be introduced in different positions to nitrogens of the tetrazole ring [<2000H\(53\)1421, 2006RJO494>](#) are clear from the material of previous sections. This research performed within the last decade made urgent the study of reactivity of substituents at ring nitrogen. We draw attention in this section to new publications significantly contributing to the understanding of this problem.

6.07.8.2 C-Linked Substituents

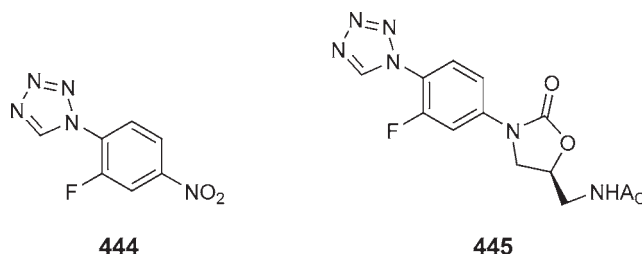
6.07.8.2.1 Aryl and hetaryl groups

In reviews of tetrazoles [<B-1967MI\(8\)8, B-1984MI149, 1994RCR797>](#), aromatic electrophilic nitration of *N*-aryltetrazoles has traditionally found detailed consideration. However, only a few recent publications treat this problem. Electrophilic nitration of 1-phenyl-5-methylthiotetrazole **442** with a mixture of concentrated nitric and sulfuric acids afforded 1-(4-nitrophenyl)-5-methylthiotetrazole **443** (Equation 86) [<1999RJO1511>](#).

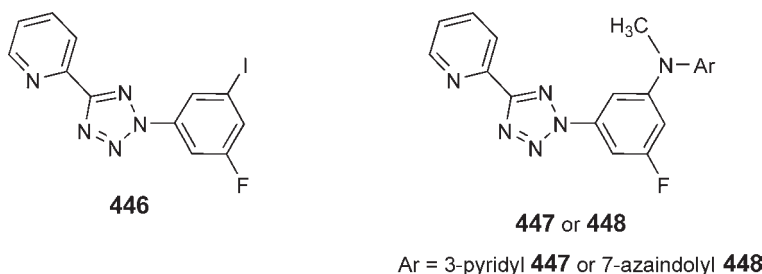


(86)

Interestingly, the electron-withdrawing substituent (tetrazol-1-yl) directed the attack of nitronium cation at position 4 of the phenyl ring. Evidently, in this event, the regioselectivity of the acid-catalyzed electrophilic aromatic nitration originated from electronic $\pi\pi$ -interaction of the carbocyclic and heterocyclic rings in the initial substrate. Similar results were obtained <1999BML1251> when *p*-nitrophenyltetrazolone **293** was synthesized by nitration of *N*-phenyltetrazolone **292** using nitronium tetrafluoroborate (cf. Section 6.07.6, Scheme 36) <1999BML1251>. However, it should be noted that the electronic structures of fully conjugated tetrazole and nonconjugated tetrazolone are different (cf. Section 6.07.2.1). The nitro group on the phenyl ring of 1-phenyltetrazoles can be converted into other functional substituents. For instance, synthesis of tetrazol-1-yl oxazolidinone **445** from the corresponding nitro derivative **444** has been described <2000JME953>.

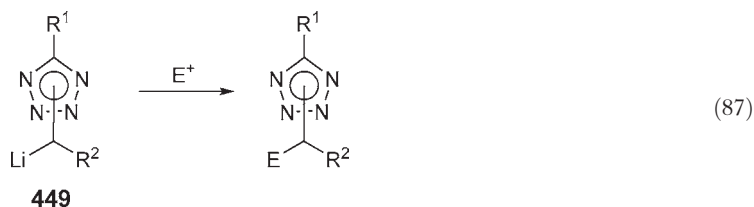


Intramolecular nucleophilic aromatic substitution (S_NAr) in *N*-2-fluorophenyltetrazoles **346** affords tricyclic tetrazolo[1,5-*a*]quinoxaline **347** in good yield <2006TL2041> (cf. Section 6.07.7.2.3, Equation 64). A selective procedure was developed for replacing one of the two halogen atoms in the aryl group on the tetrazole ring nitrogen. Using palladium-catalyzed heteroatom cross-coupling between an aryl iodide and an appropriately substituted aniline, the iodine in substrate **446** was replaced by 3-pyridyl or 7-azaindolyl to obtain derivatives **447** and **448**, respectively <2004BML5473>.

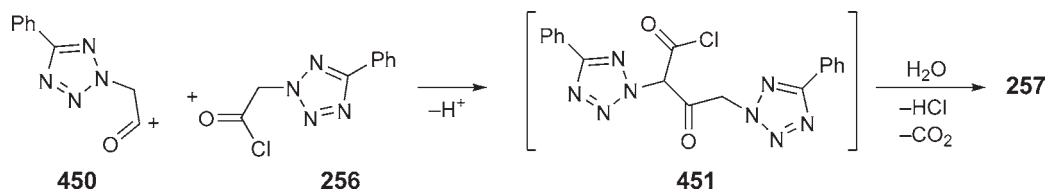


6.07.8.2.2 Alkyl group

Substituents can be introduced into the α -position of *N*-alkyl groups of tetrazoles by treating α -lithioalkyltetrazoles **449** with electrophilic reagents, such as D_2O , aldehydes, ketones, nitriles, trimethylsilyl chloride (TMS-Cl), and Me_2SO_4 (Equation 87) <1996CHEC-II(4)621>.

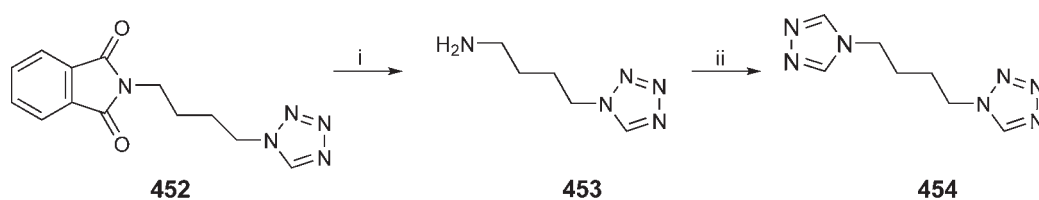


A hydrogen in the methylene group is replaced on attack by acylium ion **450** on the carbon of the α -methylene group in tetrazolylacetyl halide **256** furnishing (via intermediate **451**) ditetrazolyl ketone **257** (Scheme 55) <1996MC24>.



Scheme 55

Synthesis of 4-(1*H*-tetrazol-1-yl)butylamine **453** from 2-[4-(1*H*-tetrazol-1-yl)butyl]isoindoline-1,3-dione **452** has been reported [<2006S1504>](#). In a subsequent reaction, butylamine **453** was converted in low yield into 1-[4-(4*H*-1,2,4-triazol-4-yl)butyl]-1*H*-tetrazole **454** (Scheme 56) [<2006S1504>](#).

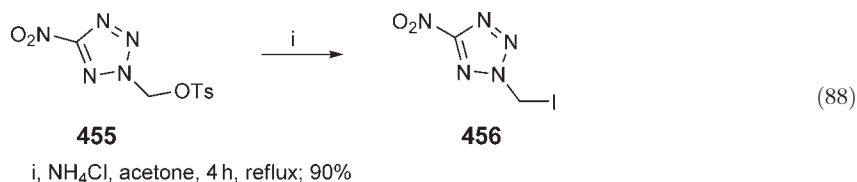


i, $\text{NH}_2\text{NH}_2 \cdot \text{H}_2\text{O}$, EtOH, reflux, 2 h; yield of compound **453** = 45%

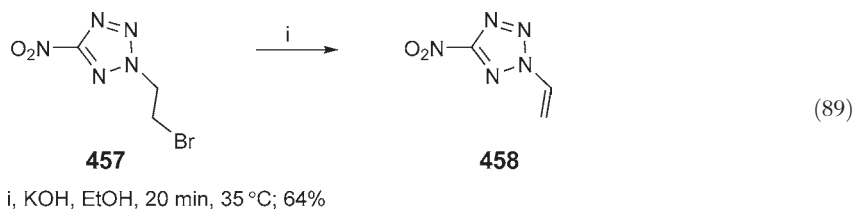
ii, formyl hydrazine, $\text{HC}(\text{OEt})_3$, MeOH, reflux, 6 h; yield of compound **454** = 9%

Scheme 56

Another example of the replacement of the terminal group in an *N*-alkyl substituent is the preparation of 2-iodomethyl-5-nitrotetrazole **456** from 5-nitrotetrazol-2-ylmethyl toluenesulfonate **455** (Equation 88) <1997RJO1771>.

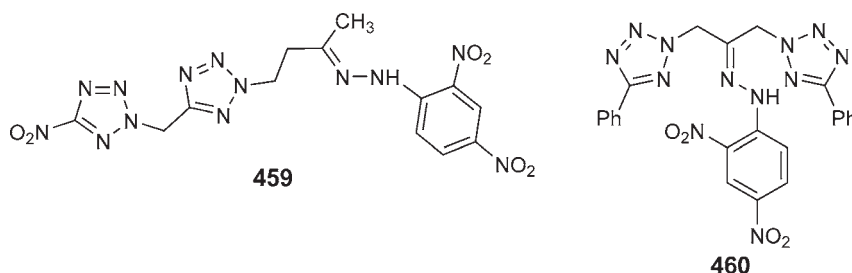


As previously mentioned (cf. [Sections 6.07.4.2.2 and 6.07.5.3](#)), 2-(1-methylvinyl)tetrazoles **201** have been obtained by regioselective alkylation of tetrazole **2** and 5R-tetrazoles **24** with 1-halopropan-2-ols and 3-bromopropene followed by dehydrohalogenation of the intermediate products **266** ([Scheme 30](#)) [<1997MC41>](#). Similarly, dehydrobromination of 2-bromoethyl-5-nitrotetrazole **457** afforded in good yield 2-vinyl-5-nitrotetrazole **458** ([Equation 89](#)) [<1997RJO171>](#).

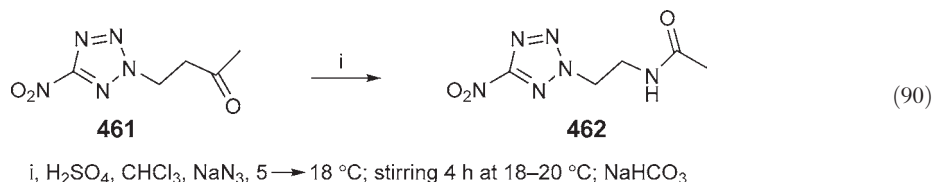


6.07.8.2.3 Aldehydes and ketones

No recent publications on the reactivity of aldehyde groups in substituents at ring nitrogen could be found in the literature. Several articles have appeared treating the problem of reactivity of ketones. 4-[5-(Nitrotetrazol-2-ylmethyl)tetrazol-2-yl]butan-2-one <1997RJO1771> and also bis(5-phenyltetrazol-2-yl)acetone <1996MC24> with 2,4-dinitrophenylhydrazine (DNP) give the corresponding 2,4-dinitrophenylhydrazones **459** and **460**. The yield of compound **460** was 70% <1996MC24>.

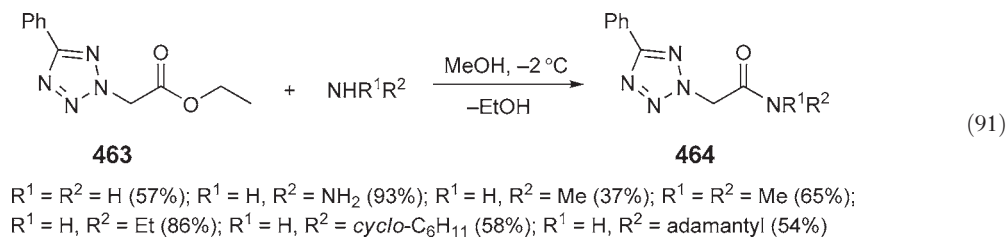


The Schmidt reaction of 4-(5-nitrotetrazol-2-yl)butan-2-one **461** has been described <1997RJO1771>. On acid-catalyzed addition of HN_3 to a protonated carbonyl group followed by sextet rearrangement, the bulkier hetarylethyl group suffered migration, resulting in formation of [(5-nitrotetrazol-2-yl)ethyl]acetamide **462** in 41% yield (Equation 90) <1997RJO1771>.

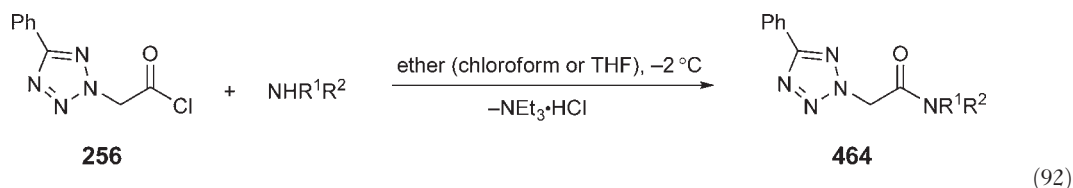


6.07.8.2.4 Carboxylic acids and their derivatives

The most interest in the preparation and reactivity of tetrazolyl acetic acids occurred in the 1970s (Raap *et al.*, 1969; Einberg, 1970; Sorensen and Klitgaard, 1972); and in the 1980s (Ostrovskii and Koldobskii, 1982). This interest was generated by development and commercialization of the semisynthetic β -lactam antibiotics cefazoline and ceftazole. Tetrazol-1-yl acetic acid **162** was involved in the production process of the corresponding active pharmaceutical ingredients <2005MI593> (cf. Section 6.07.12.1.2). Recently, new information on the reactivity of tetrazolyl acetic acid and the corresponding derivatives appeared. It was shown using ethyl 5-phenyltetrazol-2-yl acetate **463** that aminolysis is an efficient method for the preparation of corresponding primary amides **464**. The efficiency of aminolysis using primary amines depends on the basicity of the initial amine: highly basic amines possess higher reactivity regardless of the spatial structure of the substituent. Reaction of ester **463** with secondary amines gave ambiguous results (Equation 91) <2001CHE698>.

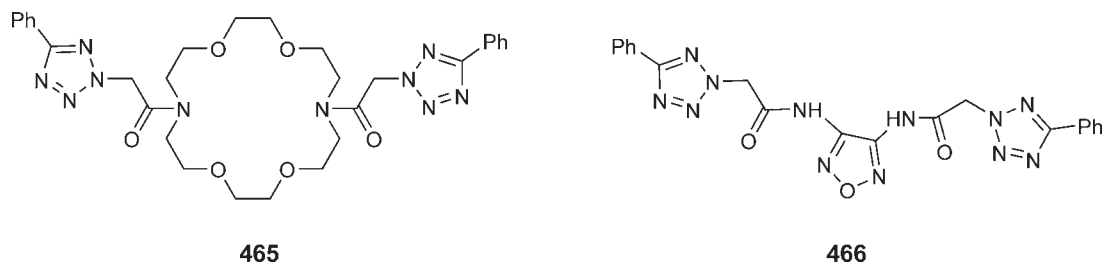


The acylation of primary and secondary amines by 5-phenyltetrazol-2-ylacetyl chloride **256** leads to the corresponding tetrazolylacetamides **464** irrespective of the nature of the substituent on the amine (Equation 92) <2004CHE854>.

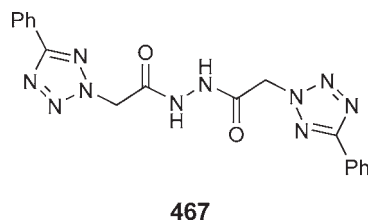


$\text{R}^1 = \text{R}^2 = \text{Et}$ (48%); $\text{R}^1 = \text{R}^2 = \text{CH}_2\text{CH}_2\text{CN}$ (73%);
 $\text{R}^1\text{R}^2 = (\text{CH}_2)_2\text{O}(\text{CH}_2)_2$ (26%); $\text{R}^1\text{R}^2 = (\text{CH}_2)_2\text{N}(\text{CO}_2\text{Et})(\text{CH}_2)_2$ (40%);
 $\text{R}^1\text{R}^2 = (\text{CH}_2)_5$ (42%); $\text{R}^1 = \text{H}$, $\text{R}^2 = \text{Ph}$ (70%), $\text{R}^2 = p\text{-NO}_2\text{C}_6\text{H}_4$ (66%);
 $\text{R}^2 = m\text{-NO}_2\text{C}_6\text{H}_4$ (78%), $o\text{-NO}_2\text{C}_6\text{H}_4$ (71%), $\text{R}^2 = 3,5\text{-(NO}_2)_2\text{C}_6\text{H}_3$ (68%), $\text{R}^2 = \text{MeCHPh}$ (65%);
 $\text{R}^2 = 1,2,4\text{-triazol-4-yl}$ (68%), $\text{R}^2 = 4\text{-methylfuran-3-yl}$ (71%)

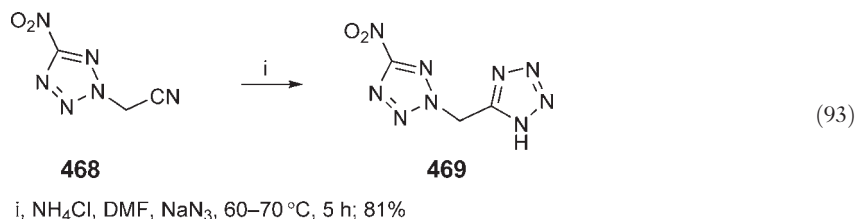
Transacylation of 5-substituted tetrazoles with acyl halide **256** affording bistetrazolyl ketones is described in Section 6.07.5.3 <1996MC24>. Effective acylation of sterically hampered and low-basic amines with 5-phenyltetrazol-2-ylacetyl chloride **256** extended this strategy to the synthesis of amides from bifunctional amines. Acylation with a 2 M excess of acyl chloride **256** was performed with model bifunctional amines: diazo-18-crown-6 having sterically blocked amino groups, and 3,4-diaminofurazan, which contained amino groups of reduced nucleophilicity. In both cases, products of exhaustive substitution were obtained, viz. *N,N'*-bis(5-phenyltetrazol-2-ylacetyl)-1,4,10,13-tetraoxa-7,16-diazacyclooctadecane **465** and *N,N'*-bis(5-phenyltetrazol-2-ylmethylcarbonyl)-3,4-diaminofurazan **466** <2004CHE854>.



Exhaustive acylation of hydrazine by 5-phenyltetrazol-2-ylacetyl chloride **256** (toluene, triethylamine, 10 h, $-2\text{ }^\circ\text{C}$) led to the formation of *N,N'*-bis(5-phenyltetrazol-2-ylmethylcarbonyl)-1,2-hydrazine **467** (yield 41%) <2004CHE854>.

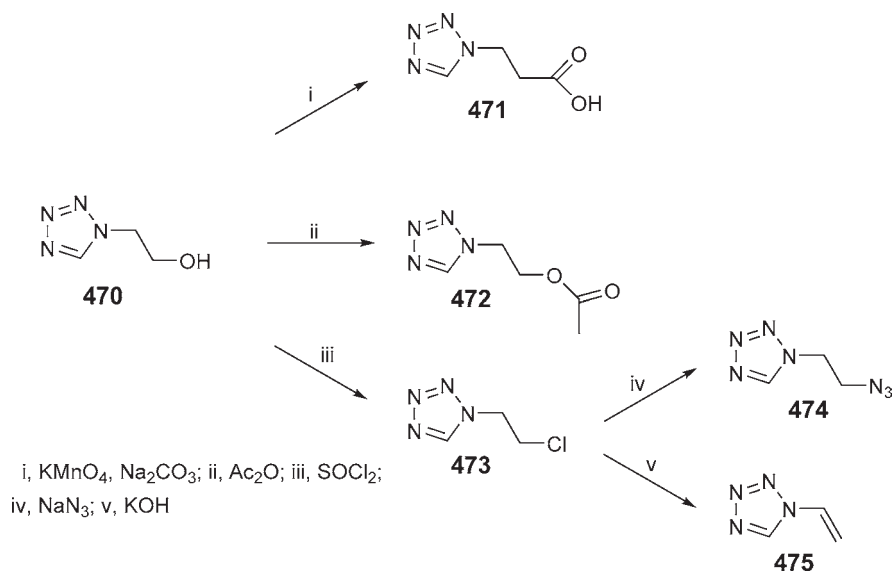


1,3-Dipolar cycloaddition of ammonium azide to 5-nitrotetrazolacetonitrile **468** afforded 5-(5-nitrotetrazol-2-ylmethyl)tetrazole **469** (Equation 93) <1997RJO1771>.



6.07.8.2.5 Other substituted alkyl groups

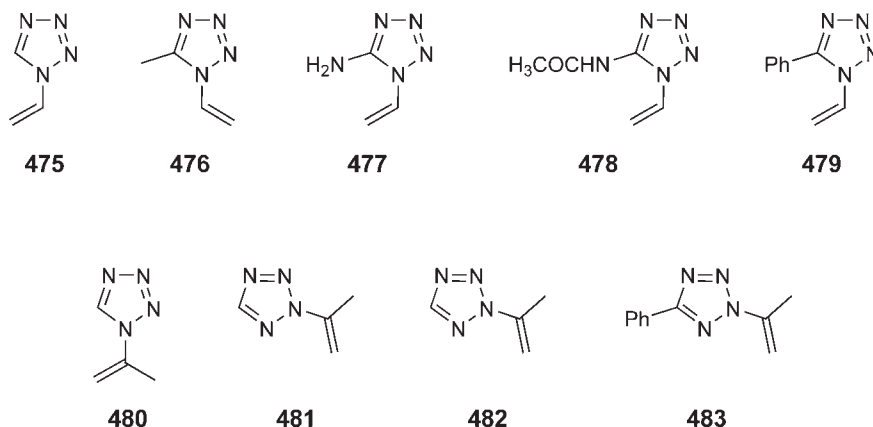
1-(2-Hydroxymethyl)tetrazole **470** was shown to be a key reagent for preparation of versatile *N*-alkyltetrazoles, for instance, compounds **471–475** (Scheme 57) <1985KGS1422, 2000TH1>.



Scheme 57

6.07.8.2.6 Vinyl group

N-Vinyltetrazoles are prone to radical polymerization commonly effected by the use of initiators. Polymerization kinetics have been thoroughly studied for 1-vinyltetrazoles **475–479** and *N*-isopropenyltetrazoles **480–483** <2003RCR143, 2003RCR143>.



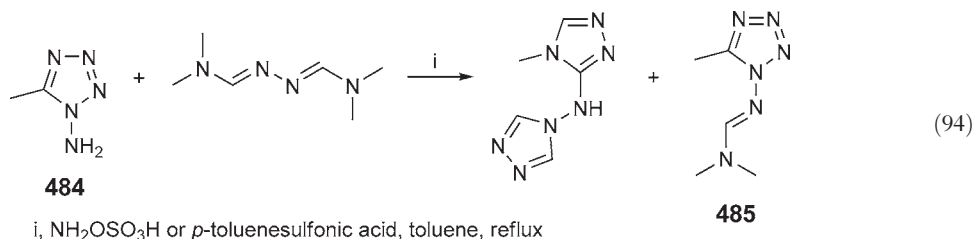
Polymerization rate, yield, and intrinsic viscosity of the macromolecular products depend on monomer structure, initiator, reaction temperature, and solvent. The reaction rate and reagent conversion sharply increased in water in the presence of a redox system [FeSO_4 –(NH_4) $_2\text{S}_2\text{O}_8$ – $\text{K}_2\text{S}_2\text{O}_5$]. Monomers **475** and **476** under these conditions polymerize virtually instantly with considerable heat liberation. Polymerization of *N*-isopropenyltetrazoles **480–483** yielded polymers of relatively low molecular weight as compared to those obtained from 1-vinyltetrazoles **475–479** <2003RCR143>.

6.07.8.3 N-Linked Substituents

6.07.8.3.1 1,5-Diaminotetrazole and 1-amino-5-methyltetrazole

1,5-Diaminotetrazole **33** with carbonyl and dicarbonyl compounds forms the corresponding Schiff bases, and the amino group at position 1 is the most reactive <2000TH1>. Reaction of 1,5-diaminotetrazole **33** with chalcones (1,3-diphenylpropenones) has been studied <2006JST(785)114> and was considered in Sections 6.07.5.2.3 and 6.07.7.3.1. The procedures for preparation from 1,5-diaminotetrazole **33** of energy-rich tetrazolium salts **77** (1,5-diamino-1*H*-tetrazolium nitrate, 1,5-diamino-1*H*-tetrazolium perchlorate, 1,5-diamino-4-methyl-1*H*-tetrazolium azide, 1,5-diamino-4-methyl-1*H*-

tetrazolium iodide, 1,5-diamino-4-methyl-1*H*-tetrazolium nitrate, and 1,5-diamino-4-methyl-1*H*-tetrazolium dinitramide) have been reported <2005IC4237>, together with the explosive and combustion parameters of 1,5-diaminotetrazole derivatives (cf. Section 6.07.4.3.2). The preparation of *N*-4-(1,2,4-triazole)-*N*-3-(4-methyl-1,2,4-triazole)amine and *N,N*-dimethyl-*N'*-(5-methyltetrazole)methanimidamide **485** from 1-amino-5-methyltetrazole **484** (Equation 94) has been described <2005IC7009>.



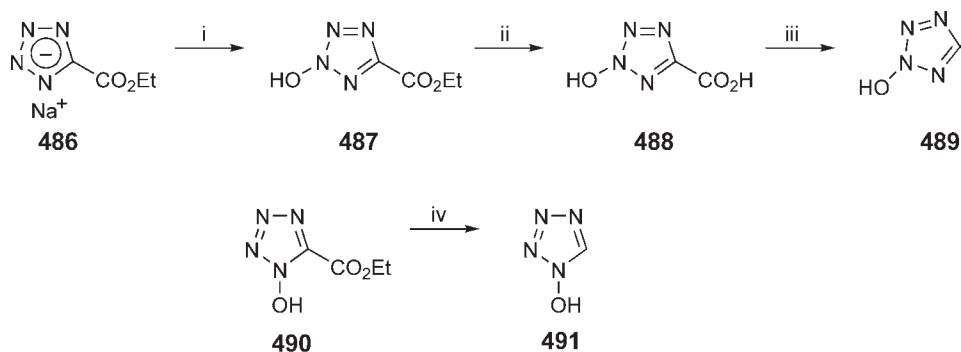
6.07.8.3.2 Tetrazolium N-aminides

Substituted tetrazolium N-aminides (N-imides) have been prepared by D. Moderhack and M. Noreiks *via* the tetrazolium salts and fully characterized. The tetrazolium aminides are reasonably stable solids with mp 85–229 °C. The preferred geometries of tetrazolium N-aminides have been determined by Hartree–Fock and density functional theory calculation <2004IH(63)2605>.

6.07.8.4 O- and S-Linked Substituents

The synthesis of 1-hydroxytetrazoles from azidoximes was thoroughly investigated by Plenkiewicz in the late 1970s. The azidoximes were shown to undergo cyclization to 1-hydroxytetrazoles only with assistance: the target process required preliminary acylation of the hydroxy group <1978T2961>. About the same time, Hegarty *et al.* suggested catalytic cyclization by blocking through hydrogen-bond formation the unshared electron pairs of nitrogen, oxygen, or sulfur in NR_2 , SR, and OR groups attached to the imine nitrogen of the corresponding imido azides <1978TL2121>.

The preparation of unsubstituted 2-hydroxytetrazole derivative **489** via direct oxidation of 1*H*-tetrazole using sodium perborate was reported by Begtrup *et al.* <1995J(P1)243, 1998J(P1)1727>. Giles *et al.* <1999TL6093> exploited the oxidation of the tetrazole ring in the sodium salt of ethyl tetrazole-5-carboxylate **486** with Oxone™ to obtain almost exclusively ethyl *N*²-hydroxytetrazole-5-carboxylate **487** (*N*²:*N*¹ selectivity ~ 70:1), which was isolated in pure form by direct crystallization. Treatment of compound **487** with sodium hydroxide in ethanol at reflux for 2 h followed by acidification gave 2-hydroxytetrazole-5-carboxylic acid **488** in 81% yield. Decarboxylation of compound **488** required forcing conditions (HCl/reflux/90 h), and after workup afforded 2-hydroxytetrazole **489** in 40% yield <1999TL6093>. In the same study, 1-hydroxytetrazole-5-carboxylate **490** was subjected to hydrolysis/decarboxylation to furnish 1-hydroxytetrazole **491** in 81% isolated yield (Scheme 58) <1999TL6093>.



i, Oxone, aq. acetone, pH 7.5; ii, NaOH, EtOH, reflux, 2 h;
iii, conc. HCl, reflux, 90 h; iv, NaOH, EtOH, reflux; conc. HCl, pH 1

Scheme 58

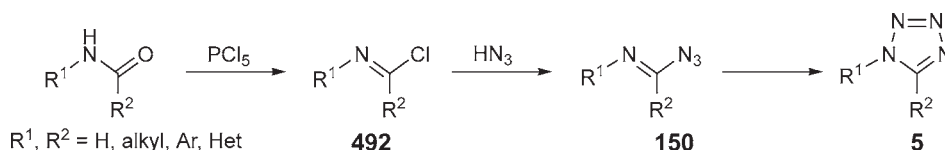
6.07.9 Ring Synthesis From Acyclic Compounds

6.07.9.1 Formation of One Bond in a Five-atom Component

6.07.9.1.1 Tetrazoles from imidoyl azides and related substrates

Cyclization of imidoyl azides **150** into 1,5-disubstituted tetrazoles **5** (Equation 10) is widely used both in the laboratory and on an industrial scale. Imidoyl azides form *in situ* in the course of various multistage processes, and sometimes in the multicomponent reactions (MCRs). The problems related to generation of imidoyl azides and also to electrocyclization of these intermediates into 1-mono- and 1,5-disubstituted tetrazoles are of crucial importance for the tetrazole chemistry. These problems are traditionally treated at length in basic reviews <1984CHEC(4)791, 1996CHEC-II(5)621>. The traditional methods for the synthesis and cyclization of imidoyl azides into tetrazoles were broadly employed and further refined in more recent works <1997MI1375>. Several new methods based on this approach have also been developed.

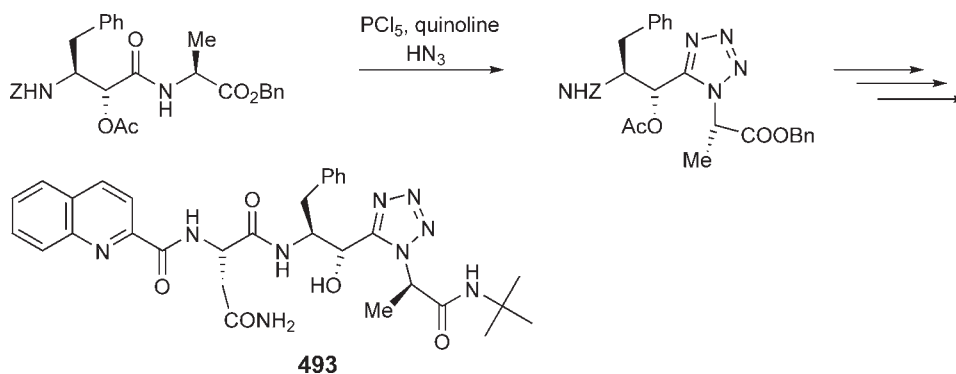
The traditional method for generation of imidoyl azides **150** consists of treating the appropriate imidoyl chlorides **492** with HN_3 or NaN_3 (Scheme 59).



Scheme 59

Caution: HN_3 is highly toxic and an explosive compound.

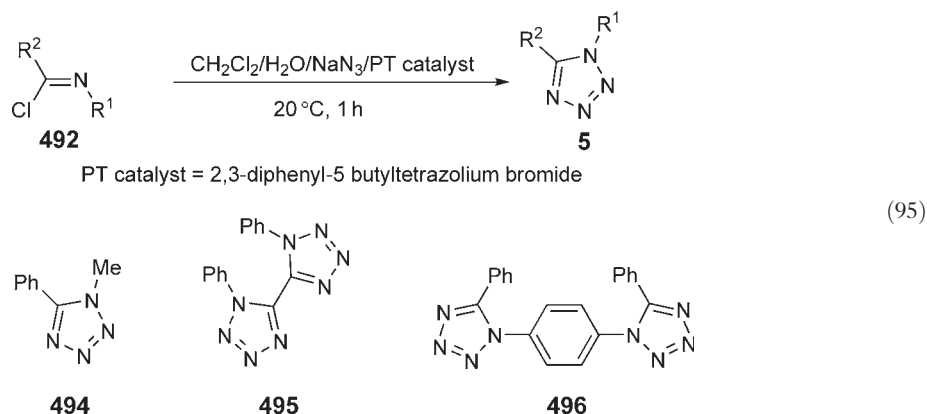
In keeping with Scheme 59, the appropriate acetanilides were converted into the following 1-aryl-5-methyltetrazoles: C_6H_5 , $p\text{-CH}_3\text{OC}_6\text{H}_4$, $p\text{-ClC}_6\text{H}_4$, and 5-methyl-1-(4'-[2.2]paracyclophanyl)-1*H*-tetrazole in high yields <2005TL2679>. From 3-aryl-5-methylisoxazoles, 1-(5-methylisoxazol-3-yl)-5-aryltetrazoles were prepared under similar conditions <1999SC2847>. Zabrocki Jr. *et al.* developed a modified version of this procedure by adding quinoline to the reaction mixture in the synthesis of tetrazole-containing peptidomimetics <1992JOC202>. The added heterocyclic base reduced the acidity of the reaction mixture at the stage of imidoyl chloride preparation and thus the process became highly stereoselective <1992JOC202>. The Zabrocki approach was used in the syntheses of peptidomimetics of various structures containing a 1-tetrazol-5-yl fragment <1998MI437, 1999JIB1, 2000T9791, 2000JIB283>. Abell *et al.* extended this procedure to the synthesis of human immunodeficiency virus (HIV) protease inhibitors similar to compound **493** (Scheme 60) <1997J(P1)2475, 2002J(P1)172>.



Scheme 60

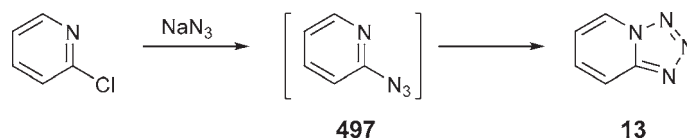
The replacement of the halogen in the imidoyl chloride by an azide group with subsequent cyclization of the intermediate imidoyl azide **150** into 1,5-disubstituted tetrazole **5** can be performed under PTC conditions <1996S1428>. This procedure avoids contact with HN_3 solutions and also removes the problem of the low solubility of HN_3 salts in organic solvents. It is important that in this procedure the losses due to hydrolysis of imidoyl chlorides

in water are reduced. The phase-transfer conditions ensure the completion of the process within 1 h at room temperature. Under these conditions, monocyclic 1,5-disubstituted tetrazoles **494** and also bitetrazoles **495** and **496** are obtained in 36–95% yields (Equation 95) <1996SI428>.



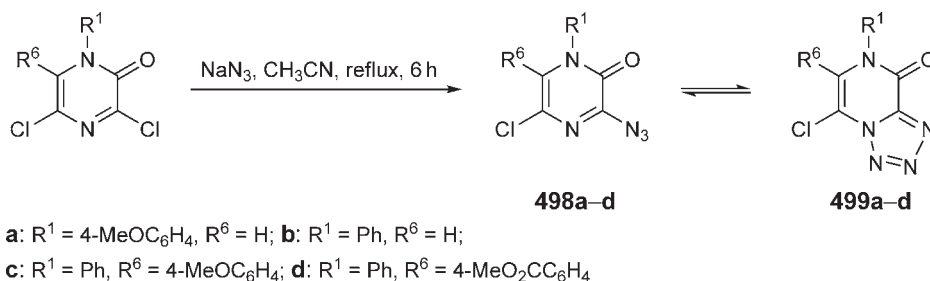
The problems of the formation of 5-substituted-1-acylated tetrazoles from the corresponding imidoyl azides have been considered <2000JOC7284>. Dabbagh and Lwowski studied the isomerization of 5-substituted-1-acylated tetrazoles into 2-acylated derivatives.

The substitution of the halogen in the cyclic imidoyl chloride, like 2-chloropyridine, with azide leads to the intermediate formation of an imidoyl azide **497** that further undergoes cyclization into a fused tetrazole **13** (Scheme 61) <2004SOS(13)861>.



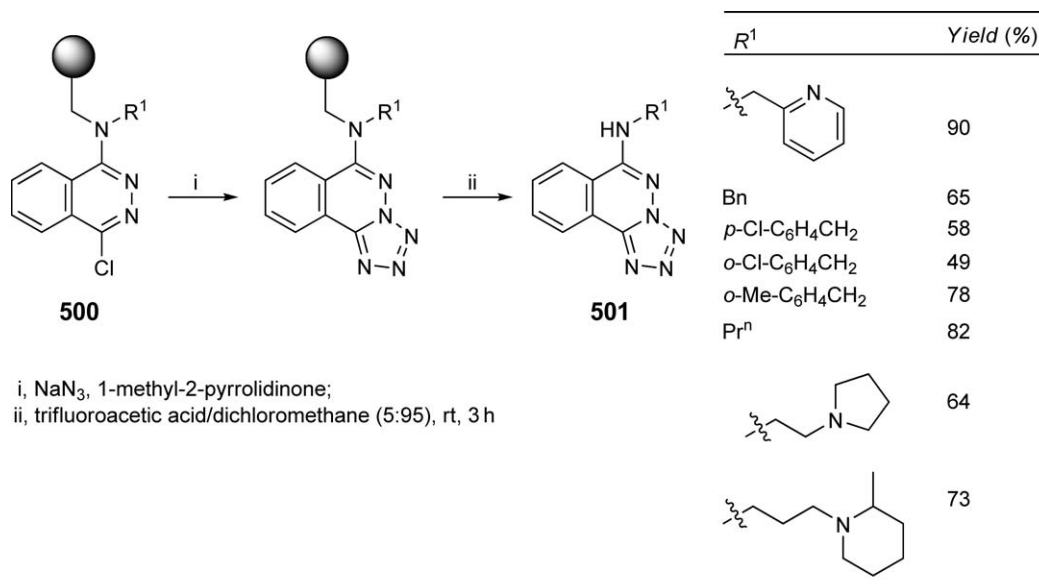
Scheme 61

Similarly, from 2-chloro(1*H*)-pyrazinone, the azides **498a–d** were obtained and these underwent reversible cyclization to the fused tetrazoles **499a–d** (Scheme 62) <2004OL4223, 2005JCO490>.



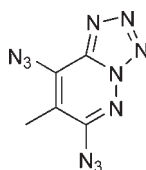
Scheme 62

A method has been reported for the solid-phase synthesis of tetrazolo[5,1-*a*]phthalazine derivatives **501** based on the cyclization of resin-bound chlorophthalazines **500** with NaN_3 in 1-methyl-2-pyrrolidinone (NMP) at 120 °C (Scheme 63) <2005TL3107>.

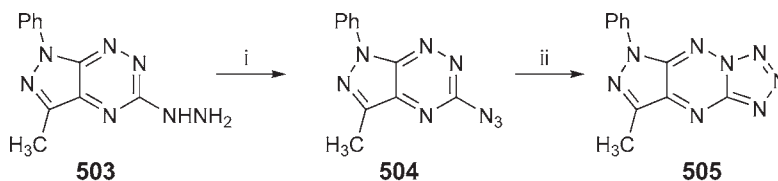


Scheme 63

Both cyclic imidoyl chlorides and cyclic imidoyl bromides have been used as starting materials for generating and further cyclization of intermediate imidoyl azides into the corresponding fused tetrazoloazines. Thus, treating 4-methyl-3,5,6-tribromopyridazine with NaN_3 in a mixed solvent (THF–DMSO) at room temperature led to 3,5-diazido-4-methyl[1,5-*b*]tetrazolopyridazine **502** (45% yield) <2004OBC1782>.

**502**

One of the classical methods for the generation of imidoyl azides as precursors to mono- and disubstituted tetrazoles is based on reactions of amidrazoles with sodium nitrite. This procedure developed by Kaufmann *et al.* in the middle of the 1960s <2004SOS(13)861> has found an extension and advancement in recent studies. By this method, 5-hydrazino-3-methyl-1-phenyl-1*H*-pyrazolo[4,3-*e*][1,2,4]triazine **503** through a cyclic imidoyl azide **504** was converted into 5-phenyl-1*H*-pyrazolo[4,3-*e*]tetrazolo[4,5-*b*]triazine **505** (Scheme 64) <2005JCX151>.

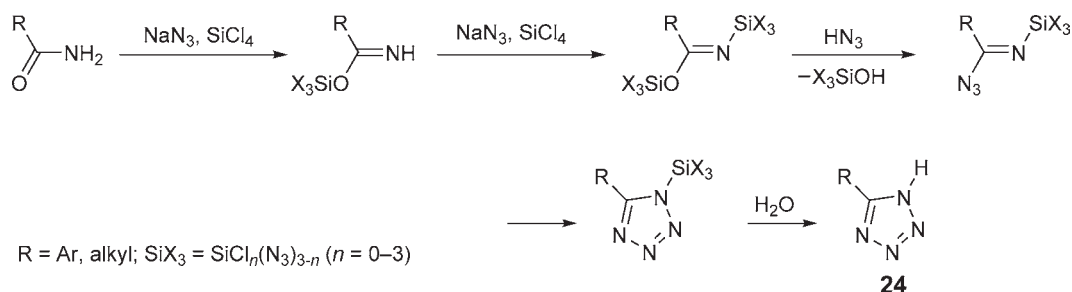


- i, 120 mg (0.5 mmol) of compound **503**, 8 ml $\text{AcOH}/\text{H}_2\text{O}$ (1:1), aqueous NaNO_2 (70 mg in 2 ml of water), below 5°C ; yield of compound **504** = 94%
ii, azido derivative **504** (119 mg, 0.47 mmol) was dissolved in boiling ethanol (5 ml) and the mixture was left to slow crystallization at rt; yield of tetrazole **505** = 78%

Scheme 64

This procedure is also efficient for the synthesis of other fused tetrazoles, such as ethyl 1,5-dihydro-5-oxo-7-phenyl-8-(phenylsulfonyl)tetrazolo[1,5-*a*]pyridine-6-carboxylate <2000J(P1)3686>. At the same time, the unexpected azido-tetrazolo tautomerization and reversible tetrazolo transformation of 3,6-diazo-1,2,4,5-tetrazine are remarkable compared to all other polyazido heteroaromatic high-nitrogen C–N compounds <2005JA12537>.

Within the last decade, the methods of ‘direct’ generation of imidoyl azides directly from carboxamides were extensively developed. These methods remove the necessity of preparation of imidoyl halides or amidrazones as starting materials because the imidoyl azides are generated from the amides *in situ* under the action of binary azidation systems ($\text{SiCl}_4\text{--NaN}_3$). Unlike the previously discussed procedures, the binary azidation systems provide a possibility to prepare not only 1-substituted and 1,5-disubstituted tetrazoles from the secondary amides but also 1*H*-unsubstituted tetrazoles from primary amides. For instance, Elmorsy and co-workers obtained imidoyl azides of various structures by treating primary carboxamides with the system $\text{SiCl}_4\text{--NaN}_3$ in acetonitrile. The subsequent cyclization of these imidoyl azides afforded the corresponding 1*H*-unsubstituted tetrazoles **24**. The formation of tetrazoles **24** from amides occurred via cyclization of the intermediate imidoyl azides. It was assumed that the azidation agent was $\text{Si}(\text{N}_3)_3\text{Cl}$ formed *in situ* from 1 equiv of SiCl_4 and 3 equiv of NaN_3 (Scheme 65) <1997TL1257>.

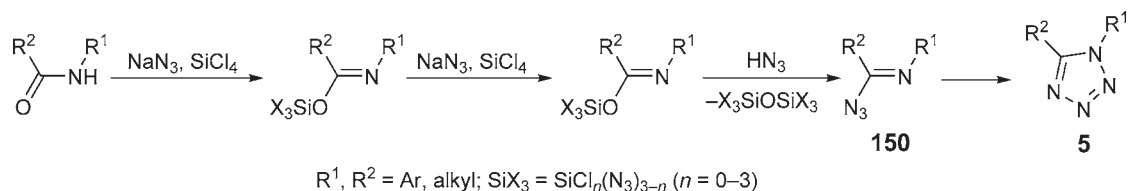


Scheme 65

The following results of reaction between primary amides and $\text{SiCl}_4\text{--NaN}_3$ in boiling acetonitrile have been published <1997TL1257>: (R, reaction time, yield of 1*H*-unsubstituted tetrazole): Ph, 2 h, 92%; *p*-ClC₆H₄, 1.5 h, 94%; *o*-ClC₆H₄, 1.5 h, 90%; *p*-MeC₆H₄, 2 h, 91%; *p*-MeOC₆H₄, 2 h, 88%; *p*-NO₂C₆H₄, 2.5 h, 76%; C₆H₅–C₆H₄, 2.5 h, 89%; PhCH₂, 2 h, 83%.

Caution: It has been reported <1996JA12752> that in systems containing more than 2.5 equiv of NaN_3 per 1 equiv of SiCl_4 , an explosive highly sensitive to various effects, $\text{Si}(\text{N}_3)_4$, was formed and accumulated. The use of a system at a ratio $\text{NaN}_3\text{:SiCl}_4$ above 2.5 is not recommended.

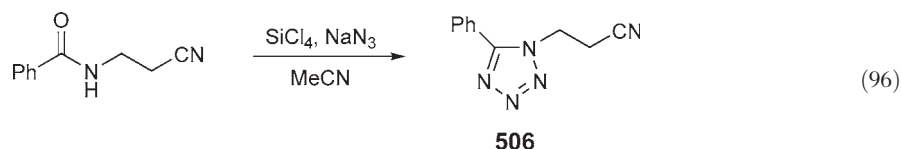
The procedure developed by Elmorsy has been adjusted to the synthesis of 1,5-disubstituted tetrazoles from secondary amides <2000CHE878, 2004RJO443, 2004RJO1528, 2004RJO1532>. By analogy with the mechanism in Scheme 65, the formation of 1,5-disubstituted tetrazoles **5** from the secondary amides may be presented as going through an intermediate imidoyl azides **150** (Scheme 66).



Scheme 66

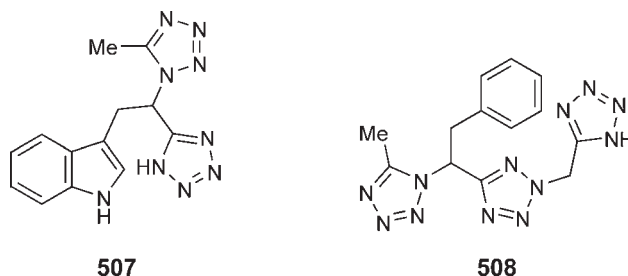
The replacement of one hydrogen in the NH_2 group of the primary amide by R^1 allowed the preparation of tetrazoles **5** in 60–70% yield <2004RJO443, 2004RJO1528, 2004RJO1532>. However, when the reaction of primary and secondary amides with the system $\text{SiCl}_4\text{--NaN}_3$ is carried out in boiling acetonitrile, the completion of the reaction with secondary amides requires increasing the reaction time from 1.5–2.5 h to 45 and sometimes even to 89 h, due apparently to steric hindrances from the substituent R^1 in the secondary amide and the corresponding imidoyl azide <1997TL1257, 2004RJO443, 2004RJO1528, 2004RJO1532>. Note that when the initial substrate contains both

an amide and a cyano groups, as in the synthesis of 1-(2-cyanoethyl)-5-phenyltetrazole **506**, only the amide group is converted into a tetrazole by the action of $\text{SiCl}_4\text{--NaN}_3$. The nitrile group was retained under the reaction conditions (Equation 96) <2000CHE878>.

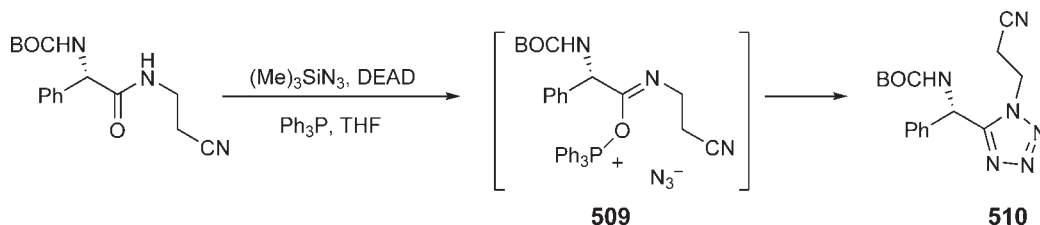


An analogous result was first observed by Thomas <1993S767> and has also been reported elsewhere <2000JME488>. However, in the latter study, the secondary amide was converted into a tetrazole using trifluoromethanesulfonic anhydride (Trf_2O) and sodium azide.

The conversion of primary and secondary amides by treating with the system $\text{SiCl}_4\text{--NaN}_3$ into 1,5-disubstituted tetrazoles **5** through intermediate imidoil azides **150** has been used <2002RJO1370, 2004RJO443, 2004RJO1528, 2004RJO1532> for the preparation of tetrazoles of various structures, in particular, bis- and tris-tetrazoles **507** and **508**.

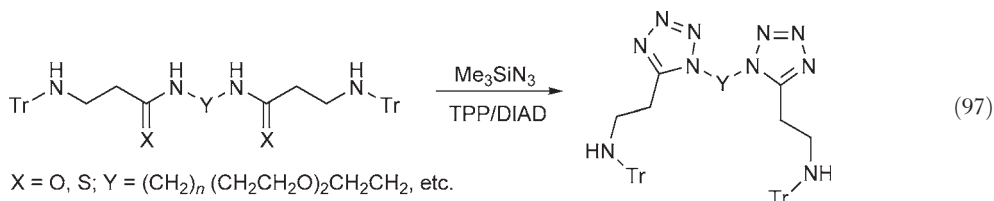


In 1991, Duncia *et al.* reported on the synthesis of 1,5-disubstituted tetrazoles from secondary amides and azidotrimethylsilane under the conditions of the Mitsunobu reaction <1996CHEC-II(4)621>. The Mitsunobu protocol was successfully applied to the conversion of *N*-(cyanoethyl)amide into tetrazole **510**. The tetrazole ring in this event forms by the cyclization of an imidoil azide (not shown in the scheme) whose precursor is the phosphonium imidate **509** (Scheme 67) <2000JME488>.



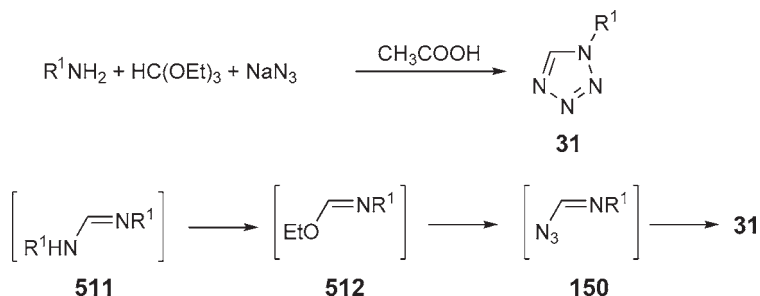
Scheme 67

The similarity of the processes shown in Equation (96) and Scheme 67 is obvious. In both cases, the tetrazole is formed by transformation of an amide group, leaving intact the cyano group in the side chain <2000CHE878, 2000JME488>. Strong evidence conforming the efficiency of the Mitsunobu protocol for the synthesis of monocyclic and bicyclic tetrazoles from amides and thioamides has been described <2004TL2571, 2005OL561>. This approach is regarded by Athanassopoulos *et al.* as a new step in the development of the previously described procedures of imidoil azide **150** generation as key intermediates in the synthesis of 1,5-disubstituted tetrazoles from amides and thioamides (Equation 97) <2005OL561>.



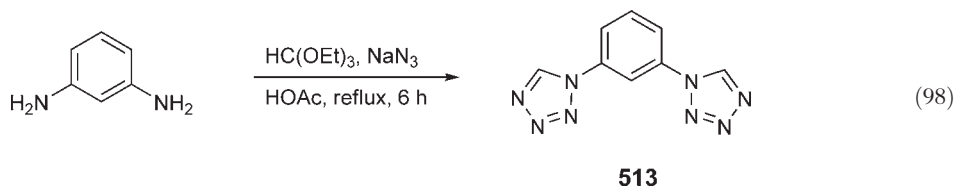
At the same time, Yang *et al.* <2004TL111> noted that the conversion of amides into tetrazoles under the conditions of the Mitsunobu reaction is disfavored by the presence of bulky substituents on the starting amides.

One of the most important syntheses of 1-substituted tetrazoles is based on an MCR involving orthoformates, amines, and sodium azide <1996CHEC-II(4)621, 2004SOS(13)861>. Although the detailed mechanism of this reaction is not established, the preliminary data suggest that tetrazoles **31** form by cyclization of the imidoyl azides **150**, which in turn originate from the corresponding iminoethers **512** and amidines **511** (Scheme 68) <1997MI80>.



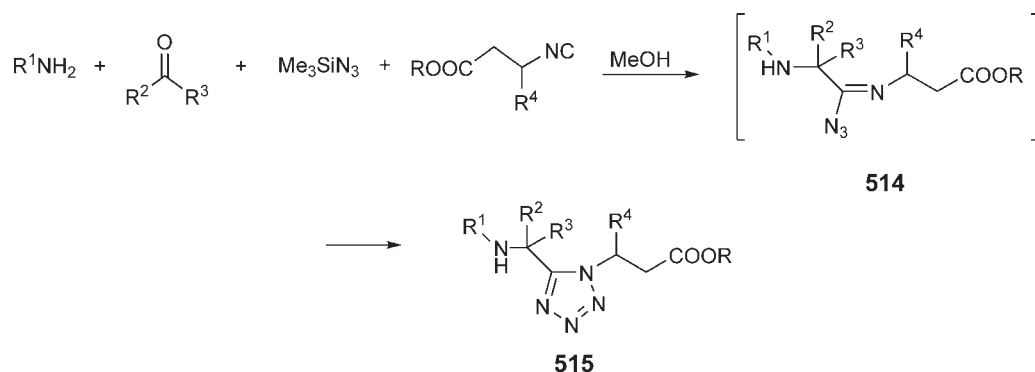
Scheme 68

Variations of this MCR have been successfully used for the preparation of a wide variety of 1-substituted tetrazoles. For instance, by reaction of 2-iodoaniline, sodium azide, and triethyl orthoformate in acetic acid (reflux, 6 h), 1-(2-iodophenyl)-1*H*-tetrazole was obtained <2004TL4113>. Under similar conditions, from (1-fluoroethyl)amine, (1-bromoethyl)amine, and (1-iodoethyl)amine, the corresponding 1-ethyltetrazoles were obtained in 20–60% yields <2003EJI2273>, 1-cyclopropyltetrazole was prepared <2005JCR421>, and from 1,3-phenylenediamine 1,3-phenylene-bis-1*H*-tetrazole **513** was synthesized (Equation 98) <1995TL1759, 2004SL2227>.



Heating α,ω -diaminoalkanes, sodium azide, and triethyl orthoformate in a molar ratio 0.15:0.3:0.3 in acetic acid (90 °C, 4 h) leads to α,ω -bis(tetrazol-1-yl)-alkanes <2005JST(733)41>. Primary amines of the azole series, 5-amino-tetrazole, 5-amino-1-methyltetrazole, 4-amino-1,2,4-triazole, and also less basic arylamines, such as 4-fluoro-3-nitro-anilines, can participate in this reaction <2005CHE999>. The preparation of tetrazoles from orthoesters usually requires heating at 90 °C and higher. However, examples of tetrazole syntheses from orthoesters under milder conditions are also known. Recently 1-aryltetrazoles were synthesized by the reaction of substituted anilines with triethyl orthoformate (3.0 equiv) and NaN_3 (1.1 equiv) in AcOH (8 equiv) at 80 °C within 3–4 h <2006S1307>. 1-(*p*-Methoxybenzyl)-5-chloromethyltetrazole was obtained in 50% yield by the reaction of 2-chloro-1,1,1-triethoxyethane, *p*-methoxybenzylamine, and NaN_3 (80 °C, 6 h) in AcOH <1998TL3367>. Under even milder conditions, the corresponding tetrazole was obtained in 67% yield by stirring at room temperature for 2 h a mixture of 2-aminobenzoic acid (0.044 mol), trimethyl orthoformate (0.13 mol), and sodium azide (0.13 mol) in a glacial acetic acid (150 ml) <2004JME2995>.

An example of another MCR affording tetrazoles has been described <2005TL7393>. In an extension of the method developed in 1961 by Ugi, Mayer *et al.* introduced into the reaction four components simultaneously: aldehyde (ketone), amine, trimethylsilyl azide, and ethyl 3-isocyano-3-phenylpropionate. 1,5-Disubstituted tetrazoles **515** formed in 37–89% yields via cyclization of the imidoyl azides **514** (Scheme 69; Table 28) <2005TL7393>.

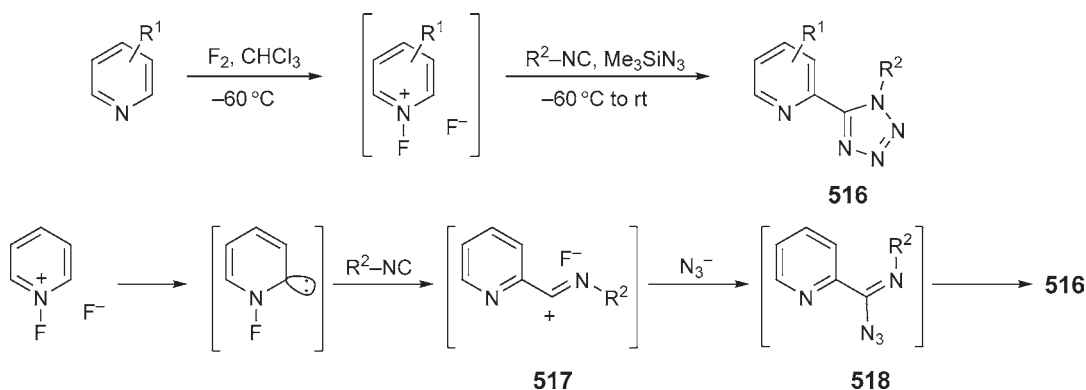


Scheme 69

Table 28 Synthesized tetrazoles **515** (Scheme 69)

R^1	R^2	R^3	R^4	R	Yield (%)
PhCH ₂	Me ₂ CH	H	C ₆ H ₅	Et	89
PhCH ₂	<i>p</i> -MeOC ₆ H ₄	H	C ₆ H ₅	Et	83
(MeO) ₂ CHCH ₂	Ph	H	C ₆ H ₅	Et	65
(MeO) ₂ CHCH ₂	<i>p</i> -MeOC ₆ H ₄	H	C ₆ H ₅	Et	40
<i>p</i> -MeOCOC ₆ H ₄	Me ₂ CH	H	C ₆ H ₅	Et	37
PhCH ₂	Me ₂ CH	H	C ₆ H ₅	Et	42
PhCH ₂	Me	Me	C ₆ H ₅	Et	67
PhCH ₂	Me ₂ CH	H	COOMe	Me	77
PhCH ₂	Ph	H	COOMe	Me	88
PhCH ₂	Me	Me	COOMe	Me	73

An uncommon version of the multicomponent Ugi reaction was reported recently [<2005TL4851>](#). The reaction of *N*-fluoropyridinium fluoride generated *in situ* from a series of isonitriles and Me₃SiN₃ led to the corresponding tetrazol-5-yl pyridines **516** in good yields (37–84%). According to the mechanism suggested by Kiselyov [<2005TL4851>](#), tetrazoles **516** result from the transformation of an intermediate iminocarbonium ion **517**. Apparently nucleophilic attack of the azide ion on the carbon atom of iminocarbonium ion **517** afforded imido-yl azide **518** that underwent cyclization into tetrazole **516** (Scheme 70).



Scheme 70

Alongside tetrazol-5-ylpyridines **516**, picolinamides and tetrazolo[1,5-*a*]pyridines were formed as by-products (not shown in the scheme), but tetrazoles **516** were obtained in good yields (37–84%) in agreement with Scheme 70 (Table 29).

Table 29 Synthesized tetrazoles **516** (Scheme 70)

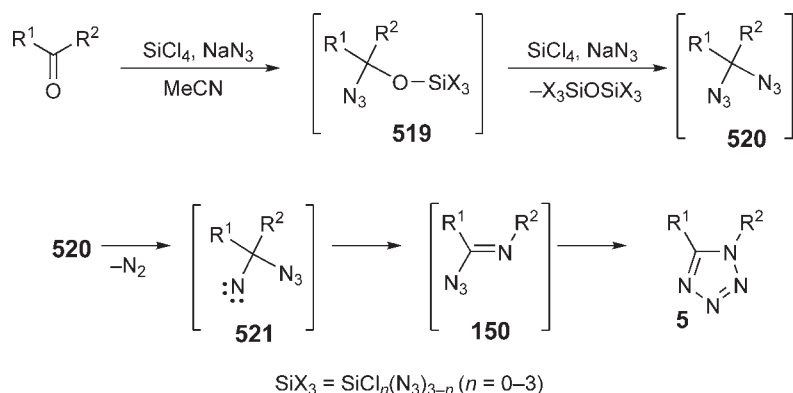
R^1	R^2	Yield (%)	R^1	R^2	Yield (%)
H	Bu ⁿ	67	2-Me	<i>p</i> -CF ₃ C ₆ H ₄	61
H	Bu ^t	69	3-Me	<i>p</i> -CF ₃ C ₆ H ₄	76 ^a
H		73	4-Me	<i>p</i> -CF ₃ C ₆ H ₄	75
H	Ph	75	2-Cl	<i>p</i> -CF ₃ C ₆ H ₄	70
H	<i>p</i> -CF ₃ C ₆ H ₄	81	4-Cl	<i>p</i> -CF ₃ C ₆ H ₄	84
H	CH ₂ COOEt	52	2-OMe	<i>p</i> -CF ₃ C ₆ H ₄	41
H	CH ₂ Ph	45	2-Ph	<i>p</i> -CF ₃ C ₆ H ₄	37 ^b
H	<i>p</i> -NO ₂ C ₆ H ₄	83	2-COOMe	<i>p</i> -CF ₃ C ₆ H ₄	34

^aMixture of 2- and 6-substituted derivatives.^bMixture contained product of Ph-ring fluorination.

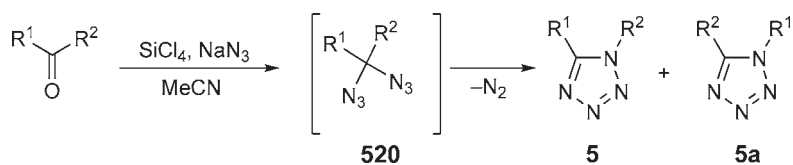
This synthetic route (Scheme 70) seemingly provides a synthetic approach to 1,5-disubstituted tetrazoles with a wide variety of substituents. For instance, the synthesis of the corresponding tetrazoles, according to Scheme 70, was carried out not only from pyridine but also from quinoline and isoquinoline <2005TL4851>. At the same time, the following factors limiting the use of this synthetic protocol should be taken into consideration: the necessity to work with the gaseous fluorine and isonitriles, and the requirement to keep rigidly to the dropwise mode of reagent addition at a specified low temperature (−78 °C, −50 °C, etc.) <2005TL4851>.

6.07.9.1.2 Tetrazole from geminal diazides

A synthesis of tetrazoles from 1,1-diazo-1-ethoxyalkanes and primary amines was reported in 1955–57 by Sinnema and Arens, but has not found significant application <2004SOS(13)861>. On the contrary, the development of procedure for tetrazole synthesis has been based on generation and transformations of geminal diazides as intermediates in multistage processes. Elmorsi and co-workers suggest that the formation of 1,5-disubstituted tetrazoles from ketones treated with SiCl₄–NaN₃ is just such a multistage process. Intermediate **519** ($R^1 = R^2$) transforms into symmetric geminal diazide **520** that loses a N₂ molecule giving nitrene **521**. The latter undergoes a rearrangement to imidoil azide **150** whose cyclization results in 1,5-disubstituted tetrazole **5** (Scheme 71) <1995TL7337, 2003M1241>.

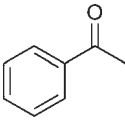
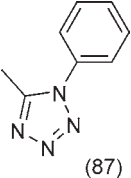
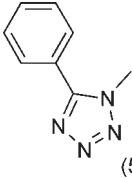
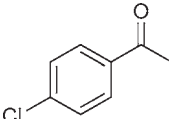
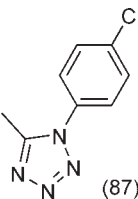
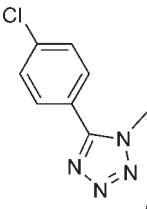
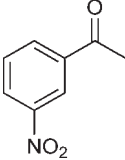
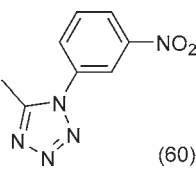
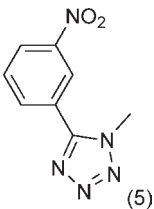
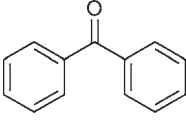
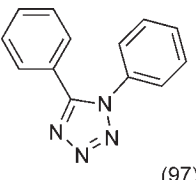
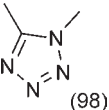
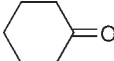
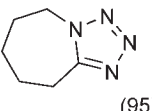
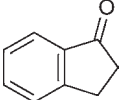
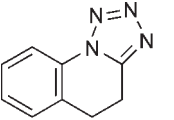
**Scheme 71**

The analogy is evident between the similar reactions of ketones (Scheme 72) <2004SOS(13)861> and the formation of 1,5-disubstituted tetrazoles **5** by the Schmidt reaction. It is known <1975KGS723> that unsymmetrical ketones ($R^1 \neq R^2$) afford isomeric 1,5-disubstituted tetrazoles **5** and **5a** through the Schmidt rearrangement (Scheme 72). The more bulky substituent predominantly undergoes migration in this rearrangement <1975KGS723>. However, this rule is not observed in all cases (Scheme 72; Table 30) <1995TL7337>.



Scheme 72

Table 30 Synthesis of tetrazoles from ketones and SiCl₄–NaN₃ via geminal diazide **520** <1995TL7337>

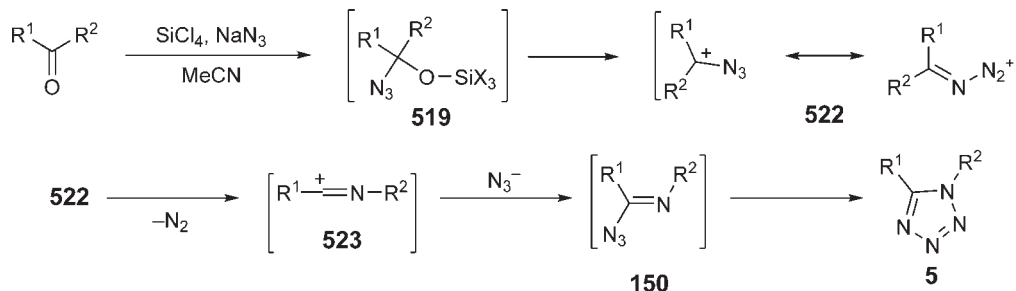
Ketone	Reaction time (h)	Yield (%)
	12	 (87)  (5)
	15	 (87)  (5)
	24	 (60)  (5)
	15	 (97)
	12	 (98)
	20	 (95)
	13	 (93)

(Continued)

Table 30 (Continued)

<i>Ketone</i>	<i>Reaction time (h)</i>	<i>Yield (%)</i>
	12	 (40)
	6	 (90)
	12	 (95)
	12	 (94)
	15	 (90)
	10	 (95)
	18	 (80)
	14	 (90)
	5	 (95)

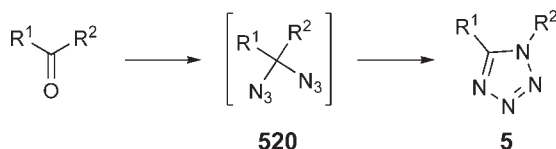
The problem of regioselective synthesis of tetrazoles from dienones and $\text{SiCl}_4\text{--NaN}_3$ is also discussed in a paper by Elmorsy and co-workers [<2003M1241>](#). Alongside the above mechanism ([Scheme 71](#)), an alternative reaction pathway was considered ([Scheme 73](#)), assuming the formation of 1,5-disubstituted tetrazoles **5** through intermediate carbocation **522**, iminocarbenium ion **523**, and imidoyl azide **150** [<2003M1241>](#).



Scheme 73

Elmorsy and co-workers showed that the regioselectivity of the substituent migration was governed primarily by the state of the charge stabilization on the ion **523** and only to a lesser extent by the bulk of the substituents R^1 and R^2 ([Scheme 73](#)) [<2003M1241>](#).

The data published before 1996 on the conversion of ketones (aldehydes) into 1,5-disubstituted tetrazoles **5** through geminal diazides **520** have been collected and systematized [<2004SOS\(13\)861>](#) ([Scheme 74](#); [Table 31](#)).



Scheme 74

Table 31 Synthesis of tetrazoles **5** from ketones and azides^a [<2004SOS\(13\)861>](#)

R^1	R^2	Condition	Yield (%)
Me	Me	$\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$, Me_3SiN_3 , 55°C , 20 h	99
Me	Me	SiCl_4 , NaN_3 , rt, 12 h	98
Me	Styryl	NaN_3 , MeCN, heat, 24 h	98
Ph	Ph	NaN_3 , TiCl_4 , MeCN, heat, 24 h	93 ^b
Ph	Ph	SiCl_4 , NaN_3 , 15 h	97
Me	Ph	NaN_3 , TiCl_4 , MeCN, heat, 24 h	63
Me	Ph	SiCl_4 , NaN_3 , rt, 12 h	87
$(\text{CH}_2)_4\text{Me}$	H	Me_3SiN_3 , ZnCl_2 , CH_2Cl_2 , rt, 72 h	63

^aReferences to the articles of Nishiyama and Watanabe (1984), Suzuki *et al.* (1993); see review, [<2004SOS\(13\)861>](#).

^bSee [<1995TL7337>](#).

A similar procedure was applied to the synthesis of isomeric 1,5-dialkyltetrazoles analogs of the most important naturally occurring fatty acids, from methyl 9(10)-oxooctadecanoate, sodium azide, and titanium(IV) chloride (MeCN, reflux, 5 h) [<2003EJO885>](#). A convenient synthesis of tetrazoles (e.g., **524**) by reaction of trimethylsilyl azide and ZnBr_2 with α -dialkylated β -ketoesters is based on the same approach ([Equation 99](#); [Table 32](#)) [<2003TL3179>](#).

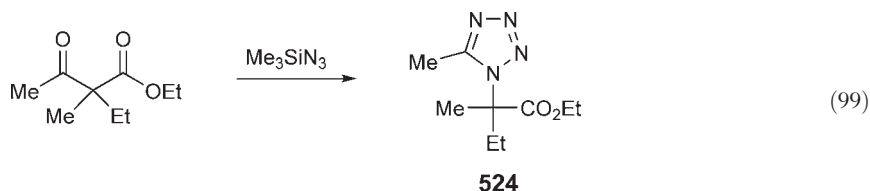
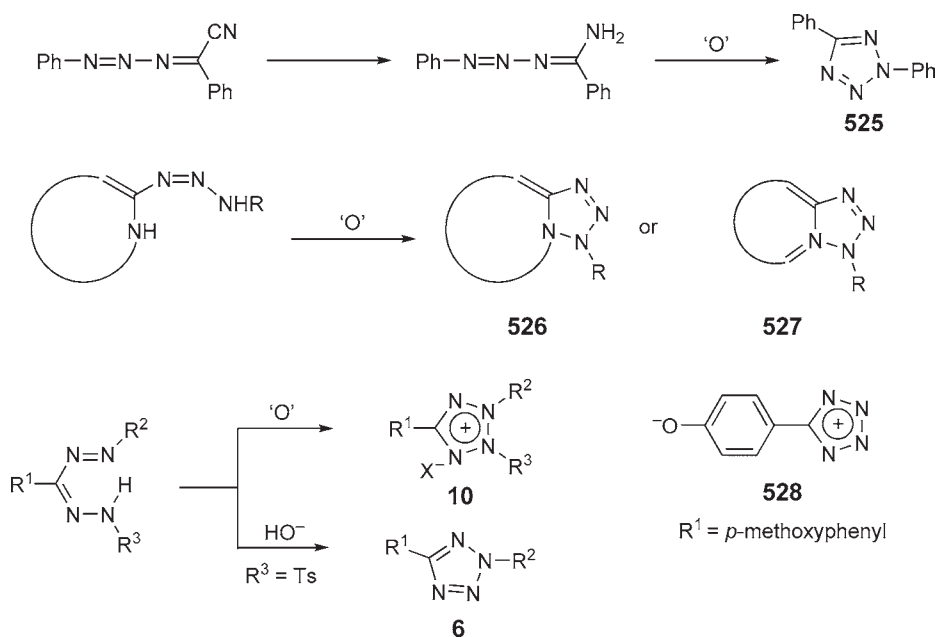


Table 32 Optimization of the conditions of Schmidt rearrangement of α -dialkylated β -ketoester (Equation 99) <2003TL3179>

Me_3SiN_3 (equiv)	Co-reagent	Solvent	Temperature ($^{\circ}C$)	Time	Yield (%)
1.1	NaN_3 , 5 mol%		20	24 h	0
2.1	$ZnBr_2$, 1 equiv	$CHCl_3$	Reflux	24 h	5
2.5	$ZnBr_2$, 1 equiv	CH_2Cl_2	Reflux	18 h	30
				3 d	70
2.5	$ZnBr_2$, 1 equiv		65	24 h	90

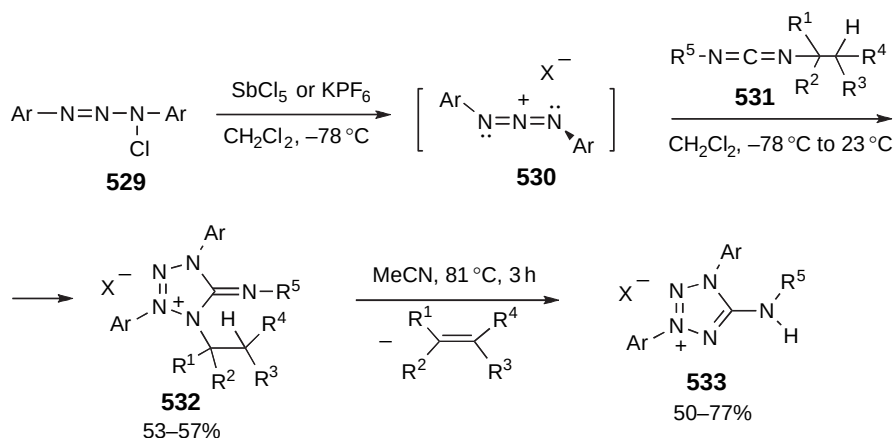
6.07.9.1.3 Cyclization of triazenes, tetrazenes, and formazans

According to Butler, acyclic systems other than imido azides that may be cyclized to tetrazoles include substituted tetrazenes, some triazenes, and formazanes <1984CHEC(4)791, 1996CHEC-II(4)621>. Examples of these reactions and of the corresponding products **6**, **10**, and **525–528** are shown in Scheme 75 <1996CHEC-II(4)621>.

**Scheme 75**

These reactions (Scheme 75) afford poorly available 2,5-disubstituted tetrazoles **6**, and also tetrazolium salts and even mesoionic structures, such as compound **528**. The oxidative cyclization of 1-aryl- and 1-hetarylformazanes is an important and widely used preparative method for 2,3,5-substituted tetrazolium salts **10** (Scheme 75). A wide range of oxidants have been applied to this process ($SOCl_2$, $Pb(OAc)_4$, N -bromoimides, H_2O_2 with catalytic $FeSO_4$, or V_2O_5 , or electrochemical oxidation). When R^2 is benzoyl, cyclization proceeds in boiling acetic acid or on oxidation with mercury(II) oxide in benzene. When R^3 is arylsulfonyl, treatment with strong base leads to 2,5-disubstituted tetrazoles **6** <2004SOS(13)861, 2004BML5473, 2004BML5477, 2005BML5061>.

Among the papers published within the last decade, only several examples of the preparation of a tetrazole ring through triazenes transformation have been found. 1,3-Diaza-2-azoniaallene salts **530** (Ar = 2,4,6- $Cl_3C_6H_2$, 4- C_6H_4) generated *in situ* from N -chlorotriazenes **529** react with carbodiimides **531** to give 4,5-dihydro-1*H*-tetrazolium salts **532** that are converted into 5-alkylamino-1,3-diaryltetrazolium salts **533** on heating (Scheme 76; Table 33) <1998J(P1)1755, 1998JPR300>.

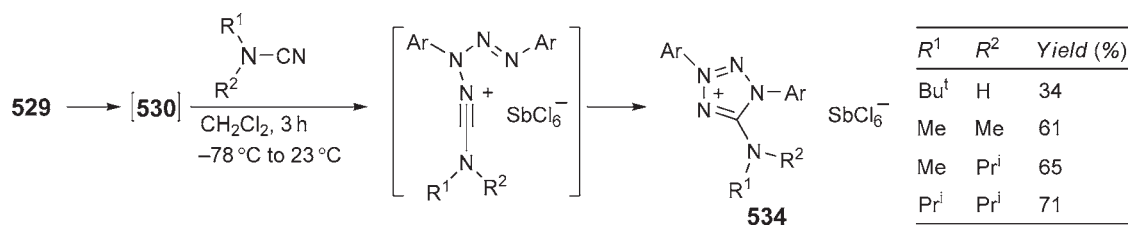


Scheme 76

Table 33 Synthesized tetrazolium salts **533** (Scheme 76)

Ar	R ¹	R ²	R ³	R ⁴	R ⁵	X
2,4,6-Cl ₃ C ₆ H ₂	H	Me	H	H	Pr ⁱ	SbCl ₆
2,4,6-Cl ₃ C ₆ H ₂	H	–(CH ₂) ₄ –	H	H	C ₆ H ₁₁	SbCl ₆
2,4,6-Cl ₃ C ₆ H ₂	Me	Me	H	H	Bu ^t	SbCl ₆
4-ClC ₆ H ₄	H	Me	H	H	Pr ⁱ	PF ₆
4-ClC ₆ H ₄	H	–(CH ₂) ₄ –	H	H	C ₆ H ₁₁	PF ₆

The use of cyanamides in this reaction leads to 5-dialkylamino-1,3-diaryltetrazolium salts **534** (Scheme 77) <1998J(P1)1755, 1998JPR300>.



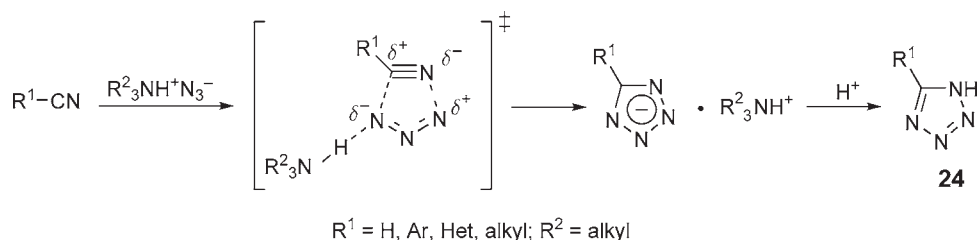
Scheme 77

6.07.9.2 Formation of Two Bonds from [3+2] Atom Components

6.07.9.2.1 1H-Unsubstituted tetrazoles from nitriles

Currently a great number of procedures for the synthesis of 1H-unsubstituted tetrazoles from nitriles differing in the nature of azidation agents, activators of the reaction, and solvents are well known. Most of them were discussed by Butler in CHEC(1984) <1984CHEC(4)791> and in CHEC-II(1996) <1996CHEC-II(4)621>. Recently, concurrent with the development of the traditional procedures, new effective syntheses of the tetrazole ring have appeared <2004SOS(19)403>.

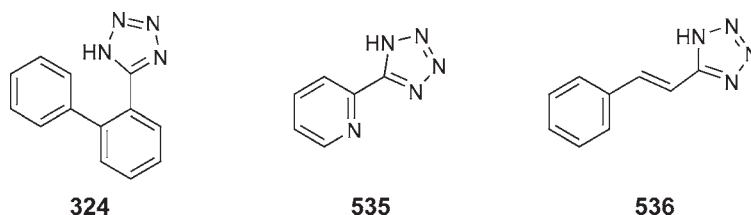
The reaction of nitriles with ammonium azide and alkylammonium azides in aprotic dipolar solvents remains the main procedure for the synthesis of versatile 1H-tetrazoles **24** (Scheme 78). This method affords tetrazole derivatives with substituents of various character attached to the endocyclic carbon. In particular, this procedure has been used in the syntheses of complex organic molecules: branched polycyclic podand-like molecules with terminal 1H-tetrazole fragments **160** <1997CHE1292, 2003CHE1317, 2005T7002, 2006CHE469>, tetrazole-containing uncommon nucleosides, for instance, 3'-deoxy-3'-(1H-tetrazol-5-yl)thymidine **248** <2002HCA2847>, and also monomer **387** and the respective polymeric structures <1999THS(3)467, 2003RCR143, 2004MI53>.



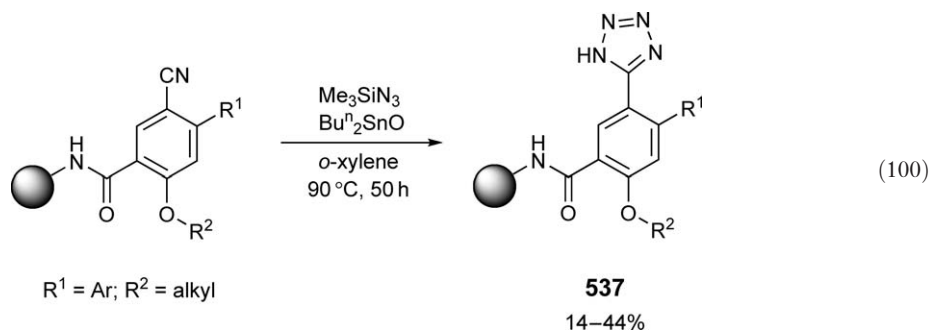
Scheme 78

Theoretical and experimental investigations <2000CHE759> show that the limiting stage of the process is 1,3-dipolar cycloaddition of alkylammonium azides to nitriles (Scheme 78). The rate of the process considerably grows with increasing electron-withdrawing properties of the substituents R^1 , and also under high and super-high pressure. However, due to the low activation entropy of the cycloaddition, in most cases a reasonable yield (50–80%) of 1*H*-tetrazoles is obtained by prolonged (8–40 h) heating of the reagents at 100–160 °C <2000CHE759>.

Performing this process under microwave conditions considerably reduces the reaction time <2000JOC7984, 2004H(63)903> and significantly raises the yield in the syntheses of biphenyltetrazoles **324**, 5-hetaryltetrazoles **535**, and alkenyltetrazoles **536** from the corresponding nitriles and ammonium azide in DMF solution <2000JOC7984>.

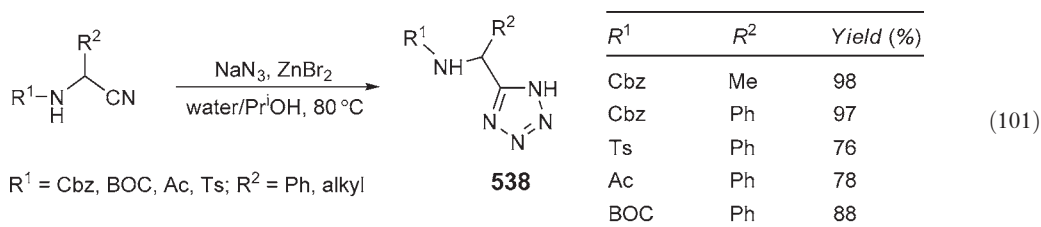


Acceleration of this reaction was also achieved by using a Lewis acid (BF_3) <1996JOC4462>. The replacement of DMF by low-polar toluene sometimes led to the acceleration of the nitrile conversion and to an increase in the yield of the 1*H*-tetrazoles <2003EJO885>, especially, for tetrazoles with a bulky substituent on the carbon atom of the ring. Under these conditions, the process can be performed at lower temperatures and trialkylammonium azides were used as azidation agents <1998S910, 2005EJO326>. Toluene <2003C773, 2005T4755> and *o*-xylene <2004OL1143, 2004JME2574> were also used as solvents in reactions of nitriles with Me_3SiN_3 or with $(\text{CH}_3)_3\text{SnN}_3$. The synthesis was carried out in the presence of a strong Lewis acid, dibutyltin oxide (Bu^n_2SnO) <2002BMC3379, 2004JOC1346>. In this case, 1*H*-tetrazoles **537** were obtained in good yields on a solid support at relatively moderate temperature (90–110 °C), but a long time (12–50 h) was required for completion of the reaction (Equation 100) <2004OL1143>. The reaction time was considerably reduced using microwave assistance in DME <2004OL3265> or 1,4-dioxane <2004TL2571, 2006T1849>. Thus the use of the system $\text{Me}_3\text{SiN}_3/\text{Bu}^n_2\text{SnO}$ combined with microwave activation at 100–160 °C made it possible to reach 25–60% conversion of the initial substrates within 10 min, depending on the character of the nitriles and the reagents ratio.



Water was not formerly regarded as a suitable solvent for the reaction of nitriles with azides. Demko and Sharpless <2001JOC7945> were the first to show that 1*H*-tetrazoles with various aromatic and heteroaromatic substituents on the ring carbon could be obtained by refluxing in water the corresponding nitriles, NaN_3 , and ZnBr_2 in equimolar

amounts. As an extension of this synthesis, the same authors [<2002OL2525>](#) heated amino acid nitriles, NaN_3 , and ZnBr_2 in aqueous 2-propanol and obtained the products **538** (Equation 101).



1*H*-Tetrazole preparation from nitriles under conditions developed by Demko and Sharpless is fairly general. However, with inactivated sterically hindered aromatic nitriles or alkylnitriles, high temperatures (140–170 °C) are usually required [<2004JOC2896>](#). Utilizing a microwave-activated cycloaddition with NaN_3 under Demko–Sharpless conditions, cyanopyridines were rapidly converted to tetrazolylpyridines [<2005BMC905>](#). Amantini *et al.* [<2004JOC2896>](#) proposed the application of tetrabutylammonium fluoride (TBAF) as an efficient catalyst for cycloaddition of trimethylsilyl azide (Me_3SiN_3) to nitriles in the absence of solvent. The 1*H*-tetrazoles were produced from the corresponding nitriles under these conditions in 80–97% yields (Equation (102); Table 34). As a consequence of the progress achieved within the last decade in improving the known and developing new synthetic procedures for preparation of 1*H*-tetrazoles from nitriles, as well as in decreasing the concomitant hazards, the compounds of this series have become realistic products for the chemical industry [<B-1998MI536, 2003C773>](#).

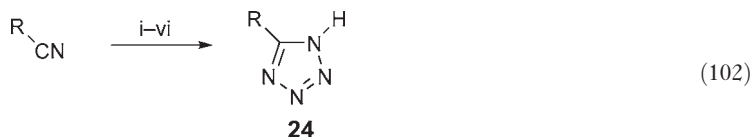
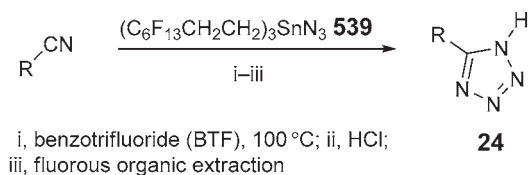


Table 34 Examples of synthesis of 1*H*-unsubstituted tetrazoles **24** (Equation 102) from nitriles

Entry	R	Reagent/conditions	Yield (%)	Reference
i	4-Methyl-1,1'-biphen-2-yl	NaN_3 , $\text{Et}_3\text{N}\cdot\text{HCl}$, toluene, 98 °C, 30 h	67	1998S910
	Phenyl	NaN_3 , $\text{Et}_3\text{N}\cdot\text{HCl}$, DMF, 98 °C, 30 h	23	
		NaN_3 , Zn/Al hydrotalcite, DMF, 120 °C, DMF, 12 h	84	
ii	Undecyl	NaN_3 , $\text{Et}_3\text{N}\cdot\text{HCl}$, toluene, reflux, 2 h	89	2003EJO885
	Phenyl	NaN_3 , $\text{Et}_3\text{N}\cdot\text{HCl}$, toluene, 100 °C, 24 h	90	
	Thiophen-2-yl		90	
iii	Phenyl	Me_3SiN_3 , tetrabutylammonium fluoride, without solvent, 85 °C, 18 h	86	2004JOC2896
	4-Methyl-1,1'-biphen-2-yl	Me_3SiN_3 , tetrabutylammonium fluoride, without solvent, 120 °C, 36 h	97	
iv	Phenyl	NaN_3 , NH_4Cl , DMF, MW irradiation (20 W), 15 min	96	2000JOC7984
	1,1'-Biphen-2-yl	NaN_3 , NH_4Cl , DMF, MW irradiation (20 W), 25 min	36	
v	2-Methyl-6 <i>H</i> -isochromeno[3,4- <i>c</i>]pyridine-3-yl	Me_3SiN_3 , $\text{Bu}_2^{\text{n}}\text{SnO}$, 1,4-dioxan, 140 °C, MW irradiation, (20 W), 8 h	74	2004TL2571
	2-Allyl-5-nitrophenyl	Me_3SiN_3 , $\text{Bu}_2^{\text{n}}\text{SnO}$, toluene, 110 °C, 8 h	28	
vi	Phenyl	NaN_3 , ZnBr_2 , water, reflux, 24 h	76	2001JOC7945
	4-Methyl-1,1'-biphen-2-yl	NaN_3 , ZnBr_2 , water, in a pressure tube, 170 °C, 48 h	67	

Finally, an unconventional synthesis of 1*H*-unsubstituted tetrazoles from nitriles and tris(2-perfluorohexylethyl)tin azides **539** has been reported [<1999T8997>](#). The yields of tetrazoles **24** increase with the ratio azide/nitrile (Equation 103).



<i>R</i>	539 (equiv)	Yield (%)	<i>R</i>	539 (equiv)	Yield (%)
<i>p</i> -MeC ₆ H ₄	2	99	C ₆ H ₅ (Me) ₂ C	5	96
<i>p</i> -MeOC ₆ H ₄	2.5	95	C ₆ H ₅ C(CH ₂) ₄	5	21
C ₆ H ₅ CH ₂	2.5	98	Bu ^t	1	23
C ₆ H ₅	2.5	99	Bu ^t	2.8	39
C ₆ H ₅ (Me) ₂ C	3	71	Bu ^t	4.5	59

(103)

6.07.9.2.2 Cycloaddition of organic azides to nitriles and nitrilium ions

[2+3] Cycloaddition of organic azides to organic nitriles or nitrilium ions is a highly regioselective approach to the synthesis of 1,5-disubstituted tetrazoles <1996CHEC-II(4)621>. The available data on the mechanism of this process have been summarized <2003JA9983>. Sharpless *et al.* reasonably state that the majority of organic nitriles are not good dipolarophiles, and the [2+3] cycloaddition should be activated by the use of Lewis acid catalysts, and sometimes by the pressure (10 kbar) <2003JA9983>. A sufficiently high reactivity was found in electron-deficient nitriles, for example, trinitroacetone nitrile <1999THS(3)467>, perfluoronitriles, trichloroacetone nitrile, N-alkylated nitriles (nitrilium salts), and also 5-sulfonyltetrazoles <2002AGE2110>. Demko and Sharpless tested the applicability of a 'click chemistry' approach to the direct synthesis of 5-sulfonyl tetrazoles **542** by intermolecular [2+3] cycloaddition of organic azides **540** to nitriles **541** (Equation (104); Table 35) <2002AGE2110>.

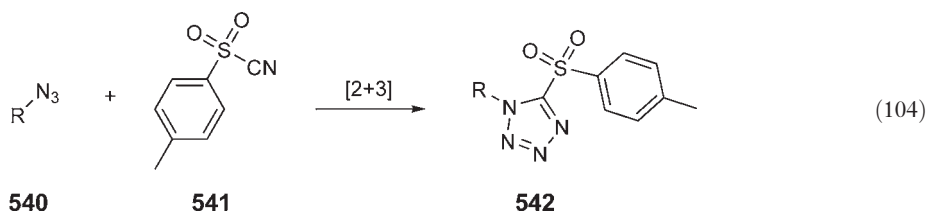
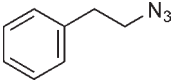
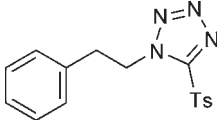
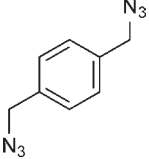
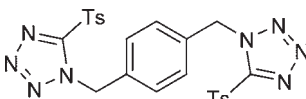
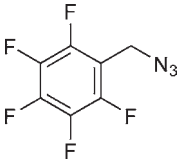
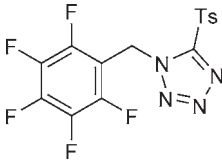
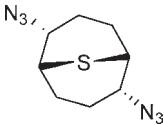
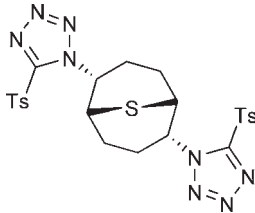
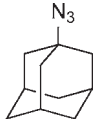
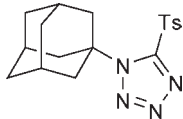
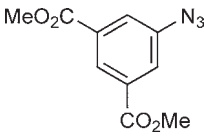
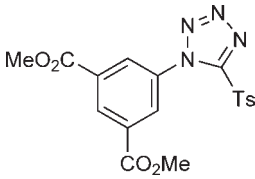


Table 35 [2+3] Dipolar cycloaddition of azides **540** to toluenesulfonyl cyanides **541** (Equation 104)^a

Reagent	Reaction conditions		Product	Yield (%)
	Temp. (°C)	Time (h)		
	100	16		99
	80	16		99

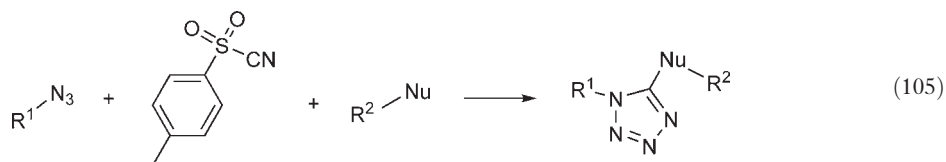
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Table 35 (Continued)

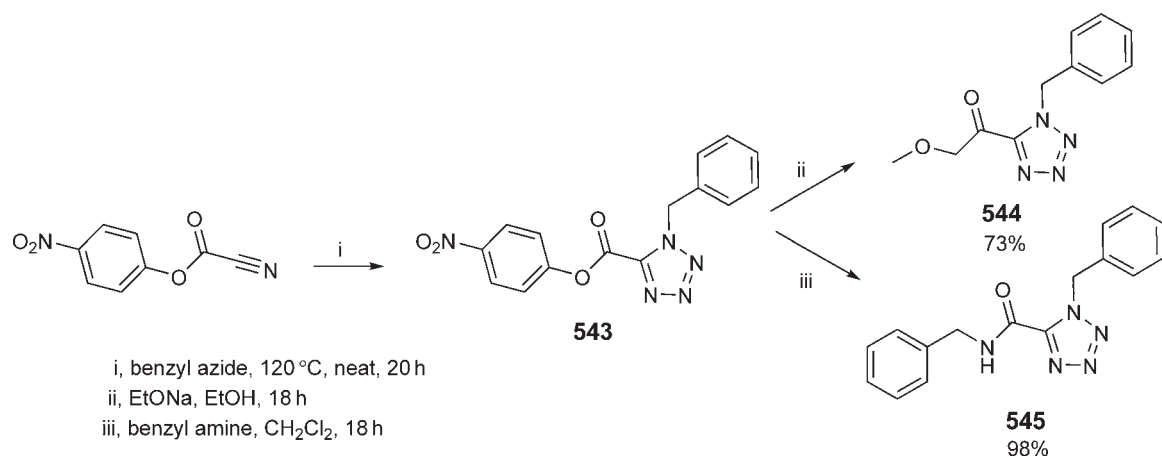
Reagent	Reaction conditions		Product	Yield (%)
	Temp. (°C)	Time (h)		
	80	40		99
	80	24		67
	100	60		46
	100	100		67

^aSelected data for reactions of unhindered, hindered, and aryl azides <2002AGE2110>.

Taking into account the results of a study of cycloadditions of azides to toluenesulfonyl cyanides (Table 35) and also the possibility of replacing the sulfonyl group in 5-sulfonyltetrazoles with a wide range of nucleophiles (R^2Nu), Demko and Sharpless suggested a scheme for an MCR (Equation 105). This version of the click chemistry approach was developed as a general route to 1,5-disubstituted tetrazoles <2002AGE2110>.

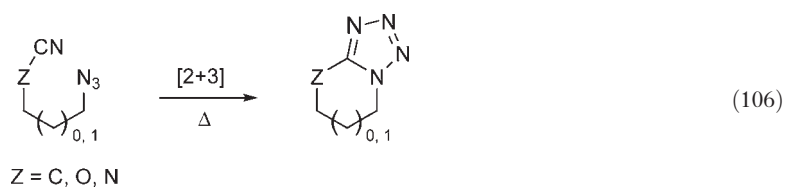


Demko and Sharpless proved the efficiency of this version of the click chemistry approach by successful syntheses of 5-acyltetrazoles from azides and acyl cyanides followed by their further functionalization. They used *p*-nitrophenyl cyanofornate to bring together an azide and nucleophiles in a one-pot process to give in high yield disubstituted acyltetrazoles, such as **544** and **545**, via 1-substituted 5-acyltetrazole **543** (Scheme 79) <2002AGE2113>.



Scheme 79

Since 1996, interest in fused heterotetrazole ring systems has grown. These compounds are synthesized via [2+3] cycloaddition of organic azides and nitriles substituted with a heteroatom within the same molecule (Equation (106); Table 36) <2001OL4091>.

Table 36 Intramolecular cycloadditions of azidonitriles (Equation 106)^a

Reactant	Conditions	Product	Yield (%)
	140 °C, DMF		96
	130 °C, DMF		96
	140 °C, DMF		53

(Continued)

Table 36 (Continued)

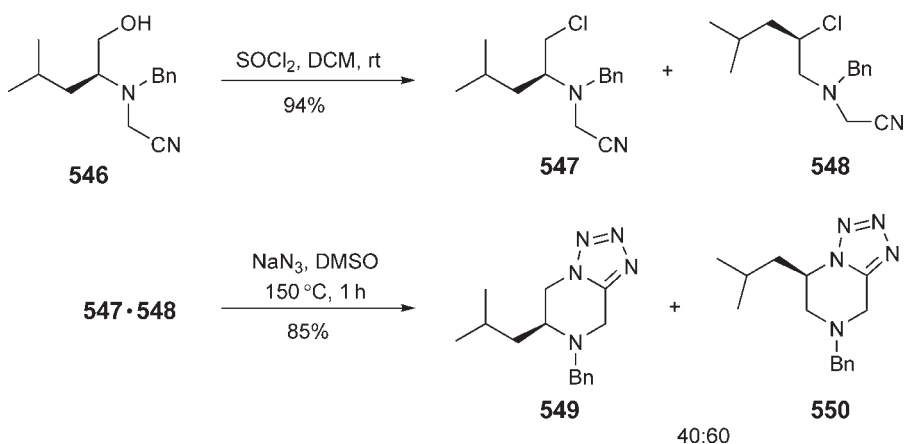
Reactant	Conditions	Product	Yield (%)
	100 °C, DMF		91
	NaSCN, 130 °C, DMF		96
	NaSCN, 140 °C, DMF		93
	NaSCN, 140 °C, DMF		0
	BrCN, rt, Et3N, DCM		92
	BrCN, rt, Me3N, H2O		80
	BrCN, 60 °C, THF		71

^aSelected data on intramolecular cycloadditions of azidocyanamides, azidothiocyanates, and activated azidonitriles <2001OL4091>.

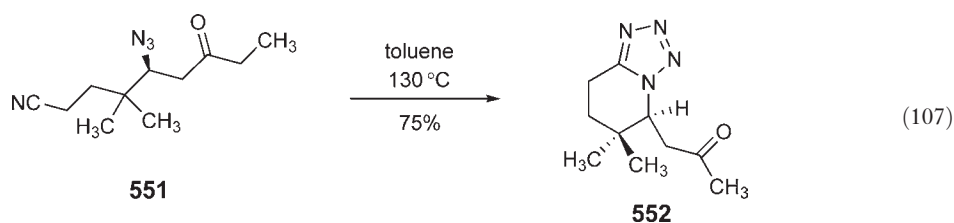
The formation of [5,5]- and [6,5]-ring systems under the same conditions is quite favorable, in contrast to that of [7,5]-ring systems (Table 36).

Couty *et al.* reported a two-stage synthesis of tetrazolopiperazines from N,N-disubstituted β -amino alcohols. The process proceeds with high diastereoselectivity and regioselectivity depending on the substitution in the starting amino alcohol. For instance, L-leucinol-derived amino alcohol **546** gave a roughly 1/1 mixture of the regioisomeric chlorides **547** and **548** upon treatment with SOCl_2 . The mixture was reacted with sodium to give separable bicyclic isomers **549** and **550** in a 4/6 ratio (Scheme 80) <2004TL3725>.

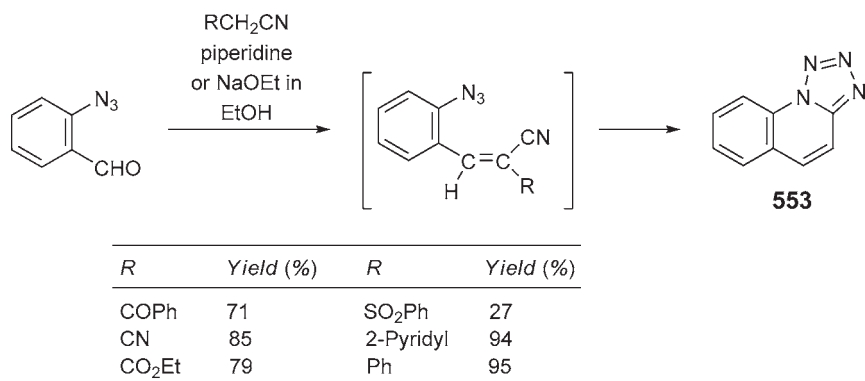
One more example of high stereo- and regioselectivity of cycloaddition has been provided by the reaction of enantioenriched azido ketone **551** that bears a tethered nitrile group which undergoes cyclization to the bicyclic tetrazole **552** (Equation 107) <2005JA1313>.



Scheme 80



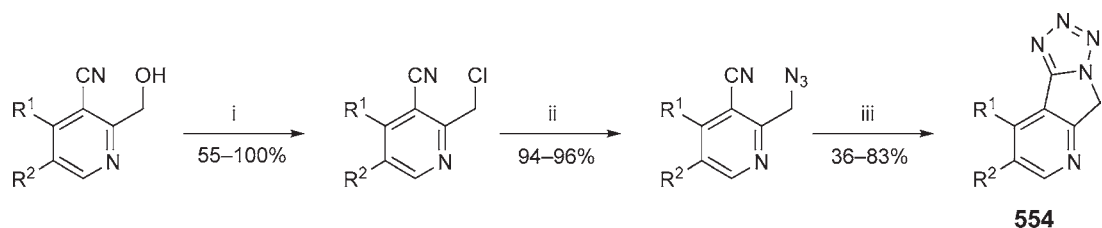
Intramolecular cycloaddition of azides and nitriles has often been used for the preparation of fused tetrazoles, tetrazoloazines, or similar compounds. In protic solvents, 2-azidobenzaldehyde undergoes base-catalyzed condensation with cyanocarbanions to yield tetrazolo[1,5-*a*]quinolines **553** (Scheme 81) <1997S773>.



Scheme 81

Similarly, 2-methyl-3-cyanopyridines were converted into novel heterocyclic systems containing a 3-(tetrazole-5-yl)-pyridine unit **554** via the corresponding 2-azidomethyl derivatives (Scheme 82) <2004TL9127>.

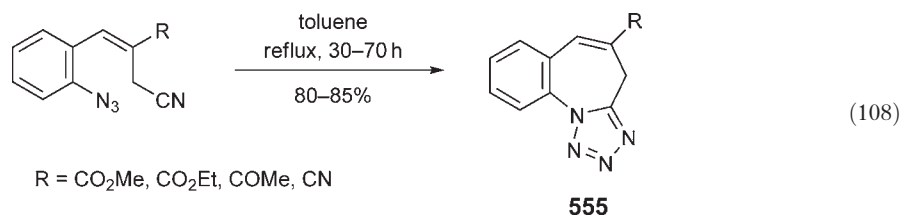
4*H*-Tetrazolo[1,5-*a*]benzazepines **555** were prepared by intramolecular 1,3-dipolar cycloaddition of azidophenylcyanomethyl compounds. The latter are readily obtained from 2-azidobenzaldehyde through Baylis–Hillman adducts (Equation 108) <2003JHC1103>.



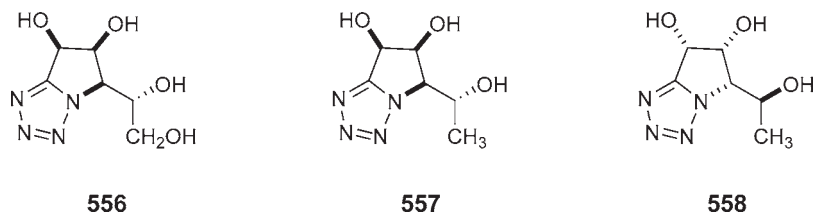
i, MsCl, TEA, CH₂Cl₂, rt; ii, NaN₃, DMSO, rt; iii, PhMe, 130–140 °C

R¹ = Bu^t, R² = H; R¹ = Ph, R² = H; R¹, R² = (CH₂)₄

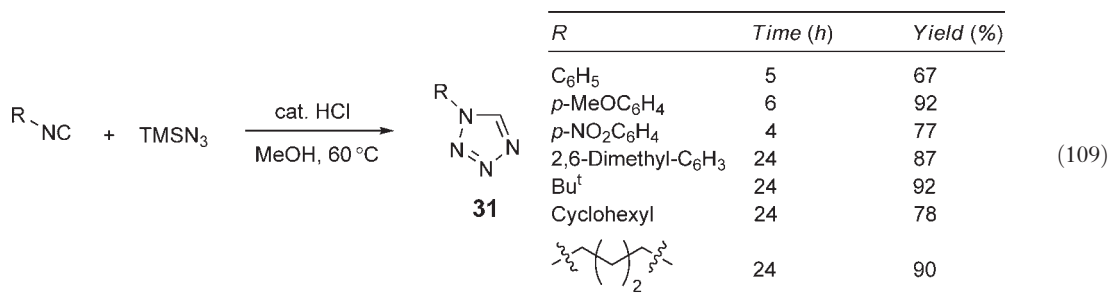
Scheme 82



The key step in the formation of the D-manno- **556** and D-rhamno- **557** tetrazoles from D-mannose and of the L-rhamnotetrazole **558** from L-rhamnose is an intramolecular 1,3-cycloaddition of the corresponding 4-azidonitriles [<1999T4501>](#).

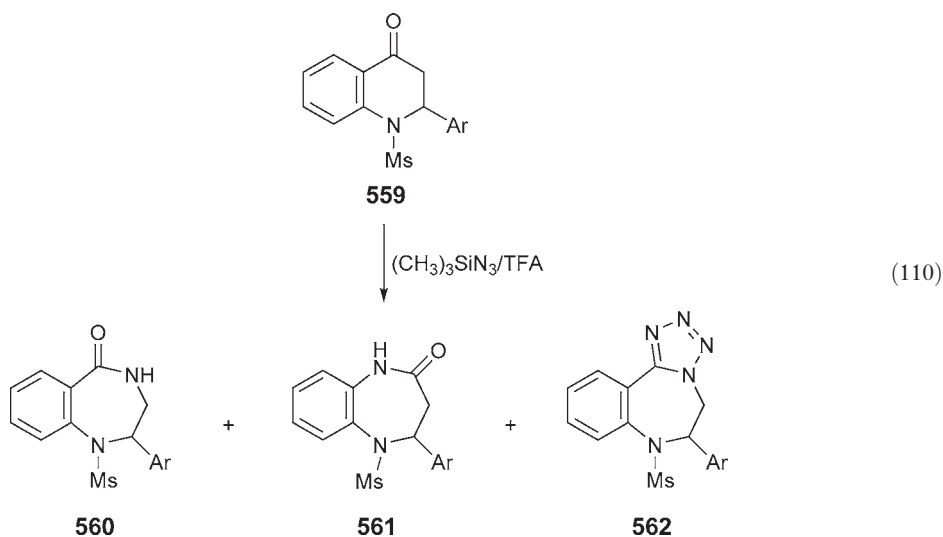


The reaction of nitrilium salts with sodium azide and tetramethylguanidium azide was reported more than 15 years ago, but is no longer widely used [<2004SOS\(13\)861>](#). However, nitrilium salts might form in various reactions as intermediates in the synthesis of 1,5-disubstituted tetrazoles, for instance, as precursors of imidoyl azides in the multicomponent Ugi reaction [<2004SOS\(13\)861, 2001T5785>](#). Nitrilium ions are also intermediates in the synthesis of 1-substituted tetrazoles **31** via the acid-catalyzed [3+2] cycloaddition of isocyanides and trimethylsilyl azide ([Equation 109](#)) [<2004TL9435>](#). The reaction of isocyanides and TMSN₃ (1.5 equiv) was carried out in MeOH (0.5 M) in the presence of a catalytic amount of HCl (2 mol%, 1.0 M in Et₂O solution) at 60 °C.



6.07.10 Tetrazoles from Transformations of Other Heterocyclic Rings

A comprehensive review of this topic, including publications up to 1998, has been published by Moderhack <1998JPR687>. About 40 examples are cited of conversions into a tetrazole ring of: three- and four-membered rings (2*H*-azirines, aziridines, 1,3-thiazetidines); five-membered rings with one or two heteroatoms (benzofurans, isobenzofurans); five-membered rings with three or more heteroatoms (1*H*- and 2*H*-1,2,3-triazoles, 1,2,4- and 1,2,5-oxadiazoles, 1,2,3,4- and 1,2,3,5-thiatriazoles). Methods of tetrazole ring formation from six-membered ring systems with one or two heteroatoms (pyridines, quinolines, isoquinolines, pyridazines, 1,3-oxaziniums, 4*H*-3,1-benzoxazines, pyrazines) and from six-membered rings with three or more heteroatoms (1,2,3-benzotriazines, 1,3,5-triazines, 1,2,3,4- and 1,2,3,5-tetrazines) were also considered <1998JPR687>. In the last decade, the main effort has been directed to methods of tetrazole synthesis from acyclic compounds. In a later review, a single publication was mentioned describing "tetrazoles from transformations of other heterocyclic rings" <2001EJO3405>. Nevertheless, we found one more article on this promising procedure: Mphahlele reported that 2-aryl-*N*-methylsulfonyl-4-quinolones **559** were treated with azidotrimethylsilane in TFA (azidotrimethylsilane-mediated Schmidt rearrangement) to give 1,4- **560**, and 1,5-benzodiazepi-nine derivatives **561**, as well as the 1,4-tetrazole derivatives **562** (Equation 110) <1999J(P2)3477>.



6.07.11 Preferred Routes to Tetrazole Classes

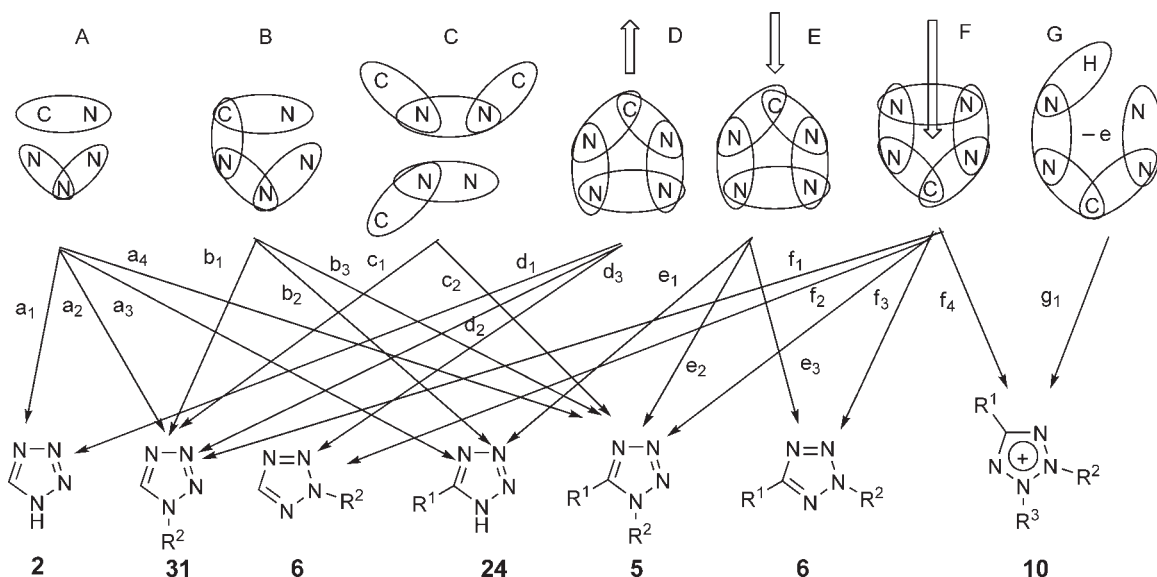
The main reactions (A–G) and the corresponding pathways resulting in the formation, or subsequent functionalization, of tetrazole rings are shown in Scheme 83. As seen from the scheme, only several elementary reaction acts leading to a five-membered heteroaromatic ring with four nitrogen atoms (tetrazole ring) are possible. These reactions follow the mechanisms depicted in Scheme 83. These are:

1. cycloaddition of azides to nitriles (A) leading to the formation of *N*-unsubstituted tetrazole **2** (a₁), 1-substituted tetrazoles **31** (a₂), and 5-disubstituted tetrazoles **5** (a₄);
2. cyclization of imidoyl azides (B) giving 1-substituted tetrazoles **31** (b₁), 5-substituted tetrazoles **24** (b₂), and 1,5-disubstituted tetrazoles **5** (b₃);
3. coupling of 1,2-disubstituted hydrazines and diazonium salts (C) *via* pathways c₁ and c₂ leading to 1-mono- **31** and 1,5-disubstituted tetrazoles **5**, respectively.

Further functionalization of the tetrazole ring occurs as a result of the following reactions:

1. oxidative decomposition of the substituents attached to the carbon of the tetrazole ring (D) that affords (d₁, d₂, d₃) both *N*-unsubstituted tetrazole **2** and *N*-substituted CH-tetrazoles **31** and **6**;
2. electrophilic or nucleophilic attacks at endocyclic carbon (E) (e₁, e₂, e₃) giving a short route to 5-substituted tetrazoles **24**, **5**, and **6**;

- electrophilic attacks at endocyclic nitrogen atoms of NH-unsubstituted tetrazoles (F) resulting in formation (f_1 , f_2 , f_3) of regioisomeric N-substituted tetrazoles **31**, **5**, and **6**;
- exhaustive alkylation of N-substituted tetrazoles (F) furnishing (f_4) corresponding tetrazolium salts **10**;
- oxidative cyclization of formazanes (G), the main route (g_1) leading to salts **10**.



Scheme 83

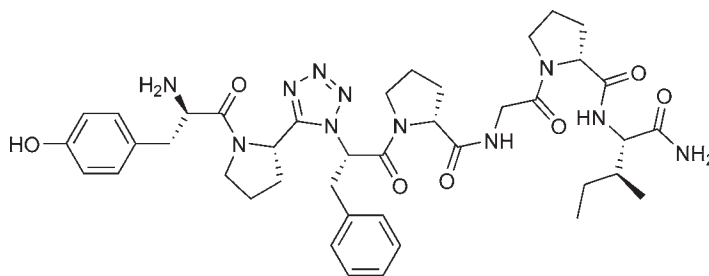
In keeping with **Scheme 83**, the most important methods for the tetrazole synthesis are reactions corresponding to the following types: A (cf. [Sections 6.07.9.4.1 and 6.07.9.4.2](#)), B (cf. [Section 6.07.9.1](#)), and F (cf. [Section 6.07.5.3](#)). Actually, the number of strategic connections (arrows) between these types of an elementary act and the products of the corresponding reactions is the largest. Note that recently the tetrazole functionalization methods of type E became closer to this special group (cf. [Section 6.07.5.4](#)). It should be stated that within the last decade no fundamentally new types or pathways of reactions were discovered. At the same time, the efforts of the leading groups dedicated to extending the knowledge on the mechanisms of key reactions (A–G) (**Scheme 83**), and to development of new, more efficient experimental protocols of these reactions, were fruitful and successful. The key theoretical studies that we believe will have major effect on the development of novel synthetic methods and functionalization procedures for tetrazoles are listed below. The possible mechanisms of azides' cycloaddition to nitriles were treated by means of DFT by Himo *et al.* [<2002JA12210>](#). Later these authors have also thoroughly investigated the mechanism of the zinc(II)-catalyzed reaction of azide ions with organic nitriles leading to tetrazoles [<2003JA9983>](#). The structure of the key intermediates and the major routes corresponding to types A and B were analyzed in a review [<2004CRV459>](#). The results of the kinetics investigation of the type F reactions were generalized and systematized in the survey [<2000H\(53\)1421>](#). All the fundamental investigations cited above gave an impact to the development of new strategy in synthetic methods and functionalization of tetrazoles.

6.07.12 Important Compounds and Applications

6.07.12.1 Biologically Active Derivatives

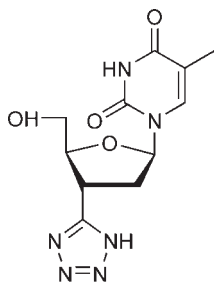
Butler listed over 20 kinds of biological activity of tetrazoles [<1996CHEC-II\(4\)621>](#). Within the last decade, the number of publications concerning application of tetrazoles in pharmaceuticals and investigations of their biological activity has grown steadily and reached several hundreds (with the exception of patents). It is impossible to discuss all

567 and investigated the biological activity of the corresponding complexes with copper(II). The results of this study <2000JIB283> and further investigation of the problem <2006MI297> confirmed the validity of predictions.

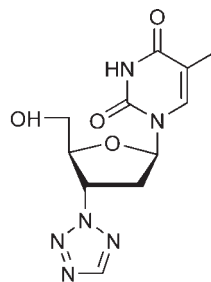


567

Tetrazolyl tymidines **247**, **249**, **568**, and **569** with a tetrazole ring in the molecular structure are regarded as individual biologically active compounds <1995NN1289, 1998RJO449, 2000H(53)1421, 2001RJO759, 2002HCA2847, 2002TL1901> and also as reagents for the synthesis of appropriate linkers and oligonucleotides <2002HCA2847> (cf. Section 6.07.5.3).

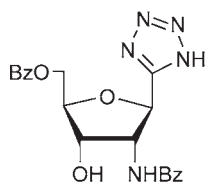


568

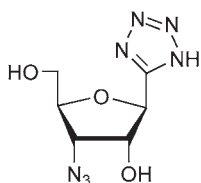


569

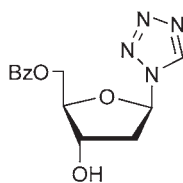
V. Popsavin and co-workers synthesized and tested the antiviral activity of the new tetrazole-related *C*-nucleosides 2-benzamido-2-deoxy- β -D-ribofuranose **570** and 3-azido-3-deoxy- β -D-xylofuranose **571** <2002T569>. The possibility of introducing tetrazole nucleosides **572** and **573** as building blocks for metal-mediated base pairing in artificial oligonucleotides has been evaluated by Müller *et al.* <2005CEJ6246>. The bioaction of alternative pseudo-*C*-nucleoside **574** containing a tetrazole ring was investigated by Rauter *et al.* <2005MI275>.



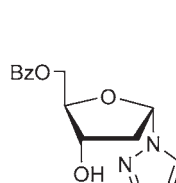
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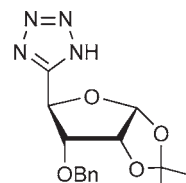
571



572

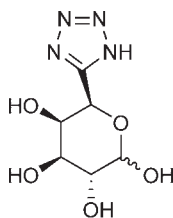


573



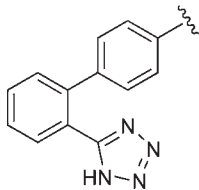
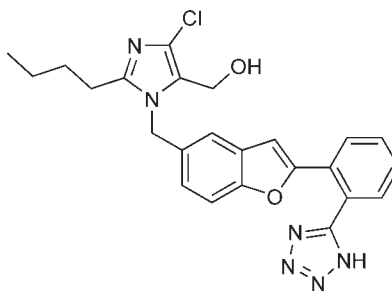
574

5-[5'-(α -L-Arabinopyranosyl)]tetrazole **575** and 5-[5'-(β -L-arabinopyranosyl)]tetrazole **576** having potential antiviral activity were described by Accorso and co-workers <2003ARK491>. Relatively less attention was given to the synthesis and evaluation of the biological action of pseudo-carbohydrates containing a tetrazole ring. Note the study of Davis *et al.* on the synthesis of D-manno- **556** and D-rhamno- **557** tetrazoles from D-mannose, and of the L-rhamnotetrazole **558** from L-rhamnose <1999T4501>.

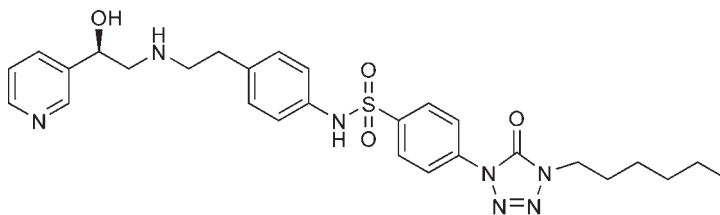
**575, 576**

6.07.12.1(i) The regulation of blood pressure

The renin–angiotensin system (RAS) plays a central role in blood pressure regulation and electrolyte homeostasis. AII, an octapeptide that is formed within the RAS from angiotensin I by angiotensin-converting enzyme (ACE), is one of the most powerful vasoconstrictors known. The most direct and potentially the most specific approach to block the RAS is to antagonize AII at its receptor sites. DuPont reported the discovery of the first potent and orally active nonpeptide AII antagonist, losartan **29** (Dup-753, COZAAR) <2000JME2685>. AII receptor antagonists (losartan **29**, candesartan, irbesartan **83**, valsartan), whose molecules contain a common structural fragment **577**, have remained at a high demand in the pharmaceuticals market for more than 10 years (cf. Section 6.07.2.1.2). The attention of researchers is focused on the molecules of these compounds and also on some modified structures, viz. benzofuran derivative **578** <1997BMC445>, and the preparation procedures for these substances are continuously refined (cf. Section 6.07.7.2.2) <1998J(P2)475, 1999FA64, 1999JME1714, 2000JME2685, 2001CRV2727, 2004MI76, 2004MI263, 2004JME5597, 2005MI146, 2006JME1526, 2006SC2079, 2006CPB706, 2006CPB626>.

**577****578**

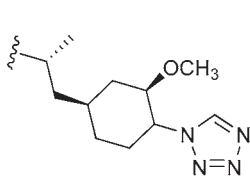
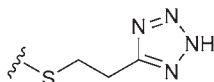
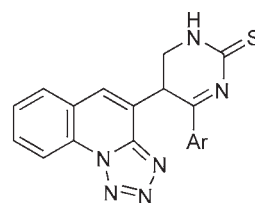
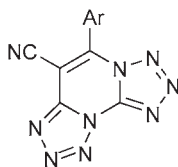
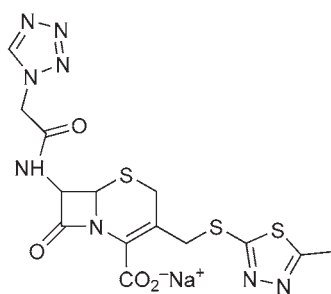
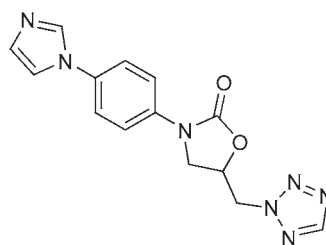
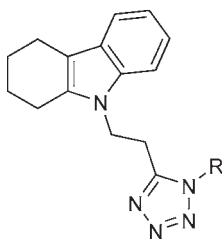
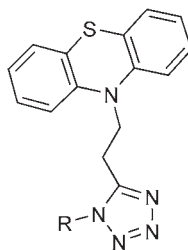
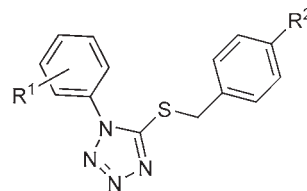
Besides the above AII receptor antagonists, another promising group of compounds containing a tetrazole ring should be mentioned: β -adrenergic receptor agonists. These compounds include substituted tetrazolones (L-764,646 and L-766,892) such as compound **579** (cf. Section 6.07.6.1) <1999BML1251, 1999TL6739>.

**579**

6.07.12.1(ii) Antimicrobial activity

Structural fragments or formulas of tetrazole derivatives endowed with a pronounced antimicrobial action and the references of the respective publications are shown: rapamycin analogs **580** <2005BML5340, 2005MRC174>; nocathiacin I derivative **581** <2005BML2069>; tetrazolo[1,5-*a*]quinoline **582** (anti-inflammatory–antimicrobial agents) <2004EJM249>, ditetrazolo[1,5-*a*;1',5'-*c*]pyrimidine **583** <2005CHJ211>, Kefzol (cefazolin, cephalazolin),

(6*R-trans*)-3-[[[(5-methyl-1,3,4-thiadiazol-2-yl)thio]methyl]-8-oxo-7-[(1*H*-tetrazol-1-ylacetyl)amino]-5-thia-1-azabicyclo-[4.2.0]oct-2-ene-2-carboxylic acid **584** and related compounds <2001PCJ169, 2000M937, 2002TML856, 2004MI79>, oxazolidinone (C-5 side-chain modification, against Gram-positive bacteria) **585** <2006BMC4227>, substituted-[5-[2-(1,2,3,4-tetrahydrocarbazol-9-yl)ethyl]tetrazol-1-yl]alkanones **586** (antinociceptive activity) <2005EJM1359>, a series of novel 5-[(β -phenothiazin-10-yl)ethyl]-1-(acyl)-1,2,3,4-tetrazoles **587** (analgesic and anti-phlogistic activity) <2004EJM273>, and 1-aryl-5-benzylsulfanyltetrazoles **588** (against mycobacterium tuberculosis) <2005MI385>.

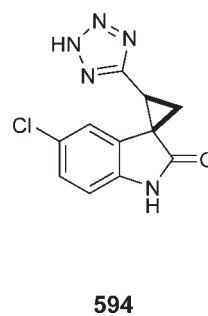
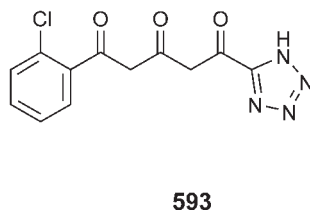
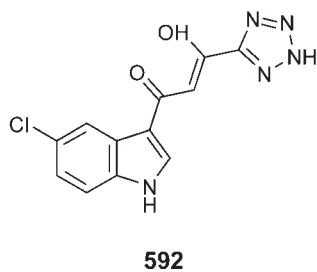
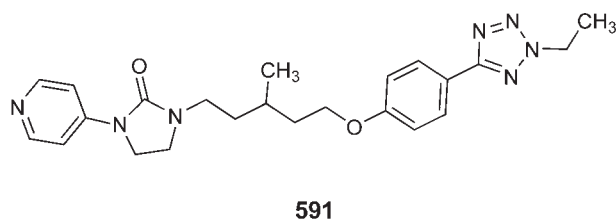
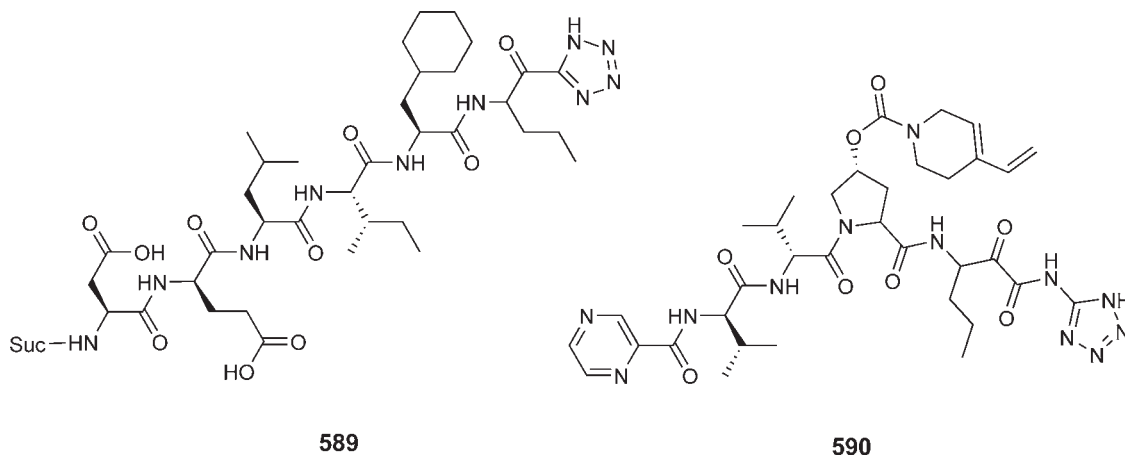
**580****581****582****583****584****585****586****587****588**

Tetrazole ligands (cf. Sections 6.07.5.3.4, 6.07.9.4.1, and 6.07.12.3), in particular polyvinyl tetrazoles, exhibit simultaneously high complexing ability (cf. Section 6.07.5.4) and potent bactericidal action. This combination of properties makes them promising ligands as components of filter materials for dialysis procedures and for ultrafiltration of water and biological liquids <2003RCR143, 2005MI605>.

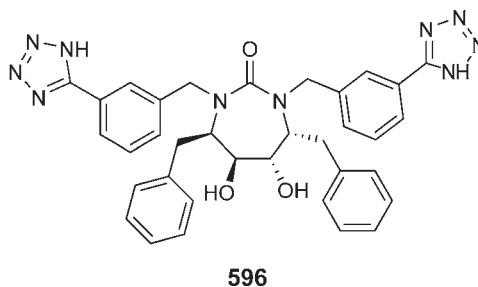
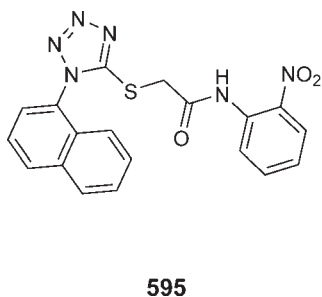
6.07.12.1.1(iii) Antiviral activity

The following tetrazole-containing compounds show antiviral activity: hepatitis C virus NS3 protease inhibitors **589** <2002BML705, 2003BMC2551, 2004BBA51>; hepatitis C virus NS3/4A protease inhibitors **590** <2004BML1441>; pyridylimidazolidinone derivatives **591** (against enterovirus 71 (EV71)) <2005JME3522>; β -diketoacid (5CITEP); 1-(5-chloroindol-3-yl)-3-hydroxy-3-(2*H*-tetrazol-5-yl)-propanone **592** (HIV-1 integrase inhibitor) <2000JME4109, 2001JME3043, 2001JA12708, 2002JBC12596, 2003MI1450, 2004MI739, 2004JCI1450, 2004BMC6371, 2004JME1879,

2005JGM317, 2005PCA5198, 2005JME111, 2005JME7084, 2005JME8009, 2006ARK224, 2006JME3994>; triketoacid **593** (HIV integrase inhibitor) <2006BML2920>; oxindole derivative **594** (HIV-1 non-nucleoside reverse transcriptase inhibitor) <2006BML2109>. Also HIV protease inhibitors were synthesized like compound **493** <1997J(P1)2475, 2002J(P1)172> (cf. Section 6.07.9.1). Nucleoside analogs of reverse transcriptase inhibitors, such as **569**, have been described <1995NN1289, 1998RJO449, 2000H(53)1421, 2001RJO759> (cf. Section 6.07.5.3).

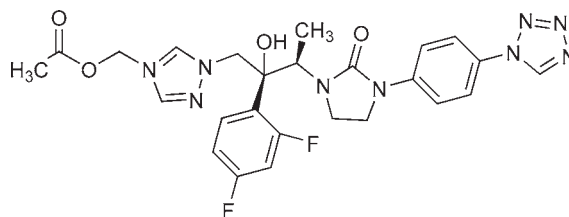


Tetrazole thioacetanilides **595** (HIV non-nucleoside reverse transcriptase inhibitors) <2006BML2748> and derivatives of cyclic ureas **596** (nonpeptide inhibitors of HIV protease) have been prepared <1998JME2019>.

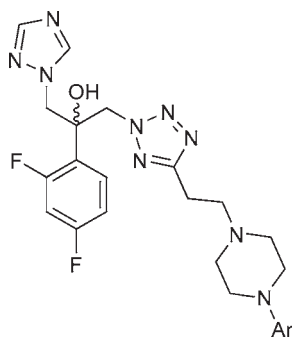
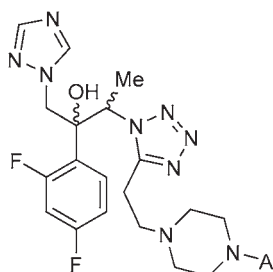


6.07.12.1(iv) Antifungal activity

Ichikawa *et al.* reported on the synthesis and antifungal activity of 1-[(1*R*,2*R*)-2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1*H*-1,2,4-triazol-1-yl)propyl]-3-[4-(1*H*-1-tetrazolyl)phenyl]-2-imidazolidinone **597**. Compound **597** was selected as an injectable candidate for clinical trials based on the results of evaluations of solubility, stability, hemolytic effect, and *in vivo* antifungal activities <2001CPB1102, 2001CPB1110>.

**597**

Arora and co-workers prepared novel optically active substituted tetrazoles, (2*R*,3*S*)-2-(2,4-difluorophenyl)-3-(5-[2-[4-aryl-piperazin-1-yl]-ethyl]-tetrazol-2-yl/1-yl)-1-[1,2,4]-triazol-1-yl-butan-2-ol **598** and **599** having antifungal activity against *Candida* spp., *Cryptococcus neoformans*, and *Aspergillus* spp. *in vitro*. The location of the methyl group at the C-3 of compounds **598** has been demonstrated to be a key structural element of antifungal potency <2004EJM579, 2004BMC2225>.

**598****599**

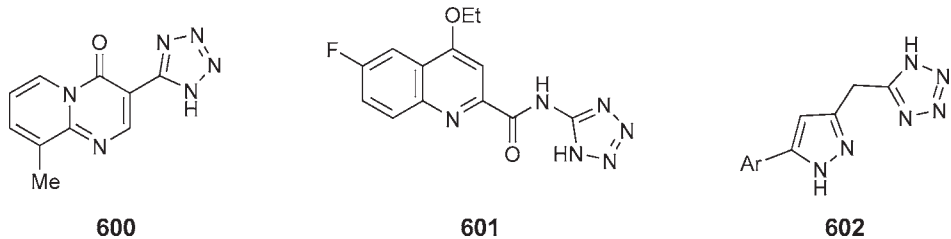
6.07.12.1(v) Antitumor agents

Aboul-Encin and co-workers obtained and examined platinum(II) complexes of tetrazolo[1,5-*a*]quinolines **45** which are structural analogs of cisplatin, *cis*-[PtCl₂(NH₃)₂], the first-generation anticancer agent. Some of the complexes synthesized have demonstrated higher efficacy than that of cisplatin <2004EJM499>. The synthesis of tetrazole derivatives that are inhibitors of thymidylate synthase and potential antitumor agents was discussed by Bavetsias *et al.* <2000JME1910>. Tetrazolo[1,5-*b*]pyridazine derivatives have been found to reveal high cytostatic activity in KB and HeLa human cancer cells <1997MI471>.

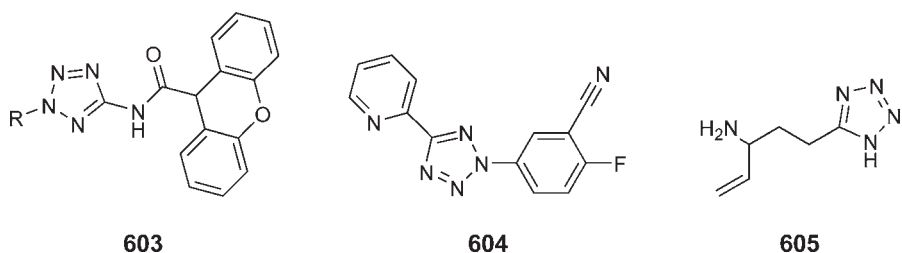
6.07.12.1(vi) Other kinds of activity

A series of 2-(5-tetrazolyl)benzopyran-4-ones were extended; to this series belong pranlukast, (*N*-[4-oxo-2-(1*H*-tetrazol-5-yl)-4*H*-1-benzopyran-8-yl]-4-(4-phenylbutoxy)benzamide), a known antiallergic drug (cf. Section 6.07.12.1.2) <1997SC1065>. Synthetic methods for antiallergic agent 9-methyl-3-(1*H*-tetrazol-5-yl)-4*H*-pyrido[1,2-*a*]pyrimidin-4-one, **600**, were described by Sano and Ishihara <1998H(48)775>. Chenault and co-workers reported on the synthesis and evaluation of quinoline derivative **601** as antidiabetic agents <2000BML1831>. Novel 5-substituted-1*H*-tetrazole derivatives as potent glucose- and lipid-lowering agents were prepared, and their antidiabetic effect was evaluated in

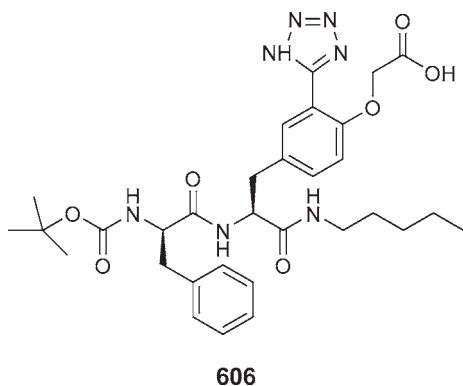
two genetically obese and diabetic animal models <2002CPB100>. Ram and co-workers developed a procedure for the synthesis and reported results of examination *in vivo* of antihyperglycemic activity of 5-[(5-aryl-1*H*-pyrazol-3-yl)methyl]-1*H*-tetrazoles **602** <2005BML2115>.



Young *et al.* <2004JME2995> showed that among the five-membered ring heterocycles with attached *ortho*-substituted aryls, the tetrazole-based thrombin inhibitors are optimal. Note that tetrazole derivatives are included in the library of 133 heparin-derived structures <2006BMC2300>. Quaternary ammonium salts of poly-C-vinyltetrazole on the contrary exhibit a high antiheparin action <2003RCR143>. The metabolism, pharmacokinetics, tissue distribution, and extraction of L-N6-(1-iminoethyl)lysine-5-tetrazole-amide (L-NIL-TA), a selective iNOS inhibitor, were investigated <2002JME1686, 2004JPS1229>. Vieira *et al.* examined (2*H*-tetrazol-5-yl)-amides **603** as potent, orally administered mGlu1 receptor enhancers. The agonist effect of compounds **603** depends on the nature of the substituent: R = Me (100%) and R = Buⁱ (28%) <2005BML4628>. Huang *et al.* reported that 3-fluoro-5-(5-pyridin-2-yl-2*H*-tetrazol-2-yl)benzonitrile **604** and 2-[2-[3-(pyridin-3-yloxy)phenyl]-2*H*-tetrazol-5-yl]pyridine **605** are highly potent and selective mGlu5 receptor antagonists with good rat pharmacokinetics, brain penetration, and *in vivo* receptor occupancy <2004BML5473, 2005BML5061>. The potential time-dependent inhibitor of GABA-AT, 1*H*-tetrazole-5-(α -vinyl-propanamine), was designed based on the structures of vigabatrin (4-aminohex-5-enoic acid); this compound showed time-dependent inhibition of GABA-AT, but its potency was lower than that of vigabatrin <2006BMC1331>.



Liljebris *et al.* synthesized 2-[4-[(2*S*)-2-[(*tert*-butoxycarbonyl)amino]-3-phenylpropanoyl]amino]-3-oxo-3-(pentyl-amino)propyl]-2-(1(2)*H*-tetrazol-5-yl)phenoxy]acetic acid **606**, peptidomimetic inhibitors of protein tyrosine phosphatase 1B <2002JME1785>.



Hydroxyethylammonium salts of poly-5-vinyltetrazole may be used as filming agent in cosmetics, and also a copolymer of 2-methyl-5-vinyltetrazole with 1-vinylpyrrolidone, methyl methacrylate, and β,ω -hexamethacryloyl oligoacrylate may be applied <2003RCR143>.

6.07.12.1.1(vii) Quantitative structure–activity relationships

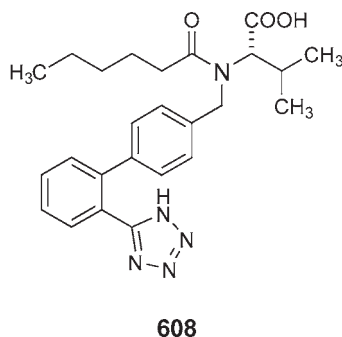
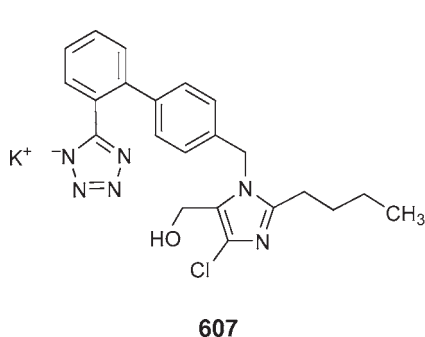
The data cited show that within the last decade studies of biological activity of tetrazoles have become systematic. In many of these investigations, QSARs were actively exploited. Examples of such research are listed below: comparative QSAR for AII antagonists <2001CRV2727, 2006JPS717>, novel substituted 1-benzyl-5-phenyltetrazole P2X7 antagonists <2006JME3659>, HIV-1 integrase inhibitors <2002BMC4169, 2002AAC3292, 2005JGM317, 2006ARK224>, imidazoleglycerol phosphate dehydratase (IGPD) inhibitors <1998BBA107>, QSAR correlation of the biological activity of 5-amino-1-aryl-1*H*-tetrazoles <1999JPR499, 2001MI259>, structure–activity relationship (SAR) analysis of cytotoxicity, antitumor and antimycobacterial activity of tetrazole <2005MI396>.

6.07.12.1.2 Drug application

Below are tetrazole derivatives exemplifying pharmaceutical substances not only endowed with biological activity (cf. Section 6.07.12.1.1), but also holding a firm place in the contemporary drug market <B-1999MI1>.

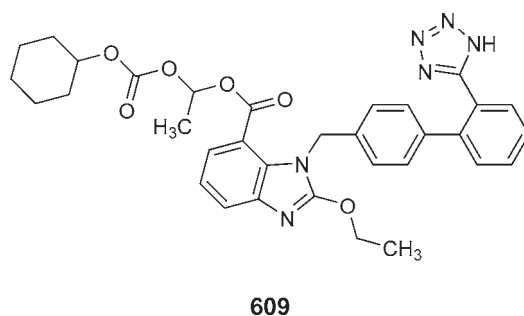
Losartan. 2-Butyl-4-chloro-1-[[2'-(1-tetrazol-5-yl)[1,1'-biphenyl]4-yl]methyl]1*H*-imidazole-5-methanol **29** monopotassium salt **607**, antihypertensive, angiotensin II blocker.

Valsartan. *N*-(1-Oxopentyl)-*N*-[[2'-(1*H*-tetrazol-5-yl)[1,1'-biphenyl]4-yl]methyl]-*L*-valine, antihypertensive, angiotensin II blocker **608**.



Irbesartan. 2-Butyl-3-[[2'-(1*H*-tetrazol-5-yl)[1,1'-biphenyl]4-yl]methyl]-1,3-diazaspiro[4.4]non-1-en-4-one **83**, antihypertensive, angiotensin II blocker.

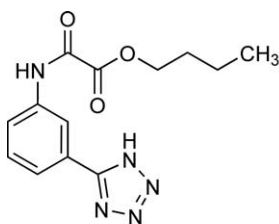
Candesartan cilexetil. (±)-2-Ethoxy-1-[[2'-(1*H*-tetrazol-5-yl)[1,1'-biphenyl]4-yl]methyl]1*H*-benzimidazole-7-carboxylic acid 1-[[cyclohexyloxy]carbonyl]oxy]ethyl ester **609**, angiotensin II blocker.



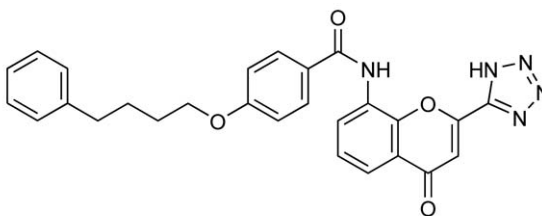
Pemirolast. 9-Methyl-3-(1*H*-tetrazol-5-yl)-4*H*-pyrido[1,2-*a*]pyrimidin-4-one **600**, antiallergic.

Tazanolast. Oxo[[3-(1*H*-tetrazol-5-yl)phenyl]amino]acetic acid butyl ester **610**, antiallergic, antiasthmatic.

Pranlukast. *N*-[4-Oxo-2-(1*H*-tetrazol-5-yl)-4*H*-1-benzopyran-8-yl]-4-(4-phenylbutoxy)benzamide **611**, antiallergic.



610

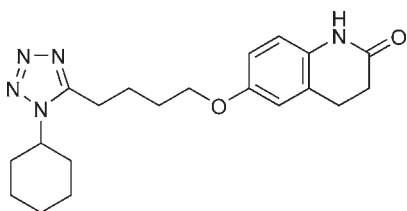


611

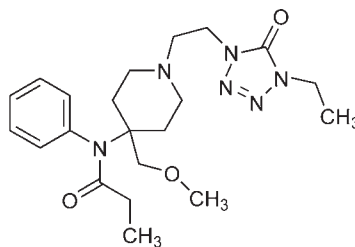
Pentetrazol. 6,7,8,9-Tetrahydro-5*H*-tetrazolo[1,5-*a*]azepine **16**, analgesic, circulatory stimulant.

Cilostazol. 6-[4-(1-Cyclohexyl-1*H*-tetrazol-5-yl)butoxy]-3,4-dihydro-2(1*H*)quinoline **612**, platelet aggregation inhibitor, cerebral vasodilating activity.

Alfentanil. *N*-[1-[2-(4-Ethyl-4,5-dihydro-5-oxo-1-*H*-tetrazol-1-yl)ethyl]-4-(methoxymethyl)-4-piperidiny]-*N*-phenylpropanamide **613**, analgesic, short-time anesthetic (for basal narcosis).



612

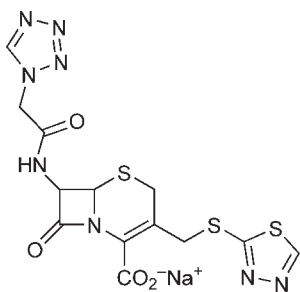


613

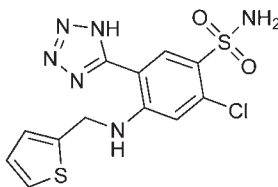
Kefzol (cefazolin, cephalazolin). Compound **584** (cf. Section 6.07.12.1.1).

Ceftezole. (6*R*-*trans*)-8-Oxo-7-[(1*H*-tetrazol-1-ylacetyl)amino]-3-[(1,3,4-thiadiazol-2-ylthio)methyl]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid sodium salt **614**, antibiotic.

Azosemide. 2-Chloro-5-(1*H*-tetrazol-5-yl)-4-[(2-thienylmethyl)amino]benzenesulfonamide **615**, diuretic.



614



615

6.07.12.2 Energetic Tetrazoles

In the series of stable five-membered nitrogen-containing heterocycles, tetrazole possesses extreme characteristics that are inferior only to those of pentazole (cf. Section 6.07.4.3). Attention should be paid to the obvious fact that, in contrast to the hypothetical pentazole, tetrazole is a thermodynamically stable compound. This heterocycle surpasses the simple azide and hydrazoic acid by a number of key tests. However, tetrazoles are thermodynamically stable in the condensed phase, relatively weakly sensitive to impact and friction, and not very toxic, unlike HN_3 which is notorious for its high sensitivity to impact, friction, thermal and electric impulses, and toxicity <1999THS(3)467>.

In the last decade, important events have occurred in this field and reviews have been published describing the state of art and prospects of development in the chemistry of energetic tetrazoles <1997MI84, 1997MI3, 1999THS(3)467, 2001MI72, 2003RCR143, 2006AGE3584>. Koldobskii *et al.* reported on the synthesis and properties of 5-nitrotetrazole

and its derivatives. Some explosive and combustion parameters of certain 5-nitrotetrazole derivatives surpass those of RDX and HMX (octahydro-1,3,5,7-tetranitro-1,3,5,7-tetrazocine) (cf. Section 6.07.4.3) <1997RJO1771>. Steel published new data on the structure of 5,5'-bitetrazole **26** <1996JCX399>. Note that 5,5'-bis-1*H*-tetrazole diammonium salt of bitetrazole **26** is considered as a promising component of low-toxic nonazide-based gas-generating composition for airbags. Salts and complexes with bis(tetrazolyl)amine **120** (cf. Section 6.07.4.3.1) are of interest as additives in pyrotechnics and ammonium perchlorate-based propellants <2006AGE3584>. Sauer *et al.* examined in detail 3,6-bis(2*H*-tetrazol-5-yl)-1,2,4,5-tetrazine <2001EJO697>. Gaponik and co-workers, Hiskey, and Klapötke and co-workers refined the preparation method and investigated the properties of 1,5-diaminotetrazole **33** <2002THE233, 2005CEN5, 2004MI3, 2005IC4237>. The preparation and properties of energetic salts of 5-cyanotetrazole were reported by Passmore and co-workers <2000IC1840>. Klapötke's team carried out experimental and theoretical research on various energetic tetrazoles, in particular, such exotic molecules like 5-azidotetrazole **3**, azotetrazole **4** derivatives, tetrazolyl-pentazole, *N*-nitroso- and *N*-nitraminotetrazoles, and 1,5-diaminotetrazolium dinitramide **77**, **121**, **172** (cf. Sections 6.07.2.1, 6.07.3.1, 6.07.4.3, 6.07.4.4, and 6.07.5.5) <2001IC3570, 2002IC906, 2002ZFA2901, 2003MI165, 2004MI325, 2005MI17, 2005THE168, 2005CM3784, 2005JA2032, 2005IC4237, 2006JOC1295>. It has been known for a long time that the main industrially produced energetic tetrazole is tetrazene **398** (cf. Section 6.07.7.3). Now many other energetic tetrazoles have become industrially available, and they are profitably employed in military and space technology <B-1998MI536, 2003C773>. For instance, in the modern pyroautomatic systems of rocket complexes in USA, blasting caps are successfully used with light-sensitive charges of tetraamine-*cis*-bis(5-nitro-2*H*-tetrazolate-N²)cobalt(III) perchlorate (BNCP) **341** (cf. Section 6.07.7.3.4) <2005MI21>.

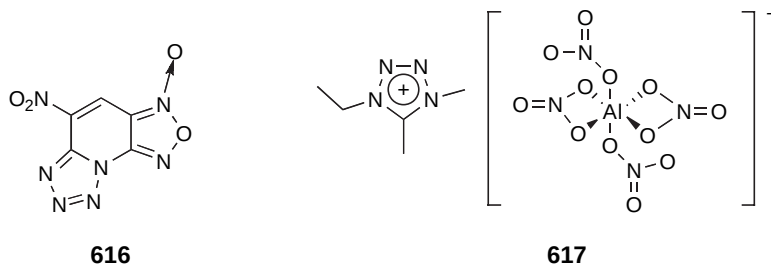
Evidently the problems of preparation of new and thorough experimental examination of already known energetic tetrazoles are a major focus of interest. We cite below new publications that were out of scope of previous discussions but are directly connected with the problem in hand. Ilyushin *et al.* studied a coordination complex of mercury(II) perchlorate with 5-hydrazinotetrazole **423** (cf. Section 6.07.7.3.4) as a potential photosensitive primary explosive <2005MI21>. This complex consisting of particles of ca. 1 mm size demonstrated the highest sensitivity to laser irradiation combined with an extremely low initiation threshold. The complex of compound **423** is a promising component of a photosensitive formulation consisting of about 90 wt.% of complex **423** and about 10 wt.% of an optically transparent polymer. For example, poly-2-methyl-5-vinyltetrazole can be used as a matrix (Table 37) <2005MI21>. It is timely to indicate that poly-2-methyl-5-vinyltetrazole is of interest as a binder for rocket propellants <1999THS(3)467, 2003RCR143>.

Table 37 Physical and chemical characteristics of poly-2-methyl-5-vinyltetrazole <2005MI21>

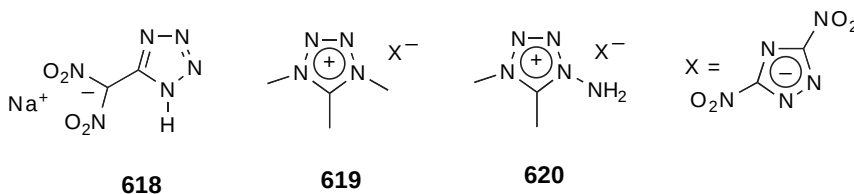
Entry	Property	Value
1	Intrinsic viscosity in DMF, 10 ⁻³ m ³ kg ⁻¹	0.64
2	Weight fraction of the residual monomer, %	0.09
3	Weight fraction of ashes, %	0.16
4	Weight fraction of moisture, %	1.9
5	Weight-average molecular weight (Da)	68400
6	Number-average molecular weight (Da)	27700
7	Polydispersity coefficient	2.5
8	Enthalpy of formation, kcal kg ⁻¹	442

Properties of Ag-salts of 1-(*N*-nitramino)-, 2-(*N*-nitramino)-, 5-(*N*-nitramino)tetrazole, and 1-methyl-5-(*N*-nitramino)-tetrazole have been examined. The initiation power of these salts was estimated from minimal blasting charge in RDX. Silver salts of 1-(*N*-nitramino)- and 2-(*N*-nitramino)tetrazole have a DDT (deflagration-to-detonation transition) period shorter than the salts of 5-(*N*-nitramino)tetrazole and 1-methyl-5-(*N*-nitramino)tetrazole. The salt of 2-(*N*-nitramino)tetrazole is a more powerful initiative explosive than lead azide <2006MI39>.

Interest in fused energetic tetrazoles has increased. Huynh *et al.* reported on the synthesis and explosive characteristics of 7-nitrotetrazolo[1,5-*f*]furazano[4,5-*b*]pyridine-1-oxide (NFP) **616**, which displays a relatively fast burn rate and is insensitive to initiation by electrostatic discharge. Also, it displays moderate sensitivity to initiation by friction and is slightly more sensitive to impact than HMX. DSC was performed to determine the thermal stability, and it was found to decompose at 160 °C <2005MI99>. Recently, the synthesis of highly energetic ionic liquid 1-ethyl-4,5-dimethyltetrazolium tetranitratoaluminate **617**, which has a good oxygen balance, was reported <2006AGE3584, 2006AGE4981>.



Katritzky *et al.* have described synthetic routes toward 1*H*-tetrazole-5-dinitromethylide sodium salt **618** <2005CHE111>. Energetic salts comprised of substituted tetrazolium cations and the 3,5-dinitro-1,2,4-triazolate anion, viz. 1,4,5-trimethyltetrazolium 3,5-dinitro-1,2,4-triazolate **619** and 4,5-dimethyl-1-aminotetrazolium 3,5-dinitro-1,2,4-triazolate **620**, were obtained and characterized by Shreeve and co-workers <2005JMC3459>.



Based on recent publications <2006AGE3584, 2006AGE4981, 2005JMC3459> and the study of 5-aminotetrazolium picrate <2005EJI3760>, we can state with confidence that a new field of knowledge has appeared: tetrazolium salts as energetic ionic liquids.

6.07.12.3 Tetrazoles in Supramolecular Chemistry and Nanotechnology

Lehn formulated the concept of 'supramolecular chemistry' as a science dealing with complex molecules capable of self-organization. Classic examples of such molecules are DNA, RNA, and also enzymes and some peptidomimetics. Nanotechnology imposes special requirements upon the molecules capable of self-organization. To solve nanotechnology problems, in particular, to design new-generation materials for medicine, dendrimer molecules containing fragments of tetrazole podands and highly efficient polydentate ligands of other types are needed. In this respect, branched polynuclear compounds (podands) with terminal tetrazole rings, and also analogs of crown ethers containing one or several tetrazole rings in the macrocyclic structure, may be of interest. Molloy and co-workers synthesized and examined the structure of organotin derivatives of polyfunctional tetrazoles. These compounds form complex supramolecular crystal structures built of hexa- and pentameric macrocyclic fragments <1996JCD835, 1996JCD847, 1996JCD1857, 1999JCD1951, 2000JCD1663, 2005T7002>. The same research team reported on the synthesis and supramolecular structures of thallium(I)- and organothallium(III)-substituted mono-, bis-, and tris-tetrazoles <2000JCD1053>. Spychala published data on the synthesis of 2-dimethylamino-4,6-bis[(5-tetrazolyl)phenyl]-1,3,5-triazines <1997SC127>. Dave *et al.* studied some tris-tetrazoles <2004TL2159>. In a series of studies by Zubarev *et al.* <1997CHE1292, 2000CHE759, 2003CHE1317, 2006CHE469, 2007CHE320>, the preparation methods, structures, and NH-acidity (for NH-unsubstituted rings) of tetrazole podands containing two, three, and four terminal tetrazole rings were investigated (cf. Sections 6.07.3.1 and 6.07.9.4.1). Vereshchagin and co-workers described the synthesis of compounds containing in the molecule several tetrazole rings combined with 1,2,3-triazole fragment <2003RJO1792, 2004RJO1203>. Finally Koldobskii and co-workers developed tetrakis(1-phenyltetrazol-5-yloxymethyl)methane and suggested its application as an intermediate for preparation of tetrazole-containing dendrimers <2002RJO1356, 2004RJO1318>. Thus, all the above-mentioned podand-like compounds should be regarded as promising units for dendrimer synthesis. Some compounds similar to the above-mentioned ones are used to fabricate modern materials, for instance, composite 'melt-blown' materials for medical applications <2005MI605>, and also new nanoporous supramolecular architectures based on tetrazolate ligands <2005IC4130>. Tetrazole-containing macrocyclic compounds are known to a lesser extent than the tetrazole podands, apparently because of unavailability of the former. Zubarev *et al.* reported on the synthesis, X-ray, and conformational studies of tetrazole-containing macrocycles 4,13-dioxo-1,7,8,9,17,18,19,20-octaazatricyclo[14.2.1.1^{7,10}]jicosa-8,10(20),-16(19),17-tetraene **59** and 4,14-dioxo-1,7,8,9,10,18,19,20-octaazatricyclo[15.2.1.1^{7,10}]jicosa-8,10,17(20),18-tetraene **60**

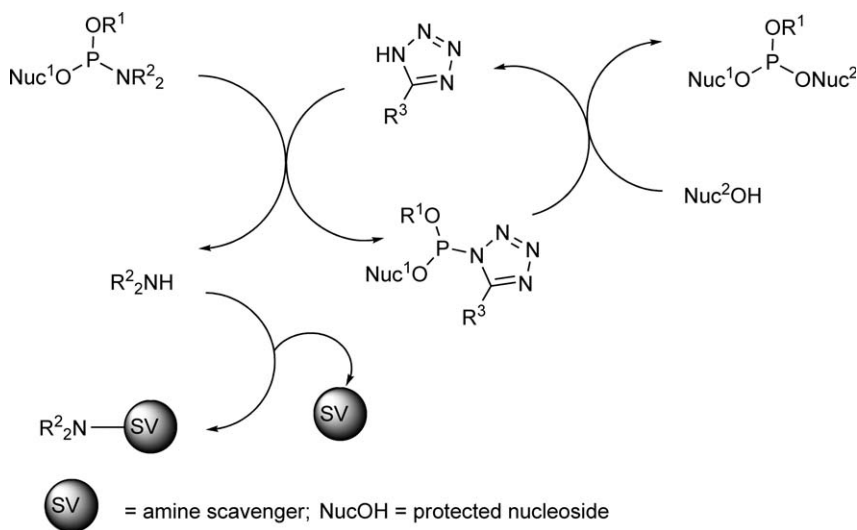
(cf. Section 6.07.5.3.2) <2001J(P2)417>. Synthesis and properties of *N,N'*-bis(5-phenyltetrazol-2-ylacetyl)-1,4,10,13-tetraoxa-7,16-diazaeyclooctadecane **465** were described by Ostrovskii and co-workers <2004CHE854>. We suggest in conclusion that the tetrazole-containing polymers (cf. Sections 6.07.7.2.7 and 6.07.12.2) and materials based thereon <2003RCR143> can find application as components of ultradisperse membranes and reagents of nanotechnological processes for preparation of sensors and molecular switches.

6.07.12.4 Tetrazoles as Activators of Chemical and Biochemical Reactions

Tetrazoles exhibit qualities of acids, bases, acceptors of hydrogen bonds (cf. Section 6.07.4.5), and polydentate ligands (cf. Section 6.07.5.3.4). NH-Unsubstituted tetrazoles behave both as substrates and intermediates in transacylation processes (cf. Section 6.07.5.4), etc. Tetrazolate anions (tetrazolides) possess high aromaticity and reactivity toward electrophilic reagents (cf. Sections 6.07.4.1 and 6.07.5.3.2). The thermal and photochemical decomposition of tetrazoles involves formation of nitrenes and other intermediates of high reactivity (cf. Sections 6.07.5.2 and 6.07.5.7). These properties provide a possibility of use tetrazoles as catalysts in chemical and biochemical reactions.

6.07.12.4.1 Oligonucleotide synthesis and related processes

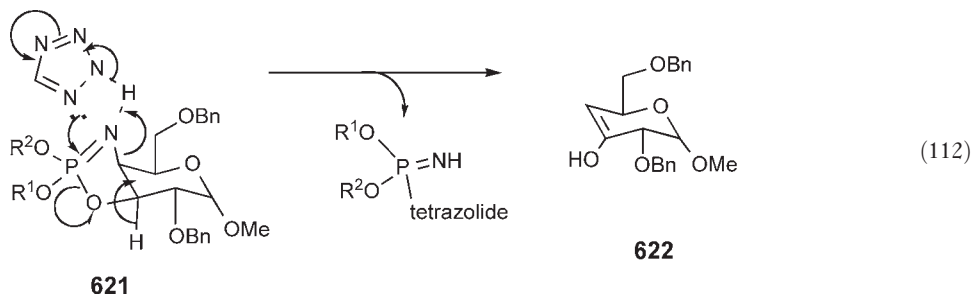
It is well known that 1*H*-tetrazole **2** is a valuable mediator in phosphitylation chemistry, especially in the preparation of oligonucleotides. 5-Ethylthio-1*H*-tetrazole was shown to be comparable with 1*H*-tetrazole **2** for the diastereoselective synthesis of phosphate triesters <1996TL969> and the activation of nucleoside phosphoramodates in oligonucleotide syntheses <2002OPD798, 2003NN1415, 2003NN1639>. 5-Ethylthio-1*H*-tetrazole was examined also as alternative to 1*H*-tetrazole **2** in mediating the synthesis of phosphonate diesters and phosphoramidates from phosphonyl dichlorides through a two-step one-pot reaction <2004TL6497>. 5-(Methylthio)-1*H*-tetrazole and 5-(4-nitrophenyl)-1*H*-tetrazole as activators in phosphoramidite alcoholysis have been studied compared to 1*H*-tetrazole **2**. Reactions of these tetrazoles with diisopropyl (diisopropylamido)phosphite were investigated in THF, and the rates were found to increase with increasing acidity of the tetrazoles <1999J(P2)2551, 2003HCA2005>. A facile phosphoramidation method using a tetrazole promoter in a catalytic manner has been developed by Hayakawa and Kataoka for the condensation of a nucleoside 3'-phosphoramidite and a nucleoside (Scheme 84). This method is particularly useful for a large-scale synthesis of short oligonucleotides <1997JA11758>.



Scheme 84

Welz *et al.* developed a procedure for synthesis of oligoribonucleotides based on application of tetrazole for activation of RNA phosphoramidites in automated solid-phase synthesis <2000MB934>. *N*-Benzoyltetrazole has been developed as a mild and selective reagent for monobenzoylation of the exocyclic amino group in nucleic acid bases <1997TL8811>. An improved procedure is described for the efficient and high yield (76–91%) synthesis of

nucleoside diphosphate sugars from the readily available nucleoside 5'-monophosphomorpholidate and sugar 1-phosphate in the presence of 1*H*-tetrazole **2** <1997JOC2144>. A new one-step reaction has been developed for converting 4-azido-4-deoxy-D-galactoside into 4-deoxy-D-*erythro*-hexos-3-ulose. It is suggested that the new reaction proceeds via an intramolecular Staudinger reaction of the phosphate intermediate and a tetrazole-catalyzed elimination reaction of the resultant phosphorimidate. Tetrazole appears to be playing a unique role by acting as a bifunctional catalyst; a concerted elimination reaction occurs through intermediate **621** to give enol **622** (Equation 112) <2004OL1365>.



In conclusion, it is appropriate to mention the example of an unusual tetrazole transacylation by tetrazolyacetic acid chlorides (cf. Section 6.07.5.3) <1996MC24>.

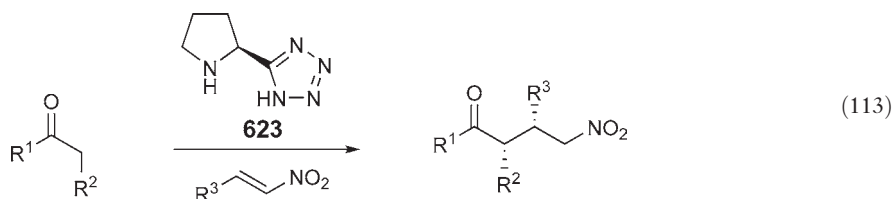
6.07.12.4.2 Julia–Kocienski olefination

We described in Section 6.07.7.5 investigations on methylenation of aldehydes and ketones under Julia–Kocienski conditions extended by using 1-substituted-5-alkylsulfonyltetrazoles <1998SL26, 2000SL365, 2002J(P1)2563, 2006JOC360>.

The Julia–Kocienski protocol proved to be efficient as a key instrument for the total synthesis of naturally occurring compounds, viz. L-mycarose and L-kedarsamine <1999TL4897>, and also (+)-triazinotrienomycin E <1999OL1491>. Wicha and co-workers demonstrated that vinylsilanes are formed in high yields in the reaction of representative acyl(trimethyl)silanes with anions generated from Kocienski's sulfones <2003OL2789>.

6.07.12.4.3 Catalytic asymmetric synthesis

5-[(2*S*)-Pyrrolidine-2-yl]-1*H*-tetrazole **623**, that is, the tetrazolic acid analog of proline, has been found to be significantly more reactive than L-proline in various organocatalyzed reactions <2005EJO4287, 2006SL889>. After the initial discovery by Ley and co-workers <2004SL558>, Yamamoto and co-workers <2004AGE1983> and Hartikka and Arvidsson <2004TA1831> expanded the use of the catalysts **623** in organocatalyzed version of enantioselective aldol condensations <2005OBC84>, asymmetric Mannich reactions <2006OL2839>, *O*-nitroso aldol/Michael reactions <2004JA5962>, Michael addition of carbonyl compounds to nitroalkenes (Equation 113) <2004CC1808, 2005OL3897, 2005SL611, 2006OBC2039>, conjugate addition of malonates to enones <2006CC66>, and in a total synthesis of LFA-1 antagonist BIRT <2005OL867>.



6.07.12.4.4 Other examples of catalytic activity

The peroxidase-catalyzed oxidation of 2,2'-azino-bis(3-ethylbenzthiazoline-6-sulfonic acid) (ABTS), *o*-phenylenediamine (PDA), and 3,3',5,5'-tetramethylbenzidine (TMB) was found to be activated by tetrazole **2** and 5-aminotetrazole and weakly inhibited by 1,5-diaminotetrazole **33** <2004MI283>. Bhattacharya and Vemula studied the effect of heteroatom insertion in the side chain of 5-alkyl-1*H*-tetrazoles on their properties as catalysts for ester hydrolysis at neutral pH <2005JOC9677>. 1-(2-Iodophenyl)-1*H*-tetrazole was successfully used in Heck reactions to give the cross-coupled products in excellent yield <2004TL4113>.

6.07.12.5 Corrosion Inhibitors

Copper corrosion and its inhibitors is a widely studied field owing to its great importance in technological processes. 5-Mercapto-1-phenyltetrazole **430** was tested as a copper corrosion inhibitor in neutral chloride and acidic sulfate solutions and showed excellent inhibition efficiency <1996MI2029, 1998MI311, 1999MI1339, 2000BEC205, 2004MI1371>. The inhibition effect of some tetrazole compounds toward the corrosion of brass in nitric acid solution has been examined. The effect of 5-mercapto-1-phenyltetrazole **430**, 1,2,3,4-tetrazole **2**, 5-aminotetrazole **135**, and 1-phenyltetrazole **31** (R=Ph) on the corrosion of brass in nitric acid was studied by weight loss, polarization, and electrochemical impedance spectroscopy (EIS) measurements. Results obtained reveal that compound **430** is the best inhibitor and the inhibition efficiency (E%) follows the sequence: **430** > **31** > **135** > **2** <2006MI2389>. 5-Mercapto-1-phenyltetrazole **430** was tested as an inhibitor of steel corrosion in 0.5 M H₂SO₄ and 1/3 M H₃PO₄ by weight loss and electrochemical methods. Results obtained showed that the inhibition efficiency of tetrazole **430** increased with the increase of inhibitor concentration and reached an optimum value (98%) at 10⁻³ M in H₂SO₄ and H₃PO₄ solutions <2003MI402>.

6.07.12.6 Analytical Uses

Tetrazolium salts are used in analytical chemistry as reagents for qualitative and quantitative determination of various compounds. These salts are also used in chemical kits for diagnostics of various diseases. The number of publications on analytical uses of tetrazolium salts is too large to be discussed in this chapter. Therefore, we direct the reader to surveys on preparative methods and properties of tetrazolium salts, where the use of these compounds in chemical analysis is also discussed <1990KGS1587, 1998RCR671, 2002RCR721>.

6.07.13 Further Developments

A brief summary of new material on tetrazole chemistry published in 2007 is given below.

The density functional theory approach is widely used in the study of properties and reactivity of tetrazoles (addition to Section 6.07.2). Thus a study of the asymmetric Michael addition of carbonyl compounds to nitroalkenes catalyzed by (*S*)-5-(pyrrolidin-2-yl)-1*H*-tetrazole has been studied at the B3LYP/6-31G** computational level <2007TA157>. Different quantitative criteria of aromaticity for unsubstituted tetrazole and its unconjugated derivatives have been calculated using this method at the 6-311+G** basis set <2007MI25>. A combined matrix isolation FT-IR and theoretical DFT(B3LYP)/6-311++G(d,p) study of the molecular structure and photochemistry of 5-ethoxy-1-phenyl-1*H*-tetrazole was performed <2007PCA2879>. The enthalpies of formation of substituted tetrazole molecules and ions containing amino, azido, and nitro substituents have been calculated using isodesmic approach at the MP2/complete basis set-level <2007PCB4788>.

New X-ray crystallography data for some tetrazoles became available (addition to Section 6.07.3.1). In the case of 2-(1*H*-tetrazol-1-yl)ethanol intermolecular hydrogen bonds are responsible for the formation of a three-dimensional network <2007AXE01573>. Also the structural characterization of the following compounds has been published: 2-(1*H*-tetrazol-5-yl)pyrazine <2007JST(828)142>, 1,5-diamino-4-methyltetrazolium based salts <2007IC932>, energetic salts of 5-nitroimine-tetrazolate <2007CM1731>, tetrazolo[1,5-*a*]- α -cycloalkanones <2007TL555>, and mesomeric betaine 6,7-dimethyl-2*H*-pyrazolo[4,3-*e*]tetrazolo[4,5-*b*][1,2,4]triazine <2007JST(829)22>.

In addition to Section 6.07.4.2 it should be noted that the chromatographic determination of irbesartan **83** in biological liquids has been developed <2007JC(B)245>. A selective thin layer chromatographic method implies a complexation of 1*H*-tetrazole and 1-methyltetrazole to Co(II) ions on a TLC plate followed by a subsequent oxidation of Co(II) by permanganate has been presented <2007JC(A)145>.

A mild procedure was developed for polysubstituted pyrazolines synthesis from 2,5-diaryltetrazoles (addition to Section 6.07.5.2.2) <2007OL4155>. This procedure involved the *in situ* photoactivated generation of the reactive nitrile imine dipoles, followed by spontaneous cycloaddition with 1,3-dipolarophiles.

Various coordination compounds incorporating the tetrazole ligand were obtained (addition to Section 6.07.5.3.4). Thus some complexes of platinum(II) and palladium(II) with terpyridine and 1-methyltetrazolate, obtained from 1-methyltetrazole by C–H deprotonation, were characterized using NMR, X-ray and theoretical calculation <2007ICA(360)255>. Coordinated compounds of Co(III) ion of cobalamin (vitamin B₁₂) with tetrazole ligands have been described <2007JOM(692)1234>. Hydrothermal treatment of CuCl₂, NaN₃, and acetonitrile resulted in double

salt of copper(I) chloride incorporated tetrazole <2007ICA(360)14>. Blue phosphorescent iridium(III) complexes based on the difluorophenyl-4-methoxypyridine and 5-(2-pyridyl)tetrazole ligands were synthesized <2007OM2017>. Also a series of iron(II) complexes of 2-(2-alkyl-2H-tetrazol-5-yl)-1,10-phenanthroline and its alkyl-substituted derivatives were characterized <2007IC2541>.

Some new methods of the tetrazole ring formation from acyclic compounds should be mentioned here (addition to Section 6.07.9). An interaction of amines with sodium azide using a room-temperature ionic liquid leads directly to 1-substituted-1H-tetrazoles in excellent yields <2007TL1721>. The inherent Bronsted acidity and high polarity of the ionic liquids result in a significant enhancement in the reaction rate. Efficient protocol for synthesis of 1,5-disubstituted tetrazoles has been developed by metal triflate catalyzed one pot reaction of alkenes, *N*-bromosuccinimide, nitriles, and TMSN₃ <2007JOC1852>. Reaction of nitriles with sodium azide in the presence of ZnCl₂ under microwave assistance leads to the formation of 5H-tetrazoles in high yields; therewith the process is 2–3 times shorter than inactivated reaction <2007RJO765>. Microwave irradiation was also used in a reaction of nitriles generated *in situ* from primary alcohols or aldehydes and iodine in ammonia water with sodium azide to afford high yield of the corresponding tetrazoles, including the α -amino- and dipeptidyl tetrazoles in high optical purity <2007JOC3141>.

The use of tetrazoles as isosteric substituents of various functional groups was examined and reviewed (addition to Section 6.07.12.1) <2007RJO1>. The antimycobacterial activity of three different series of tetrazole derivatives (i.e., the hydride molecules with estrone, tetrazole-5-thioles, and 5-benzylsulfanyl-1-phenyltetrazoles) with the same substituents on phenyl ring were compared <2007BMC2898>. Among them, the benzylsulfanyl-1-phenyltetrazoles were the most potent.

A possibility for using the tetrazole moieties as activators of chemical reactions or as intermediates was further developed (addition to Section 6.07.12.4). Thus 5-[(2*S*)-pyrrolidine-2-yl]-1H-tetrazole **623** was used as a catalyst for diastereo- and enantioselective synthesis <2007JA1190, 2007OL1343>. A stereoselective synthesis of different (*E*)-alkenes, including natural-like compounds, through Kociensky-Julia olefination using of 1-phenyl-1H-tetrazol-5-ylsulfonyl moiety have been carried out <2007SL99, 2007AG(E)545>.

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6.08

Oxatriazoles

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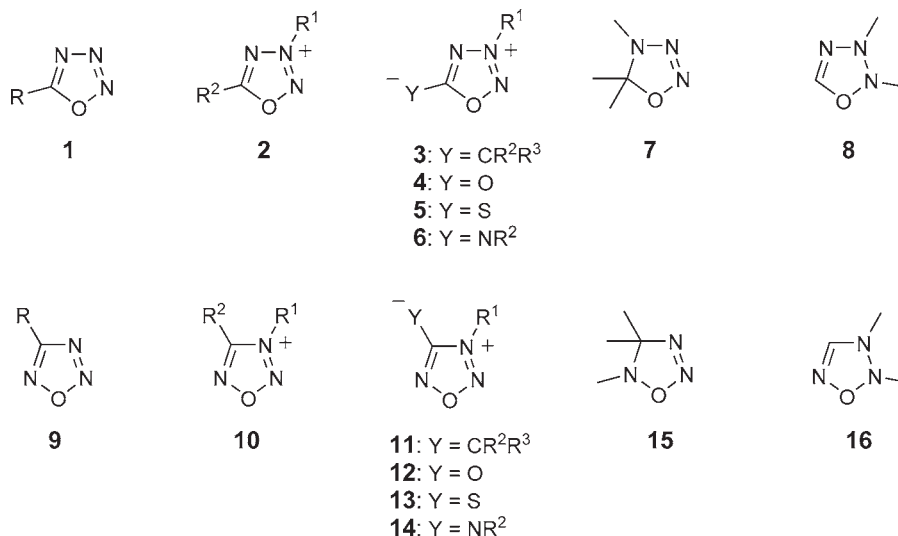
6.08.1	Introduction	425
6.08.2	Theoretical Methods	426
6.08.3	Experimental Structural Methods	427
6.08.3.1	NMR Spectroscopy	427
6.08.3.2	Mass Spectrometry	428
6.08.3.3	IR Spectroscopy	428
6.08.3.4	UV Spectroscopy	428
6.08.3.5	Dipole Moment	428
6.08.3.6	X-Ray Crystallography	428
6.08.4	Thermodynamic Aspects	429
6.08.5	Reactivity of Fully Conjugated Rings	429
6.08.5.1	Thermal Reactions and 1,3-Dipolar Cycloadditions	429
6.08.5.2	Rearrangements	429
6.08.5.3	Hydrolysis	429
6.08.5.4	Photolysis	430
6.08.5.5	Oxidation and Reduction	430
6.08.6	Reactivity of Nonconjugated Rings	430
6.08.7	Reactivity of Substituents Attached to Ring Carbon Atoms	431
6.08.8	Reactivity of Substituents Attached to Ring Heteroatoms	431
6.08.9	Ring Synthesis from Acyclic Compounds Classified by Number of Ring Atoms Contributed by Each Component	431
6.08.10	Ring Syntheses by Transformation of Another Ring	435
6.08.11	Synthesis of Particular Classes of Compounds and Critical Comparison of the Various Routes Available	435
6.08.12	Important Compounds and Applications	436
6.08.13	Further Developments	437
	References	437

6.08.1 Introduction

Although the synthesis of mesoionic <B-1997MI1, B-2000MI1, 1976AHC1, 1995PAC1307, 2002ARK224, 2002MOL791> oxatriazoles was described as early as 1896, 1,2,3,4-oxatriazole **1** and 1,2,3,5-oxatriazole **9** ring systems are not known <2000AHC157>. Various substituted derivatives and mesoionic analogues, however, are readily accessible. The purpose of this chapter is to bring the previous coverage of the subject in CHEC(1984) (<1984CHEC(4)579>, Chapter 4.28) and CHEC-II(1996) (<1996CHEC-II(4)679>, Chapter 4.18) up to date.

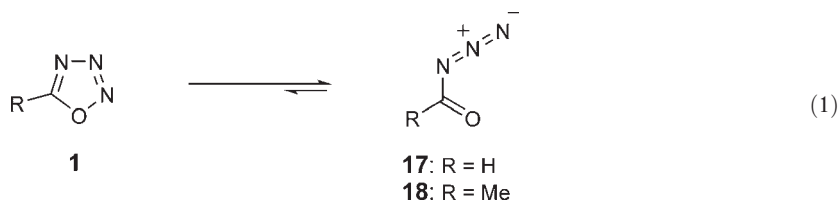
This chapter covers the literature from mid-1995 to mid-2007. Recent advances include the preparation of the first Δ^2 -1,2,3,4-oxatriazolines **7** by intramolecular [3+2] cycloaddition (Section 6.08.9), synthesis of mesoionic derivatives **4** using bromonitroformaldehyde *N*-arylhydrazones as the starting materials (Section 6.08.9), and detailed studies of the biologically active mesoionic oxatriazoles in the context of their nitric oxide donating capabilities (Section

6.08.12). Of the possible structures 1–16 shown, the known structures are represented by 1,2,3,4-oxatriazolium salts 2, mesoionic derivatives 3–6, and 1,2,3,5-oxatriazolidines 15 and 16. Derivatives of Δ^2 -1,2,3,4-oxadiazoline 7 have now been synthesized and are the first representatives of this particular ring system.



6.08.2 Theoretical Methods

Although 1,2,3,4-oxatriazole and its 5-methyl-substituted derivative are unknown compounds, the equilibrium between ring-closed 1 ($R=H$ or Me) and ring-open forms 17 and 18 has been examined theoretically (Equation 1) <2000CPL276, 2005CRV3561>.



Like the cyclic forms 1 ($R=H$ or Me), the ring-open isomers 17 and 18 also remain unknown. The calculated charge distributions of the ring-open and ring-closed isomers are compared in Figure 1. Molecular orbital calculations predict ΔE values of 20.48 (TZ**), ~ 30 (MP2), and 27 kcal mol $^{-1}$ (MP4-SDQ) for theoretical cyclization of formyl azide 17 ($R=H$) to 1,2,3,4-oxatriazole 1 ($R=H$). Similarly, the calculated ΔE values for conversion of acetyl azide 18 ($R=Me$) to 5-methyl-1,2,3,4-oxatriazole 1 ($R=Me$) are 19.08 (HF/6-31G) and 20.08 kcal mol $^{-1}$ (MP4-SDQ). With the theoretical cyclization of molecules 17 and 18 so highly endothermic, formation of isomer 1 ($R=H$ or Me) is strongly disfavored.

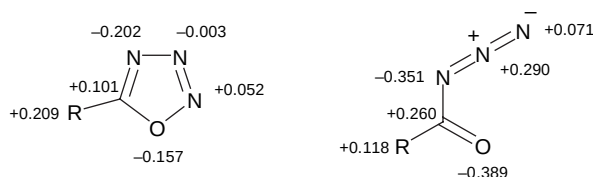


Figure 1 Charge distributions in ring-closed and ring-open isomers of 1 ($R=H$).

Averaged aromaticity indexes (AIs) for a series of oxazoles including 1,2,3,4-oxatriazole **1** ($R = H$) and 1,2,3,5-oxatriazole **9** ($R = H$) have been derived from calculated molecular geometries optimized at the self-consistent field (SCF)/6-31G* level <1998JOC2497>. The averaged AI values are: furan 27.4, isoxazole 32.8, 1,2,3-oxadiazole 25.6, 1,2,4-oxadiazole 25.9, 1,2,5-oxadiazole 35.0, 1,3,4-oxadiazole 10.4, 1,2,3,4-oxatriazole 16.9, 1,2,3,5-oxatriazole 29.7, and oxatetrazole 17.5 <2001T5715>. The results are consistent with other quantitative measures of aromaticity <2001CRV1421> and indicate that the oxazole family is, in general, more localized and exhibits less aromaticity compared with most other members of the azole series <1998JOC2497>.

6.08.3 Experimental Structural Methods

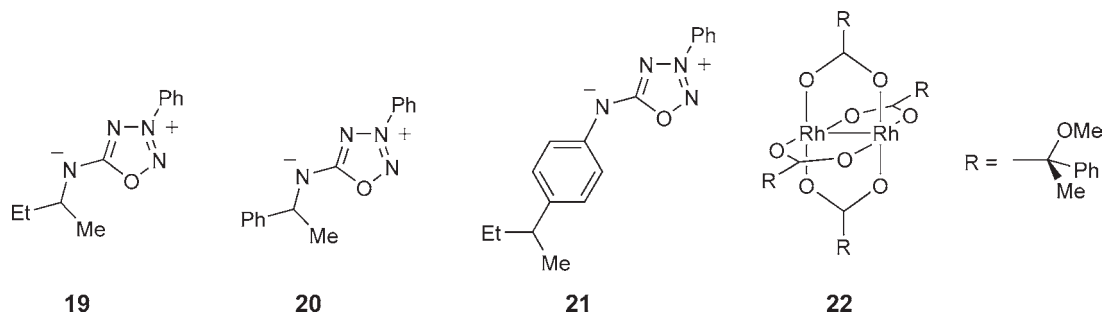
6.08.3.1 NMR Spectroscopy

Various mesoionic 1,2,3,4-oxatriazoles have been studied by multinuclear nuclear magnetic resonance (NMR). ^{14}N NMR spectra give information about the charge distribution where positively charged nitrogen atoms give rise to comparatively narrow line widths <1995CHE1027, 1998MI79, 1999AHC295>.

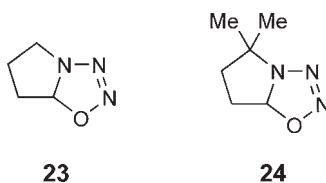
3-Substituted anhydro-5-hydroxy-1,2,3,4-oxatriazolium hydroxides **4** ($R^1 = \text{Ar}$) have been prepared and studied by ^1H , ^{13}C , ^{14}N , and ^{17}O NMR. The chemical shifts for the exocyclic oxygen attached to C-5 lie in the range -215 to -220 ppm, whereas the ring oxygen shows broader signals within the region -360 to -370 ppm <1997CHE880, 1999CHE363>. In the ^{14}N spectra, the positively charged N-3 group appears as a sharp line near -80 ppm. The chemical shifts for the C-5 signals are listed in Table 1 (Section 6.08.9). The ^{15}N – ^{15}N coupling constants in the ^{15}N labeled compound **4** ($R^1 = \text{Ph}$) have been measured: $^1J_{\text{N}(2)\text{--N}(3)} = 15.5$ and $^1J_{\text{N}(3)\text{--N}(4)} = 17.0$ Hz. These values compare well with those of nitrogen–nitrogen double bonds inferring some degree of positive charge delocalization within the ring <1996JST167>.

^{14}N , ^{15}N , and ^{17}O NMR studies of mesoionic 3-phenyl-anhydro-5-amino-1,2,3,4-oxatriazolium hydroxides **6** confirm that they exist in cyclic, mesoionic form and that protonation occurs at the exocyclic nitrogen atom <1995CHE1103, 2004JST23>. The free bases exist in solution as (*E*)- or (*Z*)-configured rotamers at the C–Y bond that depend on temperature and the nature and size of R^2 . Proton NMR spectra show one set of signals at 318 K and broad signals at 303 K. Pairs of signals are observed at 252 K corresponding to (*E*)- and (*Z*)-rotamers in near-equal proportions <2004JST23>. Slight shifts between the proton and carbon signals from ^1H and ^{13}C NMR analysis were observed for the free bases compared with their salts. The largest shift was observed for the C-5 atom in each case. The chemical shifts and line widths of the ring atoms and the nitrogen attached to C-5 in the free bases and their salts have been tabulated <2004JST23>. *Ab initio* calculations predict an energy difference of less than 1 kcal mol^{-1} between the (*E*)- and (*Z*)-isomers of compound **6** ($R^1 = H$, $R^2 = H$) <1997MI71>.

When mixed with equimolar amounts of the dirhodium complex **22**, the enantiomers of mesoionic 1,2,3,4-oxatriazoles **19–21** can be differentiated by proton NMR <2003MRC315>. The negatively charged exocyclic nitrogen atom provides the binding site to the rhodium complex <2003MRC921>.

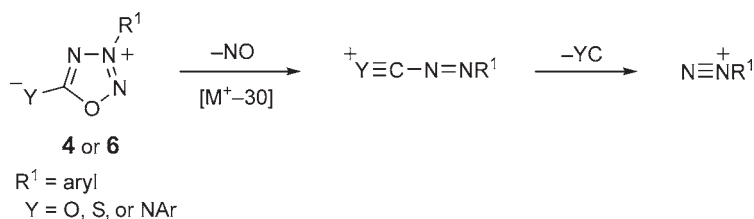


From ^{13}C NMR analysis, the chemical shift of the carbon at the respective ring junctions in Δ^2 -1,2,3,4-oxatriazolines **23** (100.4 ppm) and **24** (105.4 ppm) <2002HAC307> are considerably further upfield compared with the C-5 atoms in the mesoionic analogues **2** ($R^1 = \text{Ph}$, $R^2 = \text{OEt}$; 188.7 ppm), **4** ($R^1 = \text{Ph}$; 166.2 ppm), or **5** ($R^1 = \text{Ph}$; 193.4 ppm) <1996CHEC-II(4)679>.



6.08.3.2 Mass Spectrometry

No molecular ions appear in the electron ionization (EI) spectra of mesoionic 1,2,3,4-oxatriazoles **4** and **6** or their derivatives. Instead, $[M^+ - 30]$ peaks are observed due to loss of nitric oxide [<1979J\(P1\)747, 1999CHE363>](#). The typical fragmentation pathway for such compounds and their analogues is summarized in [Scheme 1](#) [<1984CHEC\(4\)579, 1996CHEC-II\(4\)679>](#). In their fast atom bombardment (FAB) spectra, intact molecular ion peaks are observed for the Δ^2 -1,2,3,4-oxatriazolines **23** 114 $[M+H]$ and **24** 142 $[M+H]$ [<2002HAC307>](#).



Scheme 1

6.08.3.3 IR Spectroscopy

3-Aryl-anhydro-5-hydroxy-1,2,3,4-oxatriazolium hydroxides **4** (R¹ = aryl) show one, sometimes two strong infrared (IR) absorption bands in the region 1770–1820 cm⁻¹ due to the exocyclic C=O group. Values for a series of such analogues are listed in [Table 1](#) (Section 6.08.9) [<1997CHE880, 1999CHE363>](#). Electron-withdrawing groups attached to the N-3 phenyl substituent shift the C=O absorption to a higher wave number whereas electron-releasing groups cause shifts to a shorter wave number.

6.08.3.4 UV Spectroscopy

3-Substituted anhydro-5-hydroxy-1,2,3,4-oxatriazolium hydroxides **4** (R¹ = phenyl) are colorless. The absorption wavelength in the ultraviolet (UV) is usually influenced by the substituents in the phenyl group. Values for a series of analogues are listed in [Table 1](#) (Section 6.08.9) [<1997CHE880, 1999CHE363>](#). 3-Substituted anhydro-5-thio-1,2,3,4-oxatriazolium hydroxides **5** are typically yellow [<1984CHEC\(4\)579, 1996CHEC-II\(4\)679>](#). 3-Substituted anhydro-5-amino-1,2,3,4-oxatriazolium hydroxides **6** are yellow or deep red, whereas their salts are mostly colorless [<2004JST23>](#).

6.08.3.5 Dipole Moment

Dipole moments for 1,2,3,4-oxatriazole **1** (R = H; 3.250 D) and 5-methyl-1,2,3,4-oxatriazole **1** (R = Me; 4.096 D) were estimated using molecular orbital calculations (TZ**) [<2000CPL276>](#). The calculated dipole moment for compound **6** (R¹ = H, R² = H; 5.33 D) agreed well with the observed value 5.42 D [<1997MI71>](#). Quadrupole moments, octopole moments, and polarizability of 1,2,3,4-oxatriazole **1** (R = H) have been determined by *ab initio* methods and simple models [<1996JPC8752, 1999PCA10009>](#).

6.08.3.6 X-Ray Crystallography

No further crystal structures have been reported since the structures of 3-phenyl-anhydro-5-hydroxy-1,2,3,4-oxatriazolium hydroxide **4** (R¹ = Ph) and 3-phenyl-anhydro-5-phenylamino-1,2,3,4-oxatriazolium hydroxide **6** (R¹ = Ph,

$R^2 = \text{Ph}$) were presented in the previous surveys <1984CHEC(4)579, 1996CHEC-II(4)679>. However, X-ray crystal structures of closely related 3- and 5-substituted-5-anhydro-1,2,3,4-thiazolium thiolates have been reported <1999JST181> (see Chapter 6.09).

6.08.4 Thermodynamic Aspects

Mesoionic 1,2,3,4-oxatriazoles are crystalline, polar compounds with melting points in the range 100–150 °C <1996CHEC-II(4)679>. 3-Aryl-anhydro-5-amino-1,2,3,4-oxatriazolium hydroxides **6** ($R^2 = \text{Ar}$) are comparatively stable. When alkyl groups (CH_2R) replace the aryl substituent R^2 , such derivatives decompose within 24 h at room temperature but may be stored for much longer at dry ice temperature <2004JST23>. The new oxatriazoline compounds **23** and **24** (Sections 6.08.3.1 and 6.08.9) are isolated as colorless oils <2002HAC307>.

From a multinuclear NMR study of mesoionic 1,2,3,4-oxatriazole **6** ($R^1 = \text{Ph}$, $R^2 = \text{Me}$), the barrier to (*E*)- and (*Z*)-interconversion around the C(5)–Y bond was estimated to be $\Delta G^\ddagger$ 68 kJ mol^{−1} at 298 K. The value is comparable to that measured for dimethylformamide 74 kJ mol^{−1} and simple imines of type $(\text{RX})_2\text{C}=\text{NR}$, where X is oxygen or sulfur <2004JST23>.

The dissociation energy of the C(4)–H bond in unknown 1,2,3,5-oxatriazole **9** ($R = \text{H}$) has been calculated using various methods: 128.7 (CBS-Q), 128.7 (G3), 125.8 (G3B3), and 121.7 kcal mol^{−1} (B3LYP) <2003JPO883>. The N(3)–C(4)–N(5) dihedral angle (112.1°) was also estimated <2003JPO883>.

6.08.5 Reactivity of Fully Conjugated Rings

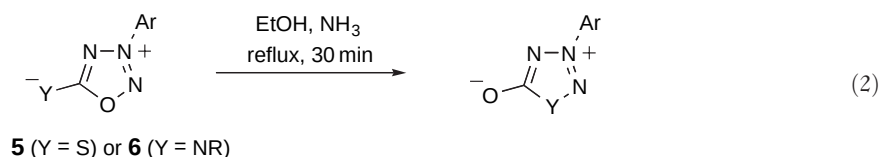
6.08.5.1 Thermal Reactions and 1,3-Dipolar Cycloadditions

3-Substituted anhydro-5-hydroxy-1,2,3,4-oxatriazolium hydroxides **6** are relatively stable under neutral conditions in the absence of salt. The stability depends on the nature of the R^2 substituent attached to the exocyclic nitrogen and decreases from very stable to moderately stable along the series $\text{RSO}_2 > \text{RNHCO} > \text{RCO} > \text{R}$ <2002MI167>.

Unlike the mesoionic 1,2,3-oxadiazoles (see Chapter 5.03), mesoionic 1,2,3,4-oxatriazoles **5** and **6** do not undergo 1,3-dipolar cycloaddition reactions. Azides formed by loss of carbon dioxide from anhydro-5-hydroxy-1,2,3,4-oxatriazolium hydroxides **4**, on prolonged heating with lithium chloride, may be trapped by cycloaddition to an alkyne <1996CHEC-II(4)679>.

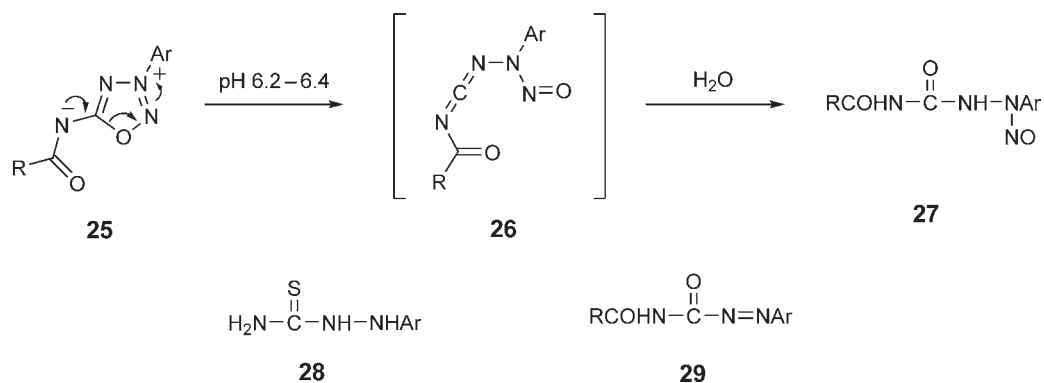
6.08.5.2 Rearrangements

Under basic conditions, mesoionic 1,2,3,4-oxatriazoles **5** and **6** rearrange in alcohol solutions to the respective anhydro-5-hydroxy-thiatriazolium hydroxides and anhydro-5-hydroxy-tetrazolium hydroxides (Equation 2) <1979J(P1)732, 1996CHEC-II(4)679>. That rearrangement of 1,2,3,4-oxatriazole **5** ($\text{Ar} = \text{Ph}$) to 3-phenyl-5-anhydro-1,2,3,4-thiazolium hydroxide can be induced electrochemically, has been reported for the first time (Section 6.08.5.5) <1997MRC124>.



6.08.5.3 Hydrolysis

The various fates met by mesoionic 1,2,3,4-oxatriazoles when subjected to hydrolysis are detailed in the previous surveys <1984CHEC(4)579, 1996CHEC-II(4)679>. The hydrochloride salts of 3-aryl-anhydro-5-amino-1,2,3,4-oxatriazolium hydroxides **25** are known to be stable for several years on storage <2002CRV1091>. In solution, however, ring opening and release of nitric oxide (NO) occurs close to the pK_a values of the salts in the pH range 6.2–6.8. The proposed mechanism of NO release begins as shown in Scheme 2.



Scheme 2

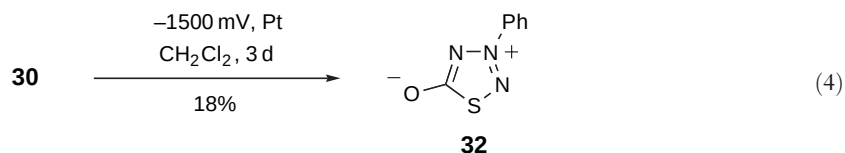
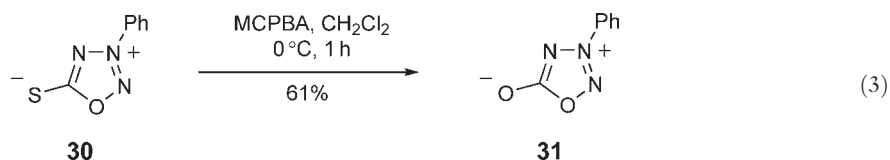
Ring opening produces the intermediate **26** to which water then adds forming the urea **27**. The fate of compound **27** *in vitro* differs from that *in vivo*. The urea **27** loses NO to give the arylthiosemicarbazide **28** *in vitro*, whereas metabolite **29** is the final product of the *in vivo* pathway <2002CRV1091>. The rate of NO release from compounds **25**, *in vitro*, depends strongly on concentration, temperature, pH, and the chemical nature of the R substituent attached to the exocyclic nitrogen <2002MI167>. The presence of thiols may contribute to the increased rate of NO release *in vivo* <1998MI97>.

6.08.5.4 Photolysis

Photolysis of 3-phenyl-anhydro-5-hydroxy-1,2,3,4-oxatriazolium hydroxide **4** ($\text{R}^1 = \text{Ph}$) gives carbon dioxide and phenyl azide. The phenyl group has been shown to migrate from the central to the terminal nitrogen position during the course of the reaction as described in the last two surveys <1984CHEC(4)579, 1996CHEC-II(4)679>. Since then, no further reports on this topic have appeared.

6.08.5.5 Oxidation and Reduction

The synthesis of mesoionic 1,2,3,4-oxatriazole **31** from compound **30** using *m*-chloroperbenzoic acid (MCPBA) has been reported for the first time (Equation 3) <1997MRC124>. Mesoionic 1,2,3,4-oxatriazole **30** is converted electrochemically to isomer **32**, albeit on a small scale and in modest yield (Equation 4) <1997MRC124>.

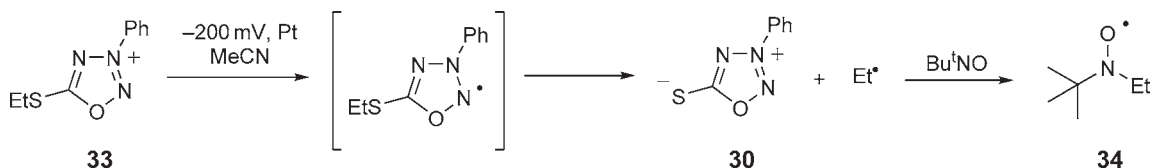


6.08.6 Reactivity of Nonconjugated Rings

New Δ^2 -1,2,3,4-oxatriazolidines **23** and **24** (Sections 6.08.3.1 and 6.08.9) have been isolated as stable materials in the form of oils and characterized by spectroscopic methods. No data on their reactivities have been reported. Δ^4 -1,2,3,5-Oxatriazolines **16** are thermally unstable, more so than their Δ^2 -1,2,3,5-oxatriazoline **15** analogues <1996CHEC-II(4)679>.

6.08.7 Reactivity of Substituents Attached to Ring Carbon Atoms

3-Phenyl-anhydro-5-thio-1,2,3,4-oxatriazolium hydroxide **30** was alkylated using triethyloxonium tetrafluoroborate to give product **33**, whereas analogue **31** failed to react under similar conditions <1997MRC124>. De-ethylation of derivative **33** to form compound **30** has been performed electrochemically (Scheme 3) <1997MRC124>.



Scheme 3

The ethyl radical formed during the dealkylation process was trapped using 2-methyl-2-nitrosopropane to form *tert*-butylethyl nitroxide **34**, where the coupling constants and g -factors of the trapped species measured by electron spin resonance (ESR) analysis matched the literature values for *tert*-butylethyl nitroxide **34** exactly.

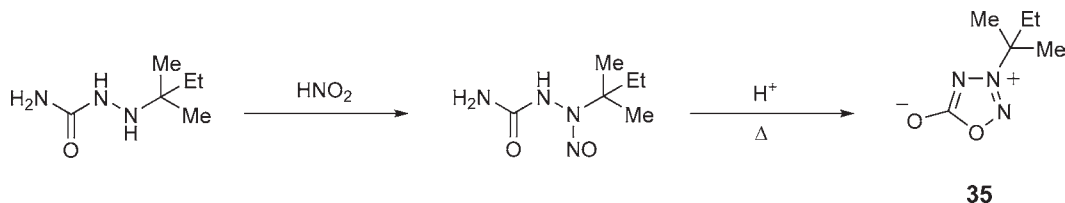
The C–H bond dissociation energy of the methyl group in unknown 4-methyl-1,2,3,5-oxatriazole **9** ($\text{R} = \text{Me}$) was estimated at 95.6 (G3B3) or 90.3 kcal mol^{−1} (B3LYP). The G3B3 method was found to be superior giving the best correlation between calculated values and the experimental ones for known compounds <2005JPO353>. Natural population analysis revealed a charge of 0.076 on the methyl group before homolysis and 0.138 for the CH_2 radical after homolysis together with a spin value of 0.698 <2005JPO353>.

6.08.8 Reactivity of Substituents Attached to Ring Heteroatoms

There are three possible sites, N-2, N-4 or Y, for protonation in mesoionic 1,2,3,4-oxatriazole **4** to **6**. In compound **6**, protonation occurs at the exocyclic nitrogen instead, as evidenced by NMR analysis (Section 6.08.3.1) <2004JST23>. No further reports on the reactivity of substituents attached to ring heteroatoms have appeared since the last survey <1996CHEC-II(4)679>.

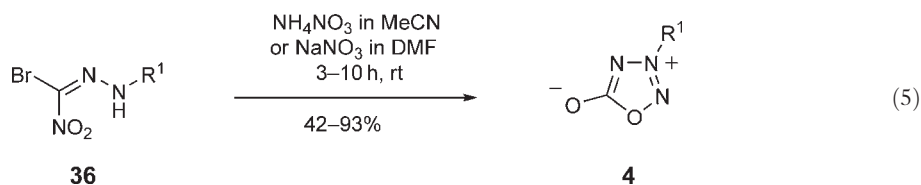
6.08.9 Ring Synthesis from Acyclic Compounds Classified by Number of Ring Atoms Contributed by Each Component

Methods of synthesis of the known 1,2,3,4-oxatriazoles <1979J(P1)732, 1979J(P1)736> and the very rare 1,2,3,5-oxatriazoles have recently been compiled <2003HOU823>. In this section, the examples that have appeared since the last survey of the area <1996CHEC-II(4)679> are presented. 3-Alkyl-anhydro-5-hydroxy-1,2,3,4-oxatriazolium hydroxides such as compound **35** are formed from semicarbazides after nitrosation (Scheme 4) <1999FA316>.



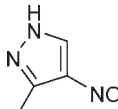
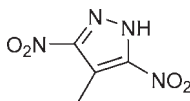
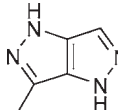
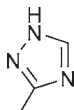
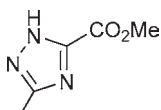
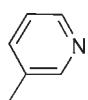
Scheme 4

Similarly, cyclization of bromonitroformaldehyde *N*-hydrazones **36** allows ready access to anhydro-5-hydroxy-1,2,3,4-oxatriazolium hydroxides **4** ($\text{R}^1 = \text{aryl}$ or heteraryl). For the first time, analogues with heterocyclic substituents attached at N-3 have been prepared by this method (Equation 5) <1997CHE880, 1999CHE363>.

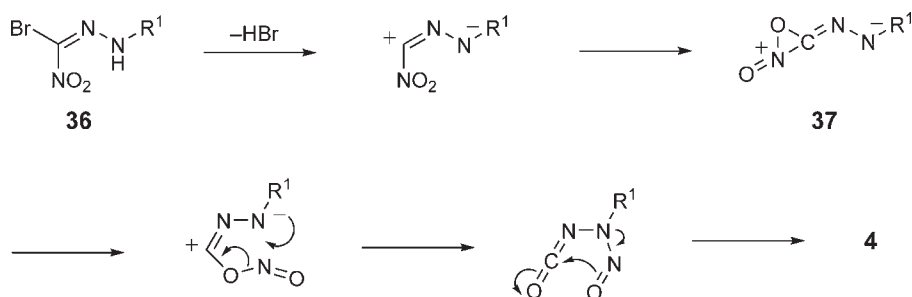


Cyclization occurs fastest when electron-withdrawing groups are attached to the C-3 phenyl substituent and slowest for electron donors. Reaction yields and selected spectroscopic data are listed in [Table 1](#).

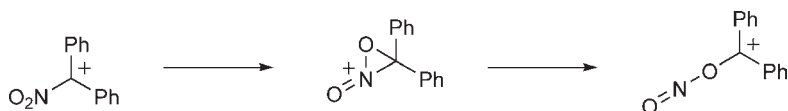
Table 1 Selected values from IR, UV, and ^{13}C NMR analysis of 3-substituted-anhydro-5-hydroxy-1,2,3,4-oxadiazolium hydroxides **4** from nitrosation and cyclization of bromonitroformaldehyde *N*-arylhydrazones **36** (Equation 5) <1997CHE880, 1999CHE363>

R^1	$C-5 \text{ C=O str KBr (cm}^{-1}\text{)}$	λ_{max} in EtOH (nm)	$C-5 \delta$ (ppm)	Yield (%)
4-O ₂ NC ₆ H ₄	1780, 1820	266	165.5	91
4-ClC ₆ H ₄	1780, 1795	272		89
Ph	1775, 1795	267	165.8	64
4-MeOC ₆ H ₄	1775		165.9	48
3-FC ₆ H ₄	1800	265	165.1	76
4-FC ₆ H ₄	1782, 1805	270	167.2	74
2-F ₃ CC ₆ H ₄	1800	270	165.0	53
3-F ₃ CC ₆ H ₄	1770, 1812	260	165.3	68
2-BrC ₆ H ₄	1800	270		54
4-BrC ₆ H ₄	1795	280		87
4-MeC ₆ H ₄	1770, 1785	278	165.8	65
3-MeC ₆ H ₄	1785	275		50
3-MeOC ₆ H ₄	1790	275		88
3-ClC ₆ H ₄		270		42
2-ClC ₆ H ₄		275		55
2-(HO ₂ C)C ₆ H ₄	1770, 1795	268		72
	1790		165.9	93
	1770		165.4	60
	1780	290	165.5	86
	1785, 1815	263	165.7	73
	1790	282	165.0	70
	1780, 1807	265	165.6	72

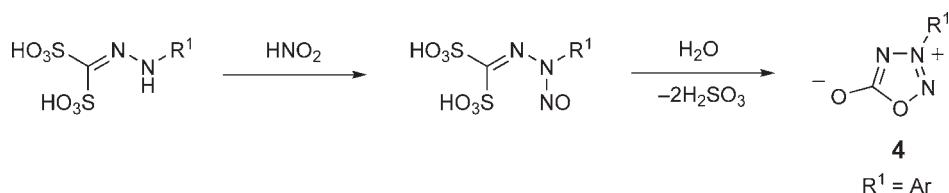
The requisite bromonitroformaldehyde *N*-arylhydrazones **36** are readily available by the standard methods <1974ZOR2229>. On treatment with ammonium nitrate, 70% nitric acid, or various other catalysts, compounds **36** firstly undergo dehydrobromination, followed by rearrangement via intermediate **37**, then cyclization to give products **4**. The proposed mechanism is shown in **Scheme 5** and is based on literature analogies shown in **Schemes 6** <1982JME1503> and **7** <1978OMS611, 1984JA2378>.



Scheme 5

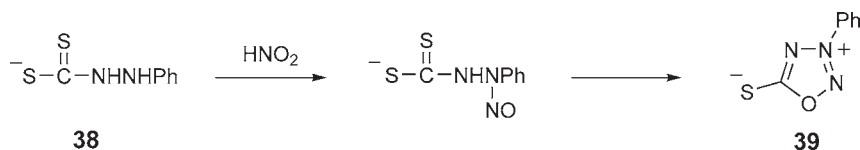


Scheme 6



Scheme 7

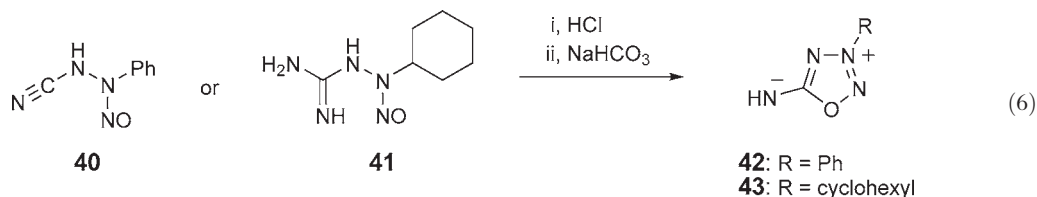
3-Alkyl-anhydro-5-thiolo-1,2,3,4-oxatriazolium hydroxides **39** are formed from arylhydrazinium dithiocarbamates **38** on nitrosation and cyclization (**Scheme 8**) <1979J(P1)732>.



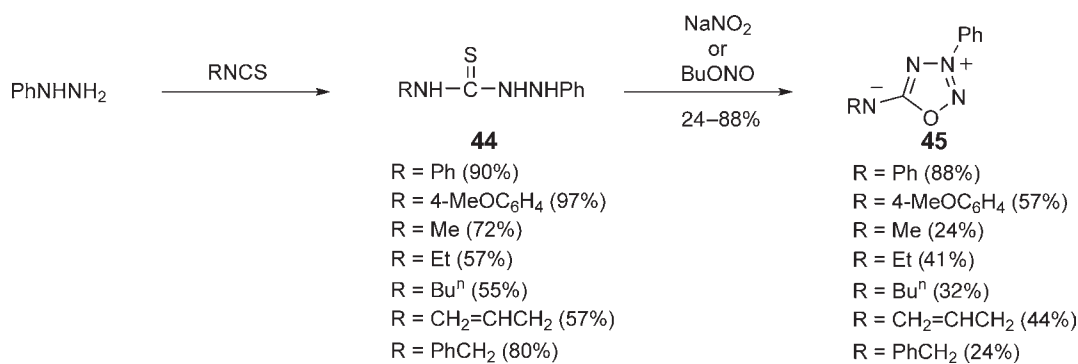
Scheme 8

When $\text{Ph}^{15}\text{NH}_2$ and $\text{Na}^{15}\text{NO}_2$ are used for preparation and nitrosation of the arylhydrazinium dithiocarbamates **38**, each of the nitrogen positions of product **39** may be labeled with ^{15}N to allow measurement of ^{15}N – ^{15}N coupling constants (Section 6.08.3.2) <1996JST167>.

The original synthesis of 3-substituted-anhydro-5-amino-1,2,3,4-oxatriazolium hydroxides relied on cyanohydrazines or guanidinohydrazines that were converted to the nitrosocyanohydrazines **40** and **41** that then cyclized to give products **42** and **43** as their hydrochloride salts (Equation 6) <2002CRV1091>.



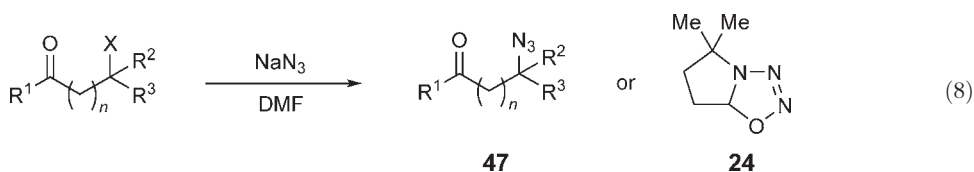
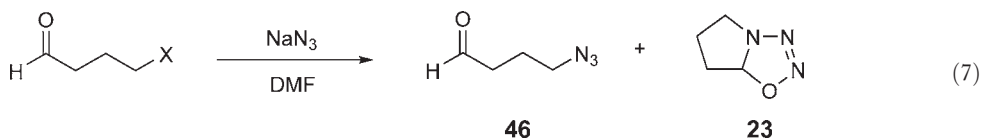
The free bases could then be liberated using sodium bicarbonate or ammonia. The exocyclic amino group at C-5 could then be converted to acyl derivatives by reaction with a variety of acylating agents. Derivatives of 3-aryl-anhydro-5-amino-1,2,3,4-oxatriazolium hydroxides **45** with substituents attached to the exocyclic nitrogen atom can be obtained directly from the arylthiosemicarbazides **44** by nitrosation with sodium nitrite followed by cyclization (Scheme 9).



Scheme 9

Use of the more expensive nitrosation reagent butylnitrite is successful when the reaction fails with the cheaper sodium nitrite reagent <2004JST23>. Introduction of a ¹⁵N label at the exocyclic nitrogen in compounds **45** where R = Me is achieved using the ¹⁵N-enriched 1-phenyl-4-methyl-3-thiosemicarbazide formed from ¹⁵N-methylamine via ¹⁵N-methylisothiocyanate <2004JST23>.

Two previously unknown Δ²-1,2,3,4-oxatriazoline derivatives, namely the 5,6,7,7a-tetrahydro-pyrrolo[1,2-*d*][1,2,3,4]oxatriazoles **23** and **24**, have been prepared (Equations 7 and 8) <2002HAC307>. When 4-bromo- or 4-toluenesulfonyloxy-butyraldehyde is reacted with sodium azide at 50 °C, high yields of product **23** are obtained (Equation 7; Table 2).



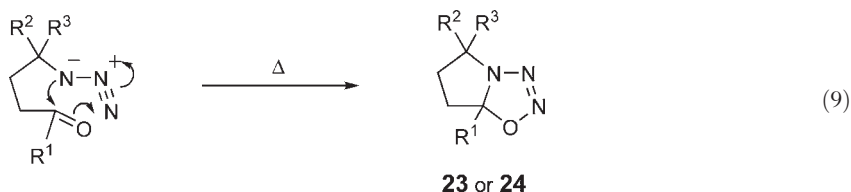
When the reaction is performed at 0 °C, the azide **46** is isolated in high yield with no accompanying oxatriazoline **23**, whereas a mixture of products **23** and **46** is obtained at room temperature. Similarly, the Δ²-1,2,3,4-oxatriazoline derivative **24** is obtained in high yield from 4-bromo-4-methylvaleraldehyde (Equation 8). When other aldehydes or ketones are employed, only the azide products **47** could be isolated (Table 3). Formation of these new oxatriazolines **23** and **24** seems likely to involve a tandem substitution–cycloaddition reaction sequence (Equation 9).

Table 2 Reaction of bromo and sulfonyloxy aldehydes with sodium azide (Equation 7) <2002HAC307>

<i>X</i>	<i>Temp.</i> (°C)	<i>Yield</i> (%)	
		46	23
Br	0	84	0
Br	rt	36	52
Br	50	0	87
TsO	50	0	85

Table 3 Reaction of bromo and sulfonyloxy aldehydes with sodium azide (Equation 8) <2002HAC307>

<i>n</i>	<i>R</i> ¹	<i>R</i> ²	<i>R</i> ³	<i>X</i>	<i>Yield</i> (%)	
					47	24
2	H	Me	Me	Br	0	89
2	Me	H	H	Br	79	0
2	Me	H	Me	TsO	81	0
3	H	H	H	TsO	83	0
4	H	H	H	TsO	86	0
1	H	H	H	Br	72	0
0	H	H	H	Br	63	0
0	Me	H	H	Cl	70	0
0	Ph	H	H	Br	94	0



6.08.10 Ring Syntheses by Transformation of Another Ring

Since the last survey <1996CHEC-II(4)679>, there have been no examples of synthesis of 1,2,3,4-oxatriazoles or 1,2,3,5-oxatriazoles by transformation of another ring.

6.08.11 Synthesis of Particular Classes of Compounds and Critical Comparison of the Various Routes Available

Direct, reliable methods for synthesis of mesoionic 1,2,3,4-oxatriazoles **4–6** are well established. All rely on the transformation of acyclic starting materials. Thus, 3-alkyl-anhydro-5-hydroxy-1,2,3,4-oxatriazolium hydroxides **4** (*R*¹ = alkyl) are readily obtained by nitrosation of semicarbazides followed by cyclization (Section 6.08.9). The 3-aryl-substituted analogues **4** (*R*¹ = aryl) are prepared either by cyclization of arylazonitromethanes or by nitrosation and cyclization of arylhydrazonomethanesulfonate salts <1984CHEC(4)579, 1996CHEC-II(4)679>.

Similarly, nitrosation and cyclization of arylhydrazinium dithiocarbamates provides a reliable and efficient route to 3-aryl-anhydro-5-thio-1,2,3,4-oxatriazolium hydroxides **5**, whereas 3-substituted-anhydro-5-amino-1,2,3,4-oxatriazolium hydroxides **6** (*R*¹ = alkyl or aryl) are directly prepared by nitrosation and cyclization of alkyl- or arylthiosemicarbazides. Alternatively, 3-aryl-substituted analogues **4** (*R*¹ = aryl) may be prepared by a newer route using bromonitroformaldehyde *N*-arylhydrazones, which has the added benefit of allowing introduction of heterocyclic substituents at the N-3 position in compounds **4** (*R*¹ = hetaryl) (Section 6.08.9).

1,2,3,4-Oxatriazolines have been prepared by intramolecular [3+2] cycloaddition but the reaction is restricted to particular starting materials and, to date, only two successful examples have been described. 1,2,3,5-Oxatriazolidines are equally rare and routes to these compounds are extremely limited. Δ^4 -1,2,3,5-Oxatriazolines, in particular, suffer badly from instability <1984CHEC(4)579, 1996CHEC-II(4)679>.

6.08.12 Important Compounds and Applications

Mesoionic 1,2,3,4-oxatriazoles display a wide range of biological activities and important new examples have been the focus of several studies since last survey of the subject area <1996CHEC-II(4)679>. These compounds are well represented by structures **48–53** among others <1995AP137, 1996WO96/11191>.

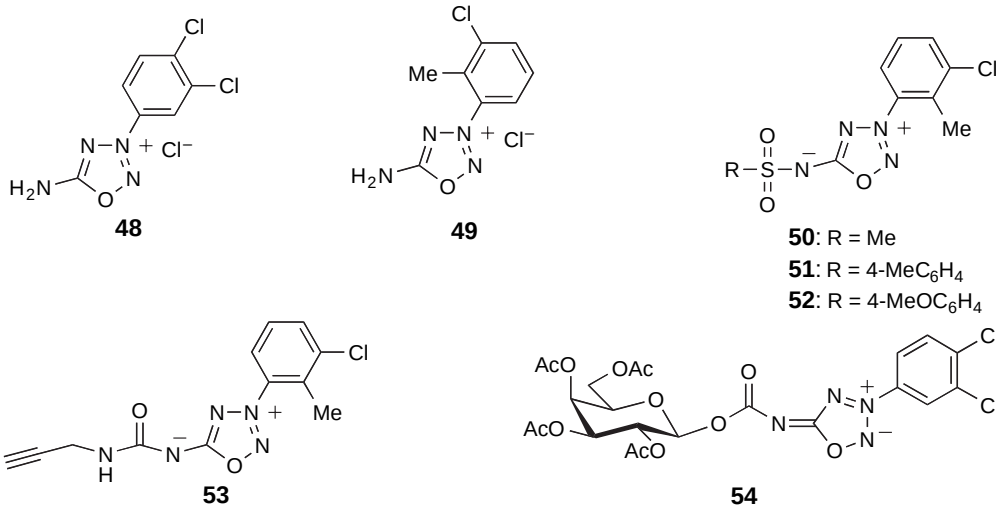
Mesoionic 1,2,3,4-oxatriazoles are structural isosteres of sydnonimines (see Chapter 5.03). Like the sydnonimines, the pharmacological effects of mesoionic 1,2,3,4-oxatriazoles stem largely from their ability to act as NO donors in biological systems <1994MI553, 1996BJP401>. These properties are well documented in recent reviews <B-2004MI1, B-2005MI1, 1998MI113, 1999FA316, 2000MI701, 2000TH1, 2002CRV1091, 2002MI167, 2002RCB1375, 2005MI67>. Application of mesoionic 1,2,3,4-oxatriazoles as blood pressure lowering agents was first reported in 1971 and detailed investigations into their NO-releasing properties began some 15 years ago <1994WO94/3442>.

Of particular note is the compound 3-(3,4-dichlorophenyl)-anhydro-5-amino-1,2,3,4-oxatriazolium hydroxide **48** (GEA 3162). This particular compound and some of its derivatives have been studied intensively. The compound possesses hypotensive <2000MI701>, vasodilatory <1996BJP1422>, vasoprotective <1997MI(161)55>, antiplatelet <1996BJP401>, antiulcer <1999MI123>, immunosuppressive <1997MI(337)55b>, and pro-apoptotic <2000BP305, 2001BBR1229, 2004BJP179> properties. Additionally, compound **48** inhibits neutrophil function <1997BJP1135> and neutrophil adhesion to endothelial cells <1999MI111>. Compound **48** also inhibits proliferation of human lymphocytes in a cGMP-dependent manner <1998MI215>, suppresses tumor cell growth <1997MI75>, stimulates chloride secretion in the colon <2002MI21>, enhances the permeability of mitochondria <2002MI45>, and inhibits mitogenesis in vascular smooth muscle <1998BJP402>. The NO-releasing ability of compound **48** has been shown to be superior to that of the mesoionic 1,2,3-oxatriazole compound SIN-1 (see Chapter 5.03) <1998MI97>. Like SIN-1, compound **48** is a generator of peroxynitrite (ONOO⁻) <2004BJP179>.

Compound **51** (GEA 3175) shows antiplatelet <1996BJP2140, 2004MI1, 2005MI149>, anti-inflammatory <1995MI107>, and antimalarial activity <2002CRV1091>. The compound also causes apoptotic cell death in murine melanoma cells in a dose-dependent manner <2002CRV1091>. Additionally, this compound **51** (GEA 3175) and its analogues **52** (GEA 3268) and **50** (GEA 5145) induce relaxation of the bronchioles <1996MI1309, 1997MI175, 1998BJP895, 2006MI179> and trachea <1998MI110>.

The structures of various substituted 3-aryl-anhydro-5-amino-1,2,3,4-oxatriazoline hydroxides **6** (R¹ = Ar) for the treatment of asthma and thrombosis have been disclosed <1996WO96/11191> and their diuretic properties have also been alluded to <2006WO2006/055542>.

Although successful in the sydnonimine series, attempted formation of a galactose conjugate of compound **48** (GEA 3162) for planned evaluation as a galactosidase-mediated nitric oxide donor proved less successful. Decomposition of the 1,2,3,4-oxatriazole ring occurred on attempted removal of the acetyl protecting groups from the sugar ring of the conjugate **54** <2005JOC3518>.



The compound 3-phenyl-anhydro-5-thio-1,2,3,4-oxatriazolium oxide **5** ($R^1 = \text{Ph}$) has been incorporated into polymer films where its electronic structure and density contribute equally to the measured changes in photoinduced refractive index. Its analogue, 3-phenyl-anhydro-5-hydroxy-1,2,3,4-oxatriazolium oxide **4** ($R^1 = \text{Ph}$), has been employed as a filter <1999MI6772, 2002MI2290>.

6.08.13 Further Developments

No further developments regarding the chemical synthesis, characterization, reactivity and analysis of 1,2,3,4-oxatriazoles or 1,2,3,5-oxatriazole have been described. Mesoionic 3-(3,4-dichlorophenyl)-anhydro-5-amino 1,2,3,4-oxatriazolium hydroxide **48** (GE3162) and analogue **51** (GEA 3175) continue to find various pharmacological uses in the context of their nitric oxide <2007BJP305> releasing properties <2006MI43, 2006MI162, 2006MI247> (Section 6.08.12).

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Biographical Sketch



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6.09

1,2,3,4-Thiatriazoles

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6.09.1	Introduction	442
6.09.2	Theoretical Methods	442
6.09.2.1	Molecular Orbital Calculations	442
6.09.2.1.1	Aromaticity	442
6.09.2.1.2	Semi-empirical, <i>ab initio</i> and DFT methods	443
6.09.2.1.3	Structure of 1,2,3,4-thiatriazole-5-thiol and its derivatives	446
6.09.3	Experimental Structural Methods	448
6.09.3.1	Crystal Structure	448
6.09.3.2	NMR Spectroscopy	448
6.09.3.3	Mass Spectrometry	452
6.09.3.4	UV Spectroscopy	452
6.09.3.5	Infrared and Raman Spectroscopy	452
6.09.3.6	Dipole Moments	452
6.09.4	Thermodynamic Aspects	452
6.09.5	Reactivity of Fully Conjugated Rings	454
6.09.5.1	Thermal Reactions	454
6.09.5.2	Photochemical Reactions	455
6.09.5.3	Electrophilic and Nucleophilic Attack at Nitrogen	456
6.09.6	Reactivity of Nonconjugated Rings	458
6.09.6.1	Thermal Reactions	458
6.09.6.1.1	Δ^2 -1,2,3,4-Thiatriazolines	458
6.09.6.1.2	5-Imino- Δ^2 -1,2,3,4-thiatriazolines	459
6.09.6.1.3	Δ^3 -1,2,3,4-Thiatriazolines	460
6.09.6.2	Reactions of Δ^2-1,2,3,4-Thiatriazolines	461
6.09.6.2.1	Bimolecular reactions of Δ^2 -1,2,3,4-thiatriazolines	461
6.09.6.2.2	Bimolecular reactions of Δ^2 -thiatriazolines formed <i>in situ</i>	462
6.09.7	Reactivity of Substituents Attached to Ring Carbon Atoms	464
6.09.7.1	1,2,3,4-Thiatriazoles	464
6.09.7.1.1	5-Chloro-1,2,3,4-thiatriazole	464
6.09.7.1.2	5-Amino-1,2,3,4-thiatriazoles	464
6.09.7.1.3	5-Hydrazino-1,2,3,4-thiatriazoles	468
6.09.7.1.4	1,2,3,4-Thiatriazole-5-thiol and its derivatives	468
6.09.7.1.5	5-Alkoxy-1,2,3,4-thiatriazoles	468
6.09.7.2	Mesoionic 1,2,3,4-Thiatriazoles	469
6.09.7.2.1	Reaction with nucleophiles	469
6.09.7.2.2	Reaction with electrophiles	470
6.09.8	Reactivity of Substituents Attached to Ring Heteroatoms	470
6.09.9	Ring Synthesis of 1,2,3,4-Thiatriazoles Classified by Number of Ring Atoms in Each Component	471

6.09.9.1	One Bond	471
6.09.9.2	Two Bonds	472
6.09.9.2.1	From [4+1] fragments: S-C-N-N + N	472
6.09.9.2.2	From [3+2] fragments: N-N-N + S-C	472
6.09.10	Ring Synthesis of 1,2,3,4-Thiadiazoles by Transformation of Another Ring	478
6.09.11	Synthesis of Particular Classes of Compounds	479
6.09.11.1	Formation of Complexes of 1,2,3,4-Thiadiazoles	479
6.09.12	Applications	480
6.09.13	Further Developments	480
References		481

6.09.1 Introduction

The chemistry of 1,2,3,4-thiadiazoles was covered previously in 32 pages in CHEC(1984) <1984CHEC(6)579> together with data on 1,2,3,4-oxatriazoles, and in 40 pages in CHEC-II(1996) <1996CHEC-II(4)691>. Older reviews were mentioned in the introductions to these two texts. The synthetic aspects of 1,2,3,4-thiadiazole derivatives and the isomeric 1,2,3,5-thiadiazoles were recently reviewed by Begtrup <2004HOU833>.

In the present chapter we have compared the data abstracted from recent publications with a summary of previous work and some new general insights and concepts are provided. Thus, the previous chapters in CHEC(1984) and CHEC-II(1996) <1984CHEC(6)579, 1996CHEC-II(4)691> should be read together with this chapter in order to achieve a really comprehensive view of the field.

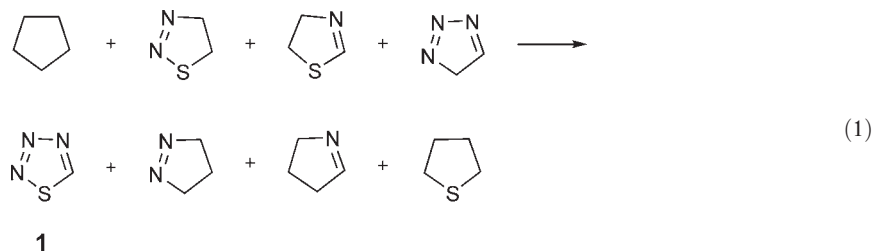
6.09.2 Theoretical Methods

6.09.2.1 Molecular Orbital Calculations

6.09.2.1.1 Aromaticity

For nearly two centuries aromaticity has remained one of the central concepts in chemistry and, because of expanding applications, it is actually increasing in importance. It should be noted that there is no precise quantitative and generally accepted definition <B-1994MI1, 2000T1783, 2001CRV1385>. The main criteria employed are energetic, geometric, and magnetic in nature. Several reviews appeared in the literature <2002JOC1333> concerning either the discussion of the aromaticity in general or dedicated to heteroaromaticity in particular <B-1994MI1, 1996CHEC-II, B-1997MI1, 2000T1783, 2001CRV1115, 2001CRV1385, 2002JOC1333, 2003T1657>.

The aromatic stabilization energy for 1,2,3,4-thiadiazole **1** was calculated according to Equation (1) based on an *ab initio* optimized geometry at B3LYP/6-311+G** and at the MP2-(fc)/6-311+G** level of the theory. A homodesmotic reaction scheme was applied in these calculations <2002JOC1333, 2003T1657>. The systems with strongly positive aromatic stabilization energy (ASE) are aromatic, while those with strongly negative values are antiaromatic.



The magnetic susceptibility exaltations (Λ , defined as a difference between the magnetic susceptibility of a given system and a reference one, without cyclic delocalization) are also based on Equation (1). Systems with strongly negative values of Λ are qualified as aromatic.

Nuclear-independent chemical shift (NICS) is the negative value of absolute magnetic shielding calculated at revealing points in or near an aromatic system. Rings with negative NICS and NICS(1) values computed at the center

or at 1 Å above the ring, respectively, qualify as aromatic, and the more negative NICS values correspond to the higher aromaticity of the aromatic system. Consequently, antiaromatic systems have strongly positive values of NICS. The NICS(1) values are considered to better reflect the π -electron effects [\[1997JA12669\]](#).

The results of the calculations on thiophene, 1,2,3,4-thiatriazole, and 1,2,3,5-thiatriazole are shown in the [Table 1](#).

Table 1 Calculated ASE (kcal mol⁻¹), exaltations of the magnetic susceptibility Λ (ppm cm³ mol⁻¹) NICS, NICS(1) (ppm)

Structure	ASE	Λ	NICS	NICS(1)
	18.57	-7.00	-13.80	-10.79
	14.72	-6.57	-15.18	-14.65
	21.62	-7.85	-15.49	-14.96

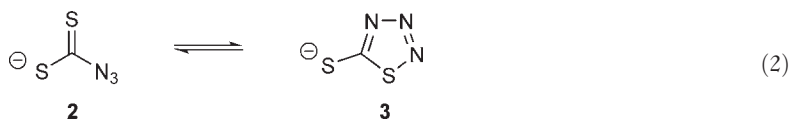
According to the data in [Table 1](#), both energetic and magnetic indices of aromaticity advocate for the strong aromaticity of the 1,2,3,4-thiatriazole molecule comparable with the aromaticity of thiophene; according to the NICS indices, it is more aromatic than thiophene. The indices of ASE and magnetic susceptibility exaltation are in favor of a higher aromaticity of the thiophene molecule. It is worth noting that according to calculations, the isomeric 1,2,3,5-thiatriazole molecule should be even more aromatic.

6.09.2.1.2 Semi-empirical, *ab initio* and DFT methods

The structure, reactivity, and spectra of 1,2,3,4-thiatriazoles were calculated at various theoretical levels including semi-empirical CNDO [\[1972JCD73\]](#), MNDO [\[1986ICA71\]](#), AM1 [\[1990JPR885\]](#), PM3 [\[1999PS201\]](#), *ab initio* HF and MP-SDQ/6-31G* [\[2000CPL276\]](#), CHIH-DFT [\[2004JMT83\]](#), [\[2005JMT61\]](#), MPW1PW91/cc-pVTZ [\[2004IC1370\]](#), HF/6-31C*, MP2/6-31+G*, BLYP/6-311++G*, B3LYP/6-31+G*, B3LYP/6-311++G* [\[1999PS201\]](#), [\[1999ICA68\]](#), [\[1998JFC153\]](#), MP2/6-31G** and MP4(SDQ) treatments [\[1998PCA9906\]](#), AIM/B3LYP/6-31+G* [\[2002JMT79\]](#), DFT at the CCSD(T)//MP2/6-31+G* level of theory [\[2003JOC6049\]](#).

6.09.2.1.2(i) Ring-opening processes

1,2,3,4-Thiatriazole-5-thiol was originally thought to possess an open structure, called azidothiocarbonic acid. Based on an IR spectroscopic study and MNDO calculations and finally on the basis of X-ray analysis for sodium 1,2,3,4-thiatriazole-5-thiolate dihydrate [\[1991AXC1018\]](#), the conclusion was made that the ring isomer is more stable than the acyclic isomer. According to the results obtained with the modified neglect of diatomic overlap (MNDO) method, the 1,2,3,4-thiatriazole-5-thiolate anion **3** is more stable than the azidodithiocarbonate **2** by 36.8 kcal mol⁻¹ ([Equation 2](#)) [\[1986ICA71\]](#). According to a more precise B3LYP calculation the difference in the heats of formation for acyclic and cyclic isomers is 8.3 kcal mol⁻¹ [\[1999PS201\]](#).



Retroelectrocyclic and retro-1,3-dipolar cycloaddition reactions of the 1,2,3,4-thiatriazole ring were theoretically studied by the HF and DFT methods [\[2000CPL276\]](#), [\[2003JOC6049\]](#).

The conversion of the parent 1,2,3,4-thiatriazole **1** to azidothiocarbonate was carefully studied by HF/TZ** and MP4-SDQ/6-31G* methods. The study of the conversion process starts from the optimized geometry of 1,2,3,4-thiatriazole and then the N-S bond is elongated in a stepwise manner. At each step, the N-S bond is frozen and the

optimized geometry is calculated as well as the energies of the intermediates. The geometry data for the cyclic conformer, for the open structure, and for the transition state are shown in **Figure 1**. The activation energy for the 1,2,3,4-thiadiazole–thioformyl azide conversion is $23.09 \text{ kcal mol}^{-1}$, the activation energy for the cyclization of thioformyl azide to 1,2,3,4-thiadiazole is $18.02 \text{ kcal mol}^{-1}$ <2000CPL276>.

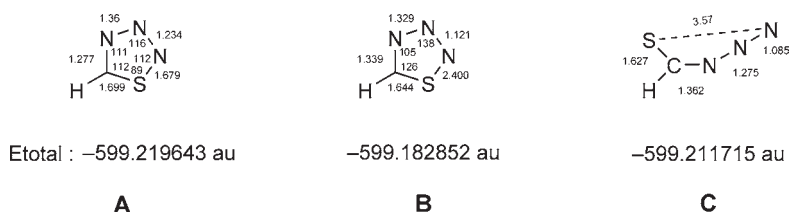
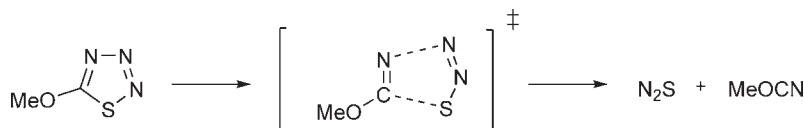


Figure 1 Geometry (bond lengths in Å, angles in degrees, energy in atomic unit) and energy data of 1,2,3,4-thiadiazole (A), transition state (B), and chain conformer (C) by MP-4-SDQ/6-31G*.

The mechanism of the decomposition reaction of 5-methoxy-1,2,3,4-thiadiazole to dinitrogen sulfide and methoxynitrile was studied by the DFT method at the CCSD(T)//MP2/6-31+G* level of theory <2003JOC6049>. The calculations indicated that this is a concerted retro-[2+3]-dipolar cycloaddition process with an activation energy of $28.9 \text{ kcal mol}^{-1}$ and a reaction energy of $1.9 \text{ kcal mol}^{-1}$. This unimolecular decomposition is favored due to the entropy gain (25.8 eu) involved in the overall reaction (**Scheme 1** and **Table 2**).



Scheme 1

Table 2 Calculated data for the activation and reaction energy in kcal mol^{-1} for the thermal decomposition of 5-methoxy-1,2,3,4-thiadiazole to dinitrogen sulfide and methoxycarbonitrile

<i>Theoretical method</i>	<i>5-Methoxy-1,2,3,4-thiadiazole</i>	<i>Transition state</i>	<i>Dinitrogen sulfide + methoxycarbonitrile</i>
CCSD(T)//MP2/6-31+G*	0	28.9	1.9
MP2/6-31+G*	0	25.9	-4.3
B3LYP/6-31+G*	0	30.6	0.1

6.09.2.1.2(ii) Thione-thiol tautomerism

Calculations of heat of formation of thiol and thione forms of HCS_2N_3 by the MNDO method have shown that both forms are unstable relative to the corresponding anion by $27.1 \text{ kcal mol}^{-1}$ for the SH form and by $29.5 \text{ kcal mol}^{-1}$ for the thioketone form <1986ICA71>. Thus, the thiol form should be predominant over the thione form by $2.5 \text{ kcal mol}^{-1}$. This is in contrast with both NMR spectroscopy <1977JHC1417> and X-ray crystallographic data <2004IC1370> which indicate the presence of the thione form in both solid and solution. Recently, the question of the site of the protonation of 1,2,3,4-thiadiazole-5-thiolate **3** ($\text{R}=\text{S}$) and relative stabilities of isomeric forms of acid **2** ($\text{R}=\text{H}$) has been carefully studied at a high theoretical level by the MPW1PW91/cc-pVTZ method (**Figure 2**) <2004IC1370>.

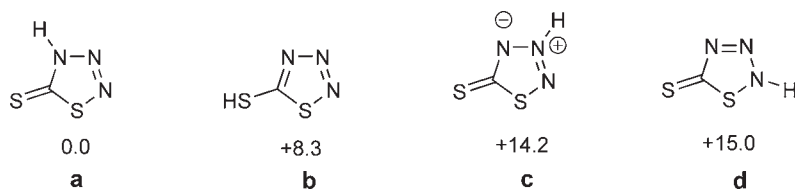


Figure 2 Calculated relative energies in kcal mol⁻¹ of HCS₂N₃ isomers by the MPW1PW91/cc-pVTZ method.

The experimentally observed isomer (**a**) with the H–N bond was found to be the lowest-energy isomer for HCS₂N₃ in the gas phase. The experimentally determined structural parameters show good agreement with the calculated data. Interestingly, that isomer (**b**) with S–H bond was calculated to have the second lowest energy (**Figure 2**).

6.09.2.1.2(iii) Structures of 1,2,3,4-thiatriazoles

As early as in 1972, a theoretical study of the structure of unknown 1,2,3,4-thiatriazole was carried out using the semiempirical complete neglect of differential overlap (CNDO) method [\[1972JCD73\]](#). Because of the known large discrepancy for the C–S length predicted by semi-empirical calculations compared with the experimental data for 1,2,3,4-thiatriazole-5-thiolate [\[1986ICA71\]](#), this study has only historical interest.

The structure of the parent 1,2,3,4-thiatriazole was also calculated by HF/TZ^{**}, MP2/6-31G^{**}, and MP4-SDQ/6-31G^{*} methods [\[1998PCA9906, 2000CPL276\]](#). These data are very similar and nicely correspond to experimental data obtained by X-ray measurements for the 5-amino-1,2,3,4-thiatriazole. However, these results are different to those obtained by semi-empirical calculations especially in respect to the prediction of the N–S and N–N bond lengths.

The structure of 5-amino-1,2,3,4-thiatriazole was successfully studied by Chihuahua heterocycles density functional theory (CHIH-DFT), a method that works well with heterocyclic compounds. The authors used the modified version of a hybrid density functional theory implying the mix where 25% of HF exchange and 75% of Perdew, Burke, and Ernzerhof (PBE) density functional exchange were used [\[2004JMT83, 2005JMT61\]](#). The 1,2,3,4-thiatriazole molecule was calculated to be planar, corresponding to the X-ray structure of this molecule. The results of calculations along with experimental data for 5-amino-1,2,3,4-thiatriazole are shown in **Figure 3**.

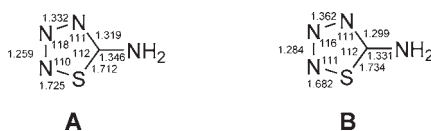


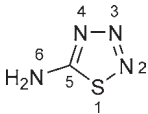
Figure 3 Molecular structure of 5-amino-1,2,3,4-thiatriazole calculated with CHIH-DFT (A) compared to the X-ray analysis data (B).

There is a good agreement between calculated and experimental results, despite the fact that the experimental structure was obtained in solid state, while calculations were performed for the gas phase. It is worth noting that the use of a larger basis set gave results that are closer to experiment.

6.09.2.1.2(iv) Reactivity indexes

Glossman-Mitnik and co-workers have performed density functional calculations with the CHIH-DFT approach to determine the molecular structure, dipole moment, energy of frontier orbitals, atomic charges, Fukui indexes, electronegativity, global and local hardness of 5-amino-1,2,3,5-thiatriazole [\[2005JMT61\]](#). The results that have been calculated using a CBSB2 basis set are shown in **Table 3**.

Charges were calculated using natural population analysis [\[1988CRV899\]](#) with the objective of obtaining a better knowledge of the reactivity of the 5-amino-1,2,3,4-thiatriazole system (see **Table 3**). Except for the N-3 atom, all

Table 3 HOMO and LUMO energies, Fukui indexes, $f(r)$, dipole moment, μ , and atomic charges of 5-amino-1,2,3,4-thiatriazole


$f^-(r)$	E_{HOMO} (eV)	E_{LUMO} (eV)	$\Delta E_{LUMO-HOMO}$ (eV)	Charges e (atom)	Dipole moment (D)
0.1800 (N ²)	-7.7455	-1.4482	6.2973	0.1611 (C ⁵)	5.5846
0.0482 (N ³)				0.4898 (S ¹)	
				0.0099 (N ³)	
0.2090 (N ⁴)				-0.3472 (N ⁴)	
0.3040 (N ⁶)				-0.3603 (N ⁵)	
				-0.8532 (N ⁶)	

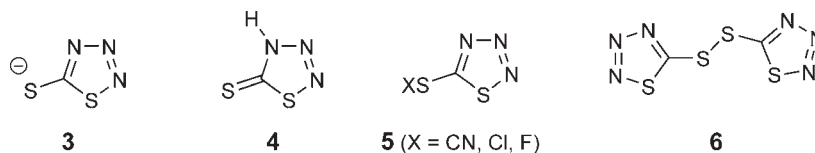
$f^-(r) = \rho_N(r) - \rho_{N-1}(r)$, where ρ_N and ρ_{N-1} are the electronic densities of neutral and cationic species, respectively.

nitrogen atoms of 5-amino-1,2,3,5-thiatriazole are negatively charged and are thus prone to react with electrophilic reagents. The local reactivity has also been analyzed by means of the Fukui indices. They indicate the reactive regions, in the form of nucleophilic and electrophilic behavior of each atom in molecule. The Fukui function $f^-(r)$ is defined as the first derivative of the electronic density $\rho(r)$ with respect to the number of electrons N at a constant external potential $\nu(r)$. The calculated indexes confirmed the conclusion based on the charges calculated by the natural bond orbital (NBO) method. The sulfur atom seems to be the site most prone to undergo nucleophilic attacks. In **Table 3**, the calculated Fukui indexes $f^-(r)$ are given for nitrogen atoms, indicating that the amino group of 5-amino-1,2,3,4-thiatriazole is the most probable center for electrophilic attack.

6.09.2.1.3 Structure of 1,2,3,4-thiatriazole-5-thiol and its derivatives

1,2,3,4-Thiatriazole-5-thiolate **3**, also known as azidodithiocarbonate by inorganic chemists, was recently recognized as a member of the interesting family of pseudohalides <1998JFC153, 1999ICA68, 1999PS201, 2000JA9052, 2004IC1370>.

The term pseudohalogen is employed to denote univalent radicals Y (e.g., Y = CN, OCN, N₃) that are capable of forming anions Y⁻, hydrides HY, dipseudohalogens Y₂, and interpseudohalogens XY (X = halogen or pseudohalogen). This concept was introduced in 1925 <1925CB786> and since then it has been widely applied, including the chemistry of 5-thio-1,2,3,4-thiatriazoles <2000JA9052>. Klapötke and co-workers reported that radical CS₂N₃ fulfills all criteria in order to be considered as a pseudohalogen. These authors published the preparation, characterization, and determination of a series compounds formally derived from such radical: pseudohalide anion [CS₂N₃]⁻ **3**, hydride CS₂N₃H **4**, interpseudohalogens CS₂N₃-X **5** (X = Cl, F, CN), and dipseudohalogen **6** (CS₂N₃)₂ <1998JFC153, 1999ICA68, 1999PS201, 2000JA9052, 2004IC1370>.



The structures of salts of [CS₂N₃]⁻ M⁺ (M = NH₄, (CH₃)₄N, Na, K, Cs) were carefully studied by both experimental and theoretical methods. IR and Raman spectra of these species were determined and compared to the quantum chemically calculated vibrational spectra by the MPW1PW91/cc-pVTZ method. A good agreement was found for these data, confirming the structure of the salts as 1,2,3,4-thiatriazole-5-thiolates. Moreover, the ¹⁴N and ¹³C NMR spectra were in good agreement with this structure. Furthermore, X-ray analysis of [CS₂N₃]⁻ M⁺ (M = NH₄, (CH₃)₄N, Na) has shown that the [CS₂N₃]⁻ anion is independent of the nature of the cation and exists

as a planar five-membered ring. The structural parameters for $[\text{CS}_2\text{N}_3]^-$ calculated by the MPW1PW91/cc-pVTZ method were also in good agreement with X-ray data. The theoretical charge density structure computed semi-empirically at the PM3 theoretical level, using the VSTO-3G* basis set, was found to yield a planar five-membered ring with C_s symmetry as the probable structure <1999PS201>. The electron density was also observed to lie above and below the plane of the ring as would be expected for pseudoaromatic species. Indeed, this compound completely fits the following requirements for a compound to be pseudoaromatic: (1) a homocyclic system; (2) a conjugated π -system which has no node in the lowest occupied π -orbital; (3) a planar system; and (4) $(4n+2)$ π -electrons <1999PS201>. The charges were calculated by a natural population analysis <1988CRV899> with the objective of obtaining knowledge of the reactive properties of the 1,2,3,4-thiadiazole-5-thiolate system (see Figure 4).

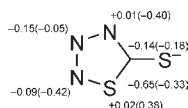
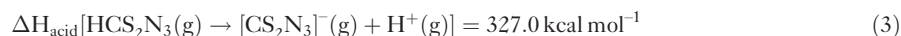


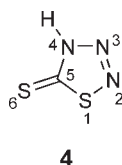
Figure 4 Calculated Mulliken and NBO charges (in parentheses) for 1,2,3,4-thiadiazole-5-thiolate.

NBO charges better predict the reactivity of this molecule. Atoms N-2 and N-4 and the exocyclic sulfur atom are calculated to be the most electrophilic centers. This is in agreement with experimental data: the reactions with methyl iodide and benzoyl chloride are directed to the sulfur atom and protonation takes place at N-4. The calculated total energy of $[\text{CS}_2\text{N}_3]^-$ and HCS_2N_3 by MPW1PW91/cc-pVTZ method allowed to predict the gas-phase acidity at room temperature (enthalpy value) (Equation 3). This value compares nicely with the calculated and experimentally determined gas-phase acidities for HCl and HCN <2004IC1370>.



The atoms in molecules (AIM) theory <2002JMT79> yields a simple, rigorous, and elegant definition of atoms and chemical bonds. This theory is based upon the critical points (CPs) of the molecular charge density, $\rho(r)$. At these points, the gradient of the electronic density, $\nabla \rho(r)$, is zero and it is characterized by way of the three eigenvalues, λ_i ($i = 1, 2, 3$), of the Hessian matrix of $\rho(r)$. In molecules there are four types of CPs having a special interest: $(3, -3)$, $(3, -1)$, $(3, +1)$, and $(3, +3)$. A $(3, -3)$ CP corresponds to a maximum in $\rho(r)$, characterized by $\nabla^2 \rho(r) < 0$ and usually it occurs at the nuclear positions. A $(3, +3)$ CP (cage) corresponds to a decreasing of the electronic charge and it is characterized by $\nabla^2 \rho(r) > 0$. The $(3, +1)$ points of ring CPs are saddle points. Finally, a $(3, -1)$ point or bond CP is frequently located between two neighboring nuclei, denoting the existence of a chemical bond between them. Several properties which can be evaluated at the bond CP make up powerful tools to classify a given chemical structure. The two negative eigenvalues of the Hessian matrix (λ_1 and λ_2 , respectively) measure the degree of contraction of $\rho(r)$ at normal direction to the bond toward the CP, while the positive eigenvalue (i.e., λ_3) gives a quantitative indication of the contraction degree parallel to the bond and from the CP toward each of the neighboring nuclei. When the negative eigenvalues are dominant, the electronic charge is locally concentrated in the region of the CP leading thus to an interaction which is attributable to covalent or polarized bonds and they are characterized by large $\rho(r)$ values, $\nabla^2 \rho(r) < 0$, and $\lambda_1/\lambda_3 > 1$. When the positive eigenvalue is dominant, the electronic density is locally concentrated at each atomic basin. The interaction is classified as closed shell and it is characteristic for highly ionic bonds, hydrogen bonds, and van der Waals interactions. This particular interaction is described by relatively low $\rho(r)$ values, $\nabla^2 \rho(r) > 0$ and $\lambda_1/\lambda_3 < 1$. Finally, the ellipticity, ε , defined as $\lambda_1/\lambda_2 - 1$, is a measure of the deviation of the electronic charge density from axial symmetry giving a quantitative measure of the π character of the chemical bond.

The topological characterization of pseudohalogens 3–6 was made by means of analysis of the electronic charge resorting to the AIM topological theory <2002JMT79>. The topological properties of hydracid 4 for ring bonds and for the exocyclic C–S bond are placed in Table 4 as an illustrative example. The data for compounds 4–6 are available from <2002JMT79>.

Table 4 Data of AIM calculations for 1,2,3,4-thiadiazole-5-thiol **4**

Topological characters (<i>ae</i>)	Bonds					
	C^5S^6	N^4C^5	S^1C^5	S^1N^2	N^3N^4	N^2N^3
$\rho(r)$	0.2166	0.3040	0.2040	0.1956	0.3680	0.4626
$\nabla^2\rho(r)$	0.0295	-0.7912	-0.3452	-0.3129	-0.7017	-1.1329
λ_3	0.4192	0.3794	0.2547	0.2572	0.9833	1.0144
λ_1/λ_3	0.4718	1.6040	1.2901	1.2041	0.9131	1.1507
ε	0.0313	0.0775	0.2111	0.8930	0.1406	0.1910

The analysis of the topological properties calculated at the bond CPs shows that the four structures possess a ring structure since a ring CP (3+1) was found for all of them and the C–N and N–N bonds are covalent while the C–S and S–N chemical bonds have an intermediate character. The same behavior is found for the exocyclic C–S bond, remarkably in structure **3**. The ellipticity values show the preferential charge density concentration on a given plane containing the bond path. These values (see [Table 4](#)) for the C–S bonds forming the rings are higher than those corresponding to the C–S exocyclic bonds and reveal the partial double bond character, which is a result of the electronic charge delocalization over the ring surface. The conclusion was made on the basis of analysis of the graphs of structures **3–6** that in the ring C–S bonds the CPs are located over a nodal surface of $\nabla^2\rho(r)$, just within the inner shell of the charge decrease. The shift of the bond CP toward the less electronegative atom reflects the bond polarity and in every case the C–S bond CP is located nearer the S atom. In structure **4**, and even more so in structure **3**, such CPs are located at the nodal surface. In the pentagonal rings, the bonds CPs are generally midway between both atoms making up the chemical bond [<2002JMT79>](#).

6.09.3 Experimental Structural Methods

6.09.3.1 Crystal Structure

X-ray analysis has been successfully used for elucidation of the structures obtained in the oxidation and alkylation reactions of 5-phenyl-1,2,3,4-thiadiazole [<1976ACA351>](#), and to determine the place of protonation and alkylation of 1,2,3,4-thiadiazole-5-thiolate [<2004IC1370>](#). The structures of 1,2,3,4-thiadiazol-5-thiolate derivatives as heterocyclic pseudohalides were carefully studied by the X-ray diffraction method [<2000JA9051, 2004IC1370>](#).

The structural data including those previously published in CHEC-II(1996) [<1996CHEC-II\(4\)691>](#) are shown in [Table 5](#).

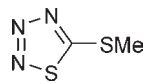
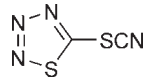
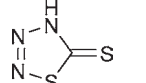
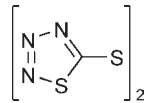
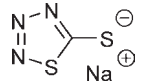
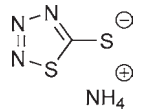
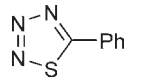
All ring atoms of the compounds studied are in-plane [<2000JA9052>](#). The bond lengths of the rings are very similar to those for other five-membered sulfur and aza heterocycles [<1998PCA9906>](#). It is worth noting that the change of the 5-substituents in 1,2,3,4-thiadiazoles does not change considerably the geometry of the ring. On the other hand, alkylation at position 3 of the ring leads to quaternary 1,2,3,4-thiadiazolium salts having shorter S–N and N–N bonds and a larger C–S bond than those in the starting 5-phenyl-1,2,3,4-thiadiazole.

6.09.3.2 NMR Spectroscopy

^1H NMR spectra are of little diagnostic value for 1,2,3,4-thiadiazoles, where one can only expect the signal for C-5(H) or any H-containing substituent at the 5-position. In fact, 1,2,3,4-thiadiazole derivatives unsubstituted at the position 5 have not been described.

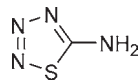
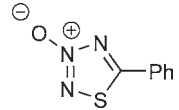
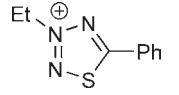
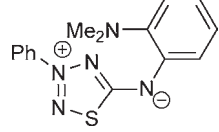
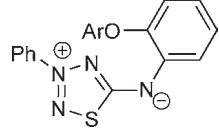
^{13}C NMR spectroscopic data were measured for 5-substituted 1,2,3,4-thiadiazoles and the C-5 signal was found at 162.5 ppm for 5-picrylamino-4-trimethylsilylmethyl-1,2,3,4-thiadiazoline [<1990JHC1059>](#), at 179.4 ppm for

Table 5 The X-ray data for some 1,2,3,4-thiatriazoles

Formula 1	Bond length (Å)					Bond angle (°)					References 12
	$S-N^2$	N^2-N^3	N^3-N^4	N^4-C^5	C^5-S	C^5SN^2	SN^2N^3	$N^2N^3N^4$	$N^3N^4C^5$	N^4C^5S	
	2	3	4	5	6	7	8	9	10	11	
	1.680	1.274	1.356	1.314	1.699	90	11	117	111	112	2000JA9052
	1.670	1.276	1.364	1.305	1.699	90	112	116	110	113	2000JA9052
	1.706	1.260	1.351	1.346	1.722	92	112	113	118	105	2000JA9052
	1.674	1.277	1.358	1.310	1.696	90	112	116	118	112	2000JA9052
	1.664	1.284	1.314	1.326	1.703	91	111	117	112	109	2004IC1370
	1.683	1.281	1.352	1.338	1.722	92	110	117	112	109	2004IC1370
	1.680	1.243	1.359	1.329	1.699	91	111	116	111	111	1996CHEC-II(4)691

(Continued)

Table 5 (Continued)

Formula 1	Bond length (Å)					Bond angle (°)					References 12
	$S-N^2$	N^2-N^3	N^3-N^4	N^4-C^5	C^5-S	C^5SN^2	SN^2N^3	$N^2N^3N^4$	$N^3N^4C^5$	N^4C^5S	
	1.682	1.284	1.362	1.299	1.734	90	111	116	111	112	1996CHEC-II(4)691
	1.664	1.314	1.380	1.318	1.719	92	109	119	109	112	1996CHEC-II(4)691
	1.631	1.243	1.315	1.307	1.707	92	109	121	109	110	1996CHEC-II(4)691
	1.660	1.308	1.320	1.372	1.783	92.4	107.6	122.7	109.3	108.1	2000JMT105
	1.658	1.298	1.317	1.367	1.777	92.4	107.4	122.8	109.3	108.0	2000JMT105

Bond lengths (Å) and bond angles (°).

N-(2,6-dimethylphenyl)-1,2,3,4-thiadiazol-5-amine <1992JOC1671>, at 175.9 ppm for 5-methyl-1,2,3,4-thiadiazole <1990S415>, at 180.0 for 5-benzylthio-, at 172.0 ppm for 5-benzoylthio-1,2,3,4-thiadiazoles, and at 186.0 ppm for the 3-ethyl-5-phenyl-1,2,3,4-thiadiazolium salt <1984CHEC(6)579>. More data on ^{13}C NMR spectra can be found in Table 6. Interestingly, alkylation at the sulfur atom of 1,2,3,4-thiadiazole-5-thiolate leads to a 13.6 ppm downfield shift of C-5.

Table 6 ^{15}N (^{14}N) NMR shifts relative to CH_3NO_2 and ^{13}C NMR shifts relative to $(\text{CH}_3)_4\text{Si}$ of some 1,2,3,4-thiadiazoles

Structure	N^2	N^3	N^4	C^5	Solvent	Reference
	-39.6	-74.2	-95.2	180.3	CD_3COCD_3	1988BAP79
	-24.7	-66.9	-53.9	201.5	CD_3COCD_3	1988BAP79
	-66.9	-74.1	-90.9	168.0	DMSO-d_6	1988BAP79
	-50.6	-70.9	-81.6	182.0	DMSO-d_6	1988BAP79
	-31.3	-82.8	-82.3	175.4	CDCl_3	1988BAP79
	(69)	(4)	(-25)	194.8	D_2O	2000JA9052
	(74)	(10)	(-17)	181.2	D_2O	2000JA9052
	(40)	(2)	(-118)	191.3	D_2O	2000JA9052

The ^{15}N and ^{14}N NMR spectral data provide important information on the structures of 1,2,3,4-thiadiazoles. Mesoionic 1,2,3,4-thiadiazoles were extensively studied by ^{15}N NMR magnetic resonance techniques. The signal assignments were made based on relationships observed for azoles, selective ^{15}N labeling, ^{14}N signal line width analysis, and ^{15}N - ^1H 2D correlation technique optimized for the long-range coupling constant <1988BAP79>. The aminide spectra consist of four signals in the ranges: -64 to -73(N-2), -74 to -76(N-3), -91 to -93(N-4), and -140 to -152 ppm for the exocyclic nitrogen atom. The exchange of the nitrogen exocyclic group for an ylide group results in a downfield shift of the N-2 signal of 10–40 ppm.

The data collected in Table 6 <1988BAP79> show that the N-2 and N-4 chemical shifts strongly depend on the kind of exocyclic group, whereas the signal of N-3 is less sensitive. ^{14}N NMR shifts were reported for the series of 1,2,3,4-thiadiazole-5-thiols. The spectra show the three peaks which correspond to the ring nitrogen atoms. It was also observed that one of the ring nitrogen peaks in 1,2,3,4-thiadiazole-5-thiol was dramatically shifted upfield with respect to corresponding sodium salt. This indicated the presence of an NH connectivity <2000JA9052>. ^1J (^{13}C - ^{13}C) coupling constants were used for the study of the structure of mesoionic 1,2,3,4-thiadiazoles. The partial double bond character of the C(5)-C(6) bond in methylides, which is formally single, was shown. Theoretical calculations of chemical shifts were also reported <1988BAP79>.

6.09.3.3 Mass Spectrometry

This subject was carefully described in <1996CHEC-II(4)691>. The data on the fragmentation of 10 mesoionic compounds were reported. The major fragmentation pathway was reported to occur via one of the four possible pathways depending on the structure of the molecule. The pathway (a) includes the formation of thionitroxyl radical $\text{NS}^\bullet$ and a daughter ion that undergoes cleavage to give the arendiazonium ion ArN_2^+ . The pathway (b) leads to the thionitroxyl cation NS^+ , (c) involves the formation of the thiocyanate radical $\text{NCS}^\bullet$ and then the RS^+ cation, and fragmentation via pathway (d) leads to the formation of azides RN_3 and isothiocyanate cation-radical $\text{NCS}^{+\bullet}$ <1996CHEC-II(4)691>. The fragmentation of 5-phenyl- and 5-amino-1,2,3,4-thiatriazoles starts from the elimination of a nitrogen molecule and involves the M-N_2^+ and $\text{M-N}_2\text{-S}^+$ ions and the ions of their further degradation, for instance, C_6H_5^+ , $\text{Ph-N}=\text{C}=\text{S}^+$, and C_6H_4^+ for 5-phenyl-1,2,3,4-thiatriazole <1974ACS97>.

6.09.3.4 UV Spectroscopy

UV spectra of 1,2,3,4-thiatriazoles have been reported: λ_{max} , nm (log ϵ): 280 (4.03) for 5-phenyl-1,2,3,4-thiatriazole <1975JA6197>; 291 (26500) and 422 (4.42) for 3-phenyl-1,2,3,4-thiatriazolium-5-bis(ethoxycarbonyl)methylide; 290 (4.30), broad peak around 440 for 3-phenyl-1,2,3,4-thiatriazolium-5-thiolate; and 213 (4.44), 305 (3.14), 377 (4.92) for 3-phenyl-1,2,3,4-thiatriazolium-5-(*N*-methylanilino)iodide <1993MRC447, 2002MI2290>. All mesoionic 1,2,3,4-thiatriazol-5-aminides are colored (red or orange) and absorb in the visible region. An electronic absorption spectrum in the visible region of these compounds contains usually one band with absorption maximum between 400 and 485 nm. The absorption is probably caused by an $n \rightarrow \pi^*$ or charge-transfer transition involving an N-6 lone pair <2000JMT105>.

6.09.3.5 Infrared and Raman Spectroscopy

IR and Raman spectroscopy were widely used by Klapotke and co-workers to elucidate the structure of new derivatives of 1,2,3,4-thiatriazole-5-thiones <1998JFC153, 1999ICA68, 1999PS201, 2000JA9052, 2004IC1370>.

Based on the calculations at the B3LYP/6-311++G* level and experimentally observed vibrational spectra for the ring and chain isomers, compounds **2** and **3**, respectively (see Equation 2), it was concluded that the compounds existed in the cyclic form. The crucial fact is the absence of a stretching band at 2206 cm^{-1} in the experimental spectra that could, according to calculation, be associated with an azido group <1999PS201>. The experimental and theoretically calculated IR and Raman spectral data for 1,2,3,4-thiatriazol-5-thiol derivatives are placed in Table 7.

6.09.3.6 Dipole Moments

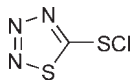
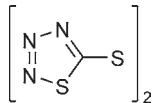
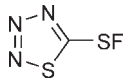
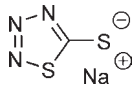
Ab initio calculations of dipole moments for a series of S-containing five-membered heterocyclic compounds, including both isomeric thiatriazoles, have been carried out for their MP2/6-31G** geometries <1998PCA9906>. 1,2,3,4-Thiatriazole was predicted to have a higher dipole moment than the isomeric 1,2,3,5-thiatriazole with the values being respectively 4.08 and 1.66 D according to the MP2/C3 orientation. The data are in accordance with the CHIH-DFT calculations of the dipole moments for 5-amino-1,2,3,4-thiatriazole (5.5846 D) and for 4-amino-1,2,3,5-thiatriazole (2.4755 D) <2005JMT61>. There have been no experimental data of the dipole moments neither for parent 1,2,3,4-thiatriazole nor for 5-amino-1,2,3,4-thiatriazole published in the literature. However, the dipole moments measured by Hanley and co-workers <1978J(P1)600> for mesoionic 1,2,3,4-thiatriazoles are not far from the calculated values (see Figure 5).

6.09.4 Thermodynamic Aspects

In general, 1,2,3,4-triazoles are polar compounds and therefore many derivatives are crystalline although some 5-alkylthiatriazoles are oils.

Chromatographic (LC) separations have been reported although in many cases crystallization is the method of choice to purify the compounds. 1,2,3,4-Thiatriazole derivatives will decompose readily to form nitrogen, sulfur, and an organic fragment, usually a nitrile. The temperature of decomposition is variable, depending on the substitution pattern (see Section 6.09.5.1). In many cases melting of the crystalline thiatriazole derivatives is accompanied with decomposition. Therefore, distilling thiatriazoles is out of the question. Some low molecular weight

Table 7 Experimental and calculated IR and Raman spectra for 1,2,3,4-thiatriazole-5-thiol derivatives

Formula	Experimental		Theoretical	Reference
	IR frequencies (cm^{-1}) (intensity)	Raman frequencies (cm^{-1}) (intensity)	Frequencies (cm^{-1}) (B3LYP/6-311++G*) (intensity)	
	220 s, 275 s, 392 s, 500 w,sh, 540 w,sh, 645 w, 680 m, 905 w, 995 m, 995 m, 1060 m, 1305 s	382(1), 650(4), 675(2), 1012(2), 1071(3), 1331(3)	49(4), 124(3), 218(1), 290(0), 403(2), 502(40), 537(4), 542(1), 644(0), 681(4), 920(5), 1017(20), 1104(98), 1334(160), 1385(3)	1999ICA68
	630 w, 705 w, 909 m, 1017 m, 1070 s, 1342 s	156(4), 236(7), 326(7), 423(4), 475(3), 525(8), 633(10), 700(1), 1009(5), 1335	27(3), 29(9), 43(2), 127(0.5), 144(5), 215(1), 218(1), 243(0.5), 307(1), 411(12), 421(13), 482(2), 519(10), 521(15), 543(1), 554(1), 643(0.5), 647(0.5), 686(1), 689(11), 915(33), 916(2), 1019(0.5), 1020(1.5), 1069(36), 1070(190), 1342(120), 1344(122), 1397(7), 1399(10)	1998JFC153
	221 w, 392 m, 480 w, 520 w, 645 w, 675 w, 728 s, 900 m, 1015 m, 1070 m,br, 1320 w	205(1), 316(1), 415(3), 496(100), 530(2), 650(9), 673(1), 722(1), 904(1), 1015(4), 1073(3), 1333(5), 1360(2)	75(7), 2145(6), 217(0.3), 340(0.2), 409(8), 529(15), 539(1), 639(0.2), 681(5), 724(80), 918(10), 1006(27), 1107(75), 1346(145), 1393(8)	1998JFC153
	632 w, 648 m, 710/720 m, 903 m, 1008 m, 1070/1080 s, 1237 m, 1335 sh, 2170 m	154(5), 254(2), 266(80), 376(3), 498(2), 645(10), 685(3), 717(1), 903(1), 1003(4) 1077(2), 1236(7), 1334(7), 2179(10)	42(0), 111(2), 231(0), 251(3), 373(2), 394(2), 497(6), 561(1), 611(7), 667(0), 711(0), 733(12), 939(12), 1065(3), 1124(100), 1362(71), 1426(2), 2316(5)	2004IC1370

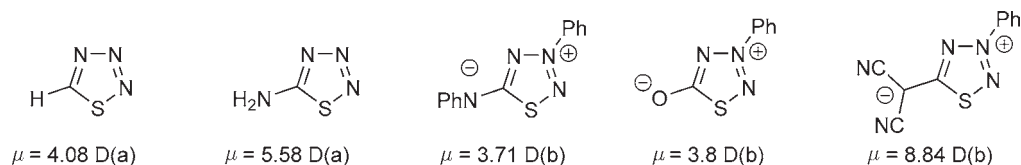
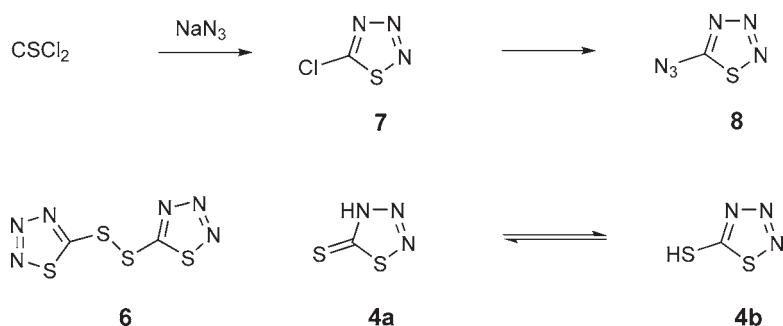


Figure 5 Structures with dipole moments μ (in debye (D)) according to (a) calculated data <1998PCA9906, 2005JMT61> and (b) experimental data <1978J(P1)600>.

1,2,3,4-thiatriazoles are explosive compounds, even at room temperature, and the 5-azido-1,2,3,4-thiatriazole **8** may be the most hazardous among them. This compound may be formed as a by-product in the reaction of thiophosgene with azide anion, normally leading to the 5-chlorothiatriazole **7**, and violent detonation may be observed because of the presence of the azide **8** <1961JOC1644>. The extremely shock-sensitive α,ω -bis(1,2,3,4-thiatriazolyl-5-sulfanyl)-alkanes and the 4,5-maleimide derivative were prepared by Pilgram and co-workers <1965AG348, 1971JHC899>, and the corresponding disulfide **6** may explode even under water.

Quaternization (see Section 6.09.5.3) significantly increases the stability of the 1,2,3,4-thiatriazole ring. Moreover, many mesoionic and imine derivatives are quite stable in comparison with the parent compounds.

Thiatriazole-5-thiol **4b** was described as being in equilibrium with the thione tautomer **4a** (Scheme 2). The thione tautomer is predominant in acetone solution, as is apparent from the ^{13}C NMR spectrum <1977JHC1417>. However, methylation and acylation under basic conditions occur at the sulfur atom. The analogous amino compounds do not occur as the imine tautomers. More data can be found in the earlier reviews <1964AHC263, 1976AHC145>.



Scheme 2

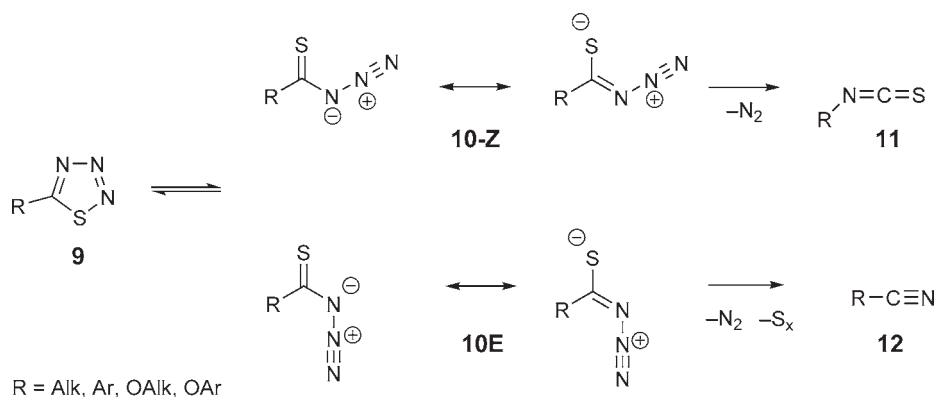
6.09.5 Reactivity of Fully Conjugated Rings

Only a few new works have been published on this subject that were not previously covered in the corresponding chapters of CHEC(1984) and CHEC-II(1996) <1984CHEC(6)579, 1996CHEC-II(4)691>. The most recent work reported the reactions of 1,2,3,4-thiatriazoles leading to mesoionic compounds <1998JMT27>.

6.09.5.1 Thermal Reactions

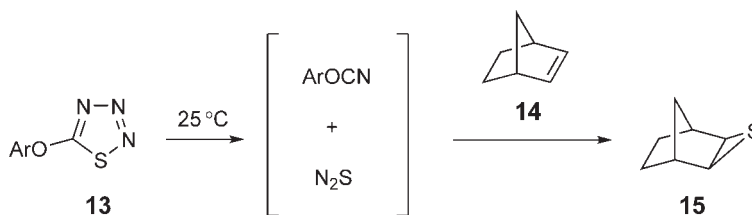
The most common thermal reaction of 1,2,3,4-thiatriazoles **9** is decomposition forming molecular nitrogen, sulfur, and an organic fragment <1984CHEC(6)579, 1996CHEC-II(4)691>. This decomposition may follow different pathways depending on factors such as substituents, solvent, and temperature.

In some cases at higher decomposition temperatures (above 100 °C), isothiocyanates **11** may be formed after concerted Curtius-type decomposition/rearrangement of a (*Z*)-thioacyl azide **10-Z**, while the corresponding (*E*)-isomer would give the nitrile **12** in a Grob-like fragmentation. The nitrenes are formed after nitrogen extrusion from the thioacyl azides, which are the open-chain isomers of the 1,2,3,4-thiatriazoles (Scheme 3).



Scheme 3

The formation of the unstable nitrogen sulfide under pyrolysis conditions was proved to be a major alternative pathway by Wentrup *et al.* <1986JOC1908, 1988JA3458, 1992JPC2065>. More recently, the thermolysis of 5-aryloxy-1,2,3,4-thiatriazoles **13** at room temperature in the presence of strained alkenes **14** was reported to give the episulfidation product **15** in low yield via an S_N2 -like transition state involving simultaneous sulfur addition and dinitrogen extrusion rather than a [3+2] dipolar cycloaddition (Scheme 4) <2001EJO1959, 2003JOC6049>.



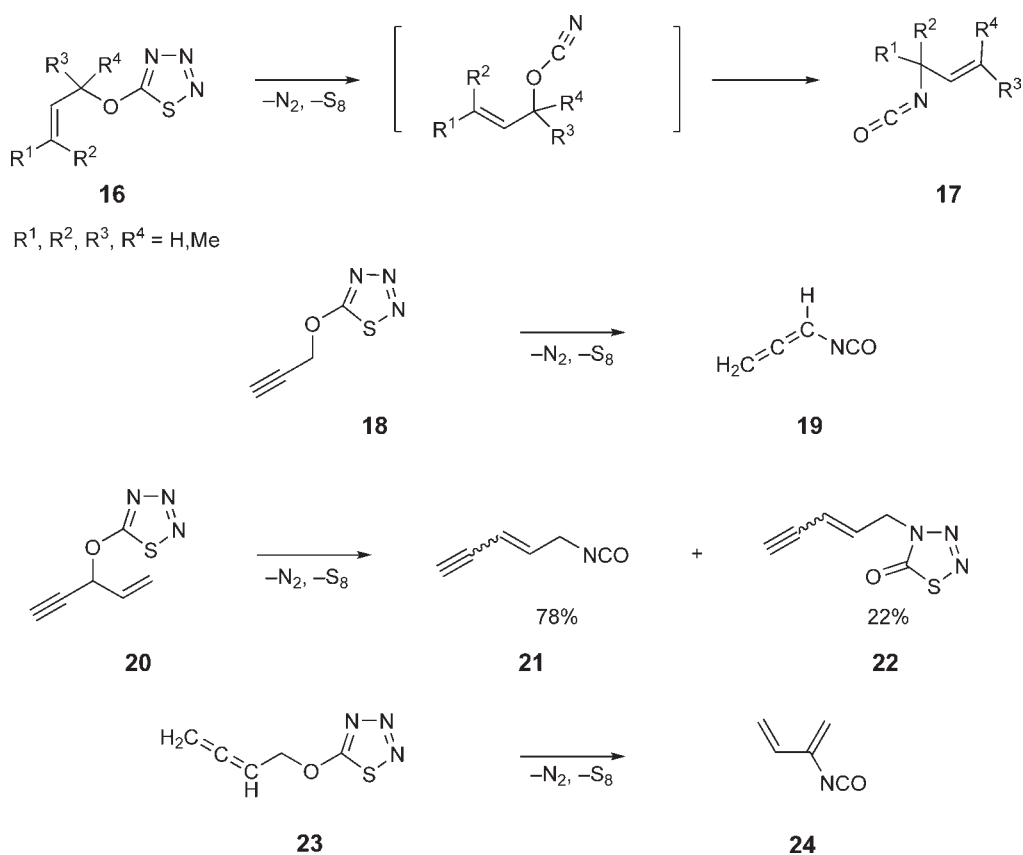
Scheme 4

The rate of the decomposition of compound **9** is dependent on the substituent R, with 5-alkylthiatriazoles being very labile and decomposing at 0 °C. 5-Arylthiatriazoles, on the other hand, may be stored at room temperature for longer times, sometimes several years, without noticeable decomposition. Thiatriazoles with heteroatoms have intermediate thermostability, the latter increasing with increasing donor strenght of the heteroatom: NH > O > S. Synthetically, this may be used for the preparation of (thio)cyanates. 5-Amino-1,2,3,4-thiatriazoles may explode violently upon heating to their melting point, but in solution either cyanamides <1993T4439> or melamine derivatives may be formed <1984CHEC(6)579, 1996CHEC-II(4)691>.

The decomposition reaction leading to cyanates **17**, **19**, **21**, **24** may be used in tandem with [3,3]-sigmatropic rearrangements of allylic, allenic, or propargylic substrates **16**, **18**, **20**, **23**. Banert and co-workers described the formation of allylic isocyanates **17** starting from the corresponding allyloxy-1,2,3,4-thiatriazoles **16**. In the same way, allenyl isocyanates **19** could be formed from the corresponding propargyloxythiatriazoles **18** and an isocyanate derivative of butadiene **24** from an allenylmethoxythiatriazole **23**. The reaction of thiatriazole **20**, from which both allylic and propargylic sigmatropic rearrangement would be possible, led to the exclusive allylic rearrangement and the isocyanate **21** with an enyne moiety was obtained. At the same time, sigmatropic rearrangement without decomposition occurred, leading to a thiatriazol-5-one **22** derivative as the minor product (Scheme 5) <1992AGE866, 2001TL6133>.

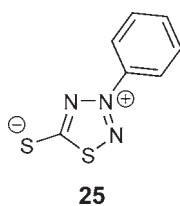
6.09.5.2 Photochemical Reactions

No new data were reported since the last reviews <1984CHEC(6)579, 1996CHEC-II(4)691>. We can only mention the use of the mesoionic thiatriazole derivative **25** to induce refractive index changes in polymer films upon



Scheme 5

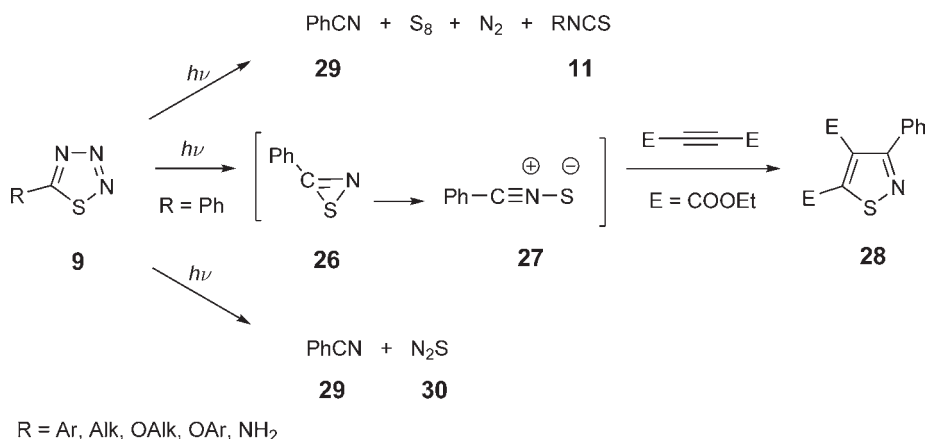
irradiation. The polymethyl methacrylate (PMMA) polymer contained 30 wt.% of this compound and was found to have a significant refractive index change of 0.036 on irradiation with a 450 W lamp. The quantum yield for the photoreaction was 30% but it was not mentioned what the photoproducts were that were obtained under these conditions <2002MI2290>.



From the earlier work <1984CHEC(6)579, 1996CHEC-II(4)691>, it can be summarized that the photochemical decomposition of 1,2,3,4-thiatriazoles is a complex process that generally results, as for thermal reactions, in the formation of nitriles, sulfur, nitrogen, and a small amount (5–10%) of isothiocyanates. However, trapping experiments in the case of 5-phenyl-1,2,3,4-thiatriazole **9** ($R = Ph$) or its alkylated and monooxo derivatives point to the intermediate formation of highly unstable benzonitrile sulfide **27**, via ring opening of the hypothetical antiaromatic thiazirine **26**, affording a small amount of the isothiazole **27** along with benzonitrile **29**. On the other hand, under different photochemical conditions nitrogen sulfide **30** is detected instead of benzonitrile sulfide **27** (Scheme 6).

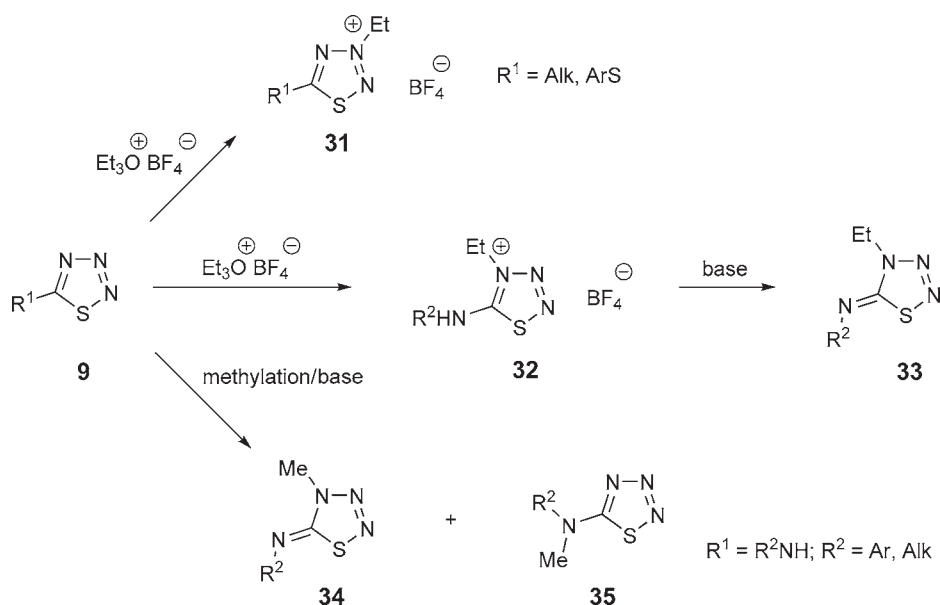
6.09.5.3 Electrophilic and Nucleophilic Attack at Nitrogen

Alkylation of 5-alkyl or 5-(arylsulfanyl)-1,2,3,4-thiatriazoles **9** ($R = Alk, ArS$) with Meerwein's salt produces 3,5-disubstituted thiatriazolium salts **31**, although the 5-amino derivatives **9** ($R^1 = NHR^2$) are exclusively alkylated by



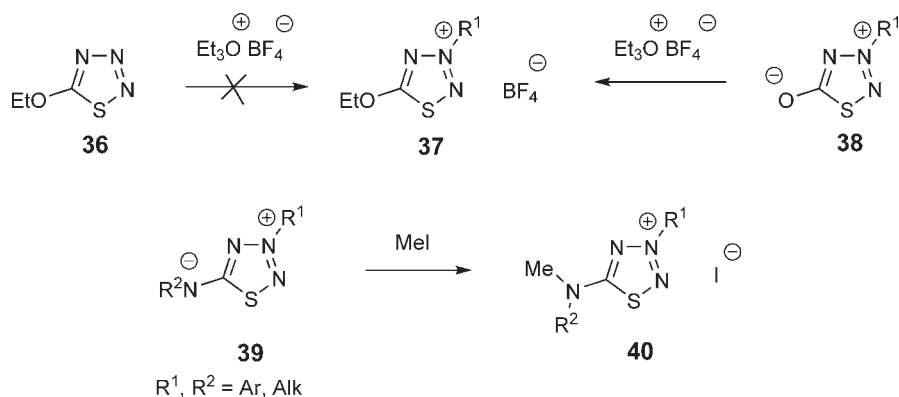
Scheme 6

Meerwein's salt at the 4-position, affording the salts **32**. The latter, on treatment with the weak base sodium bicarbonate, can be converted into the thermally labile imines **33**. The methyl variant of Meerwein's reagent is less specific and in combination with monosubstituted aminothiatriazole mainly gives the corresponding 4-substituted derivative together with a minor amount of the 3-substituted isomer [<1991BSB25>](#). Methylation of 5-aminothiatriazoles with diazomethane or methyl sulfate, in the latter case followed by treatment with base, gives mixtures of the imines **34** and the thiatriazoles **35** alkylated at exocyclic nitrogen ([Scheme 7](#)).



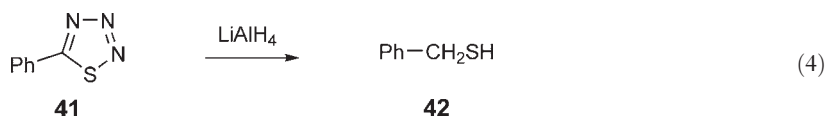
Scheme 7

5-Ethoxy-3-alkylthiatriazolium salts **37** cannot be obtained from the corresponding 5-ethoxythiatriazole **36** which instead decomposes under the reactions conditions. Alkylation of the mesoionic olate **38**, however, gives access to this compound. In the same way, the aminide derivatives **39** can be alkylated to give the ammonium salts **40** ([Scheme 8](#)) [<1998JMT27>](#).



Scheme 8

Otherwise, the 1,2,3,4-thiatriazole ring is chemically rather inert, for example, surviving treatment with alcoholic base, under chlorination, and nitration conditions. An exception is the reduction of 5-phenyl-1,2,3,4-thiatriazole **41** with LiAlH_4 to give benzylthiol **42** (Equation 4) <1964AHC263>.



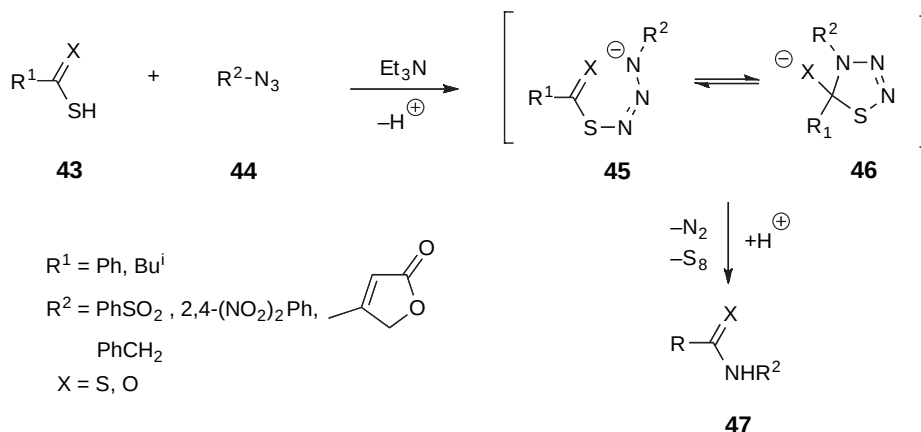
6.09.6 Reactivity of Nonconjugated Rings

The reactivity of the nonconjugated 1,2,3,4-thiatriazole derivatives is determined by the energy that is gained after liberation of stable fragments such as nitrogen, nitrogen sulfide, and molecular sulfur.

6.09.6.1 Thermal Reactions

6.09.6.1.1 Δ^2 -1,2,3,4-Thiatriazolines

1,2,3,4-Thiatriazolines have been described as transient intermediates in the synthesis of thioamides under mild conditions <2006TL1163>. The outcome of the reaction of dithioacids **43** ($\text{X} = \text{S}$) with electron-deficient organic azides **44** depends on the reaction conditions. When triethylamine was used as the base, thioamides **47** were formed (Scheme 9). Electron-rich azides (e.g., benzyl azide) need significantly longer times for conversion, and the yield is

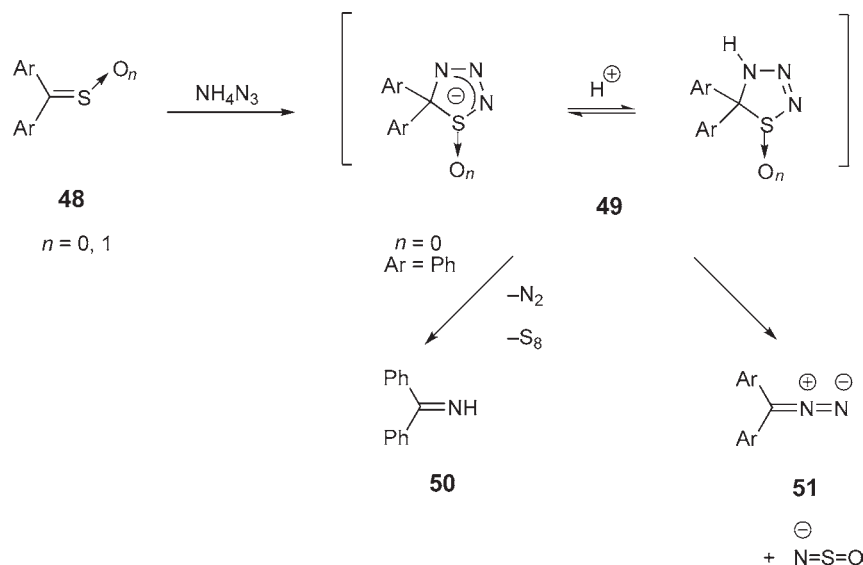


Scheme 9

lower. The authors suggest that no concerted 1,3-dipolar cycloaddition takes place, but rather a nucleophilic addition pathway, followed by cyclization of an intermediate triazenyl anion **45** to a thiatriazoline intermediate **46**, which loses nitrogen and sulfur to form the thioamide **47**. The presence of the intermediate **46** was supported by ESI mass spectra, in which one of the fragments was dinitrogen sulfide <2006TL1163>.

The previously described amidation reaction starting from thioacids **43** ($X = O$) but using 2,6-lutidine as the base is thought to occur in the same manner <2003JA7754>.

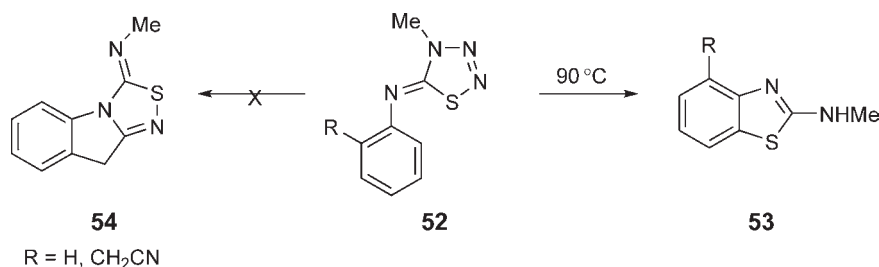
Previously, thermally unstable 1,2,3,4-thiatriazolines **49** were mentioned as intermediates in the reaction between inorganic azide and thiobenzophenone or substituted thiobenzophenone oxides **48**. The products of the two different decomposition reactions are, respectively, benzophenone imine **50** and diaryldiazomethanes **51** (Scheme 10) <1976ACA997>.



Scheme 10

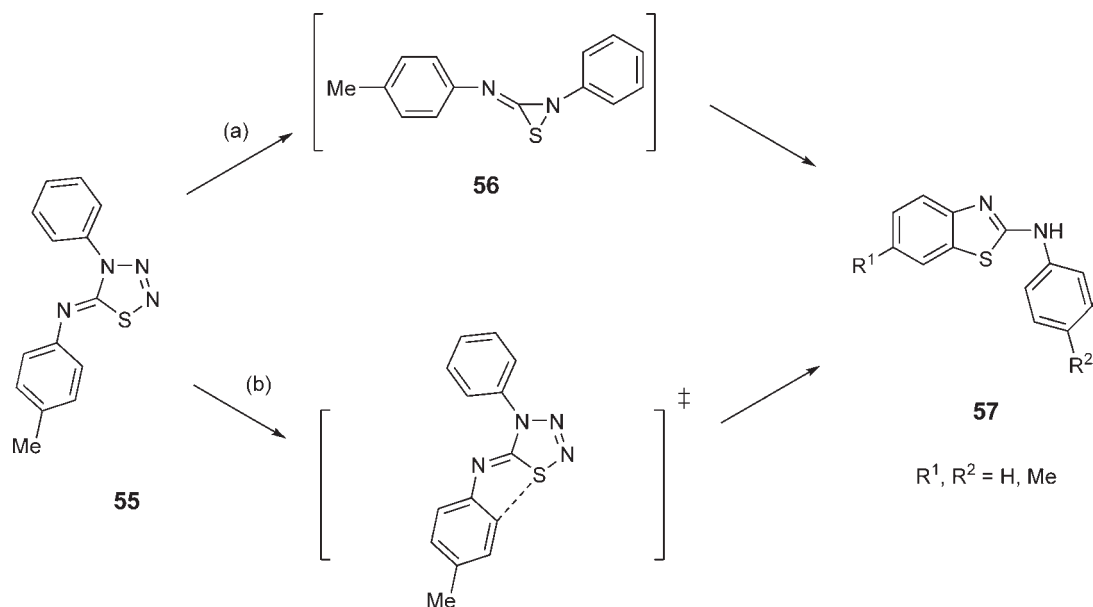
6.09.6.1.2 5-Imino- Δ^2 -1,2,3,4-thiatriazolines

4-Alkyl- Δ^2 -1,2,3,4-thiatriazolines **52** decompose on heating above 90°C to form benzothiazole derivatives **53** <1971AP687, 1977JOC1159>. The (2'-cyanomethyl) derivative **10** ($\text{R} = \text{CH}_2\text{CN}$) decomposes at 90°C to the 2-(methylamino)benzothiazole derivative **52** rather than to the fused 1,2,4-thiadiazolimine **54** that would have been expected as the result from an intramolecular 'masked 1,3-dipolar' (see Section 6.09.6.2) cycloaddition (Scheme 11) <1992J(P1)181>.



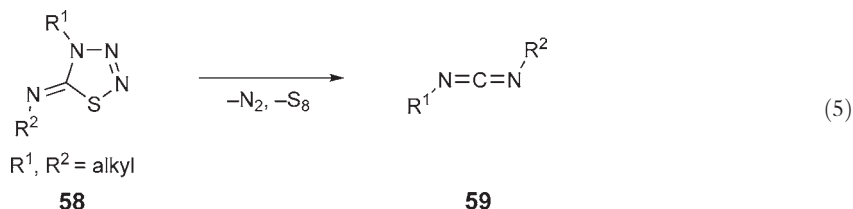
Scheme 11

4-Phenyl-5-arylimino-1,2,3,4-thiatriazolines **55** also gave benzothiazoles **57** on heating <1990JHC923>, L'abbé and co-workers suggested that two pathways (a) and (b) could operate either via a thiaziridineimine intermediate **56** or via a concerted pathway. From product analysis (for the *N*-*p*-tolyl derivative of **57**), it was concluded that both mechanisms occur in a 1:2 ratio (Scheme 12) <1990JHC923>.



Scheme 12

The related 4-alkyl-5-alkylimino-1,2,3,4-thiatriazoles **58** are much less stable than the corresponding aryl derivatives **52** and **55**, and liberate nitrogen and sulfur to give the carbodiimides **59** in low yields (Equation 5). In many cases heterocumulenes **59** participate in consequent masked 1,3-dipolar reactions (see Section 6.09.6.2) with a second equivalent of compound **58** leading to complex reaction mixtures and explaining the low yields <1978J(P1)1440>.

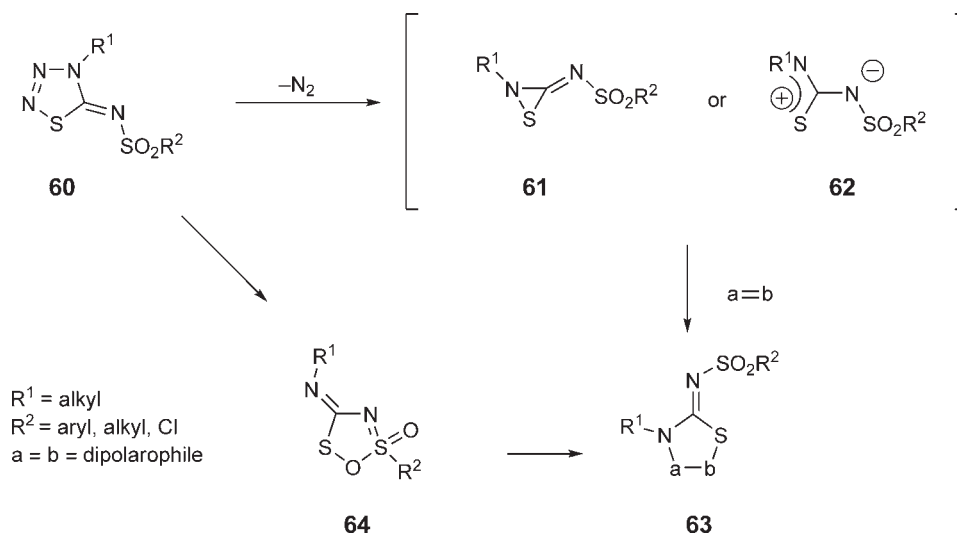


Iminothiatriazoles **60** with electron-poor substituents (e.g., arylsulfonyl) undergo decomposition reactions with a different outcome at relatively low temperatures (60°C). After loss of nitrogen the reactive intermediate present was postulated to have either a thiaziridinimine or 1,3-dipolar structure (respectively **61** and **62**). In the absence of a reaction partner, sulfur is lost and a carbodiimide **59** is again formed. However, different dipolarophile reagents $a = b$ can be added *in situ* to trap the intermediate **61/62**, affording different five-membered heterocyclic rings **63** often with high regioselectivity (Scheme 13). The reaction follows first rate kinetics, proving the decomposition of compound **60** to be the rate-determination step. This subject was already covered extensively in CHEC-II(1996) and since then no new work has appeared <1996CHEC-II(4)691>.

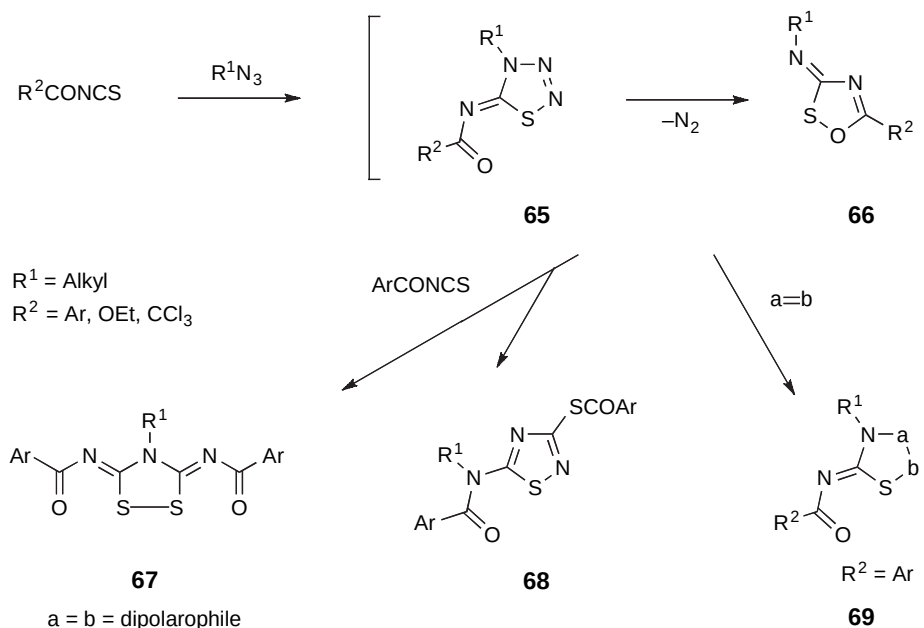
An alternative explanation for the formation of intermediate **61/62** at relatively low temperature is the anchimeric assistance offered by the sulfonyl group in the precursor **60**. The intermediate oxadithiazolimine **64** then collapses to **61/62** (Scheme 13). The analogous 5-acyliminothiatriazoles **65**, products from the reaction between azides and acyl isothiocyanates, cannot be isolated but decompose directly to reactive oxathiazolimines **66**, which then undergo further reactions, leading to the dithiazolimine **67** and 1,2,4-thiadiazole **68**, or the products **69** of masked 1,3-dipolar cycloadditions (Scheme 14) <1979BSB245, 1992JHC17>.

6.09.6.1.3 Δ^3 -1,2,3,4-Thiatriazolines

No new reactions have been reported since the first report <1978JOC2500>.



Scheme 13

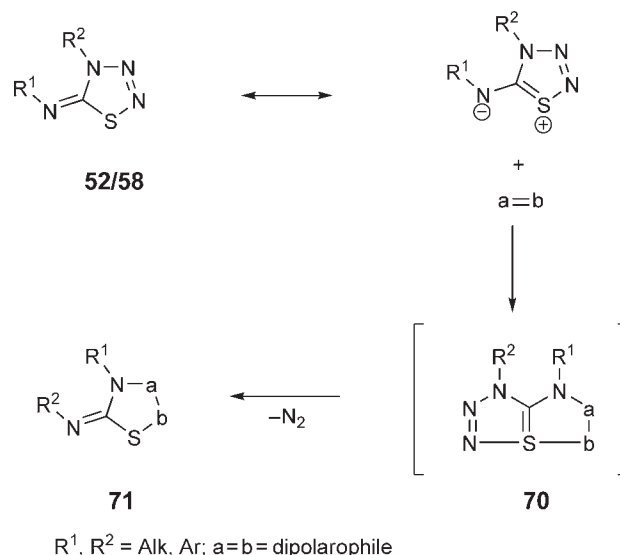


Scheme 14

6.09.6.2 Reactions of Δ^2 -1,2,3,4-Thiatriazolines

6.09.6.2.1 Bimolecular reactions of Δ^2 -1,2,3,4-thiatriazolines

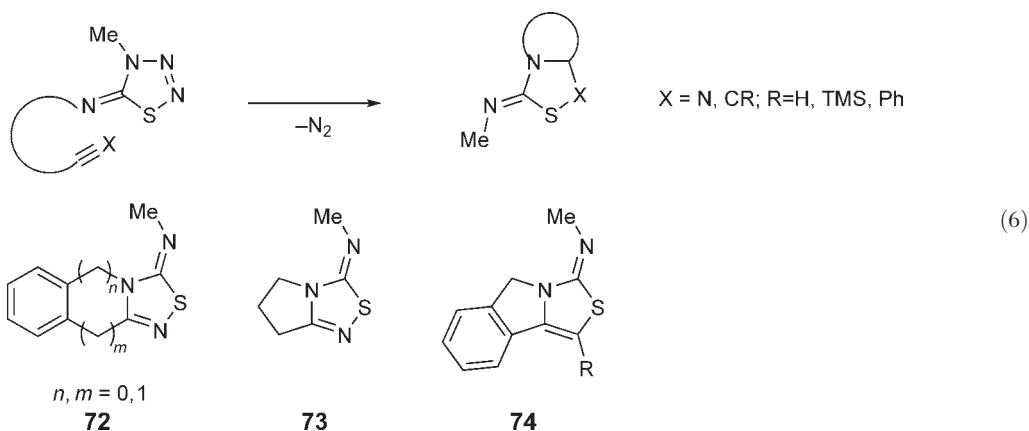
Reaction kinetics for the interaction of 5-alkyliminothiatriazoles **52** or **58** with heterocumulenes, nitriles, ketones, imines, or other dipolarophiles $a=b$ show that the decomposition of the thiatriazole is bimolecular, and new heterocyclic five-membered rings **71** are formed (Scheme 15). The term ‘masked 1,3-dipolar cycloaddition’ was used by L’abbé and co-workers for this type of reaction <1978JOC4951>, the thioimide function being the masked 1,3-dipole. The reaction is thought to involve a thiapentalenic intermediate **70** with hypervalent sulfur. The product **71** is itself a masked dipole and often further reactions take place.



Scheme 15

These complex cycloaddition reactions have been reviewed extensively in CHEC-II(1996) <1996CHEC-II(4)691> and practically no new data on this subject have appeared since then.

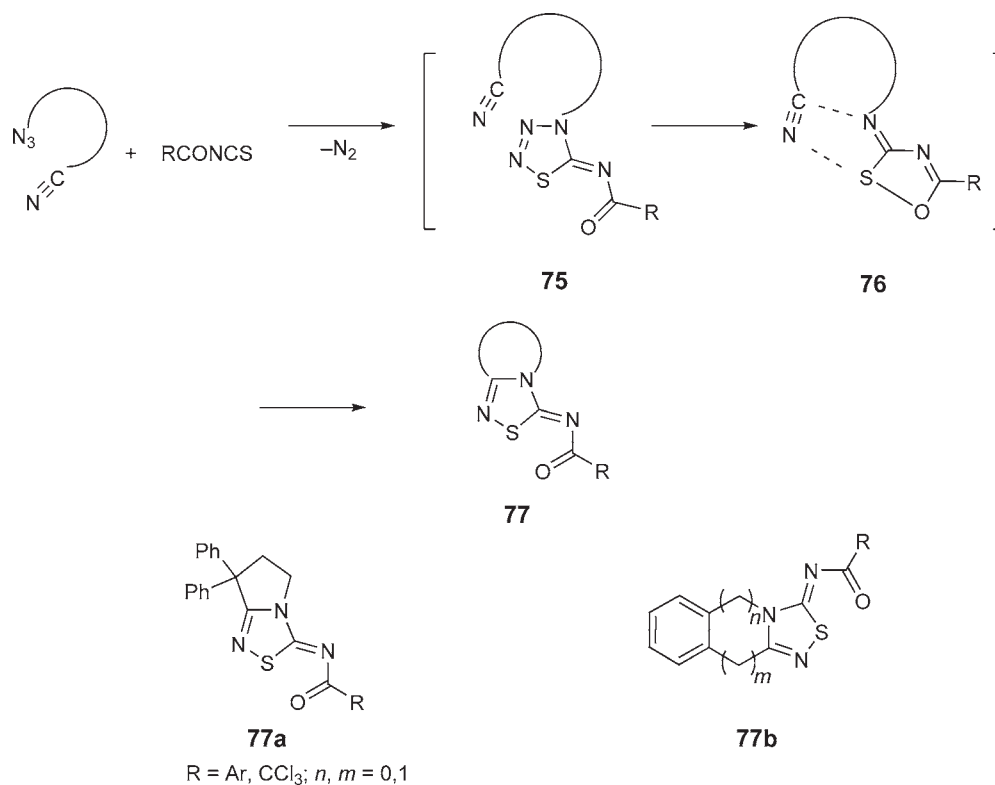
An interesting case worth mentioning is the intramolecular variant, leading to fused N, S-containing heterocycles. In this case nitriles, alkynes, or electron-poor alkenes were the dipolarophiles <1992J(P1)181, 1992T7505, 1993T4439>. A few representative examples of the reaction products **72–74** are given in (Equation 6).



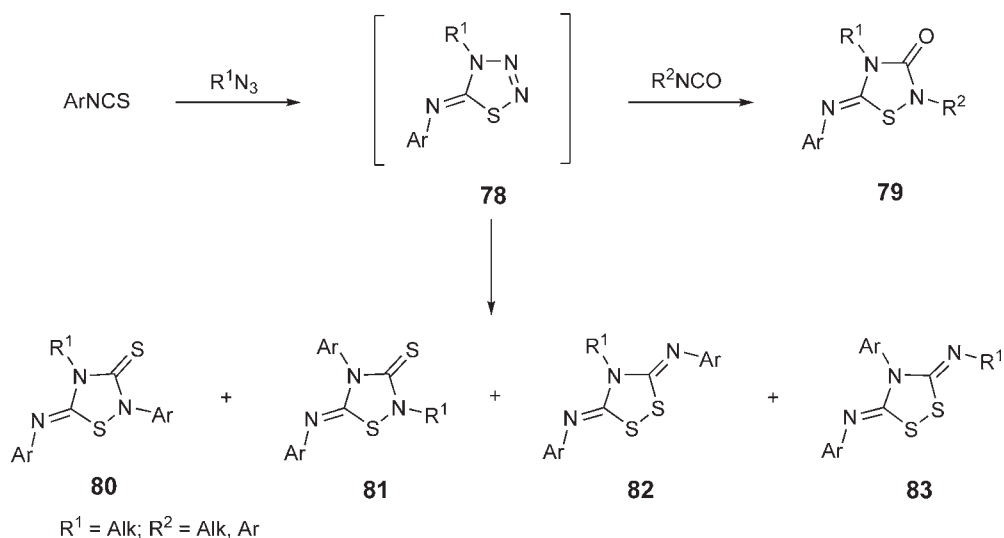
6.09.6.2.2 Bimolecular reactions of Δ^2 -thiadiazolines formed *in situ*

The reaction of acyl isocyanates and ω -cyano alkylazides affords fused products via the postulated thiadiazoline intermediate **75**. Then, the masked 1,3-dipole oxathiazoline **76** is generated, and intramolecular reaction takes place, affording the fused 1,2,4-thiadiazole derivatives **77** (Scheme 16) <1993J(P1)27>.

An interesting three-component reaction of aryl isothiocyanates, alkyl azides, and isocyanates leads to 5-arylimino-1,2,4-thiadiazolidin-3-ones **79** <1976AG510>. Given the current interest in multicomponent reactions, it is perhaps surprising that there have been no further reports on this reaction. One reason may be the long reaction times (7 days at 80 °C) due to the low reactivity of the aryl isothiocyanates toward alkyl azides. The second step, the masked 1,3-dipolar cycloaddition of isocyanate to the intermediate **78** prepared in an alternative way, was found to occur readily at room temperature. In the absence of isocyanate reagent, a more complex reaction mixture is found, containing products **80–83** from cycloaddition/cycloelimination reactions with additional equivalents of isothiocyanate (Scheme 17) <1977JOC1159>.

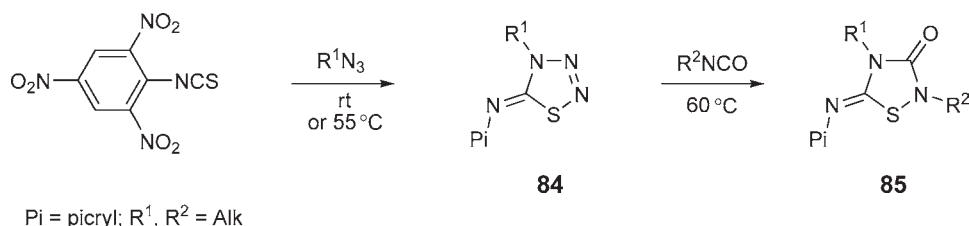


Scheme 16



Scheme 17

The very electron-poor picryl isothiocyanate in fact gives very stable thiatriazoline adducts **84** (decomposition temperature $>100^\circ\text{C}$) with alkyl azides (room temperature, 3 days or at 55°C , 6–24 h). On the other hand, the reaction of products **84** with alkyl or aryl isocyanates is substantially slower and needs 60°C (24 h) to take place (Scheme 18). The reaction follows second-order kinetics, and thus is following the masked 1,3-dipole route rather than the thiaziridinimine route [<1990JHC1059>](#).



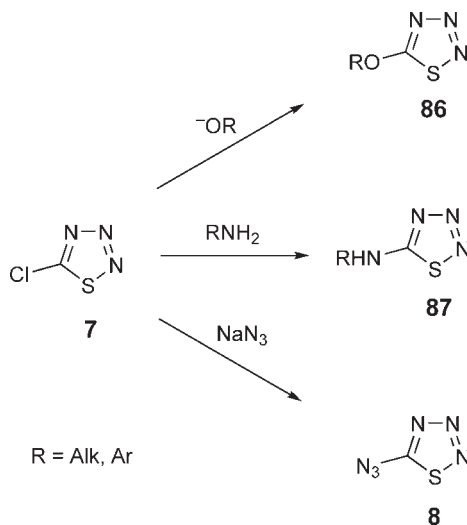
Scheme 18

6.09.7 Reactivity of Substituents Attached to Ring Carbon Atoms

6.09.7.1 1,2,3,4-Thiadiazoles

6.09.7.1.1 5-Chloro-1,2,3,4-thiadiazole

In principle, the 5-chloro-1,2,3,4-thiadiazole **7** is an ideal precursor toward 5-substituted thiadiazoles via nucleophilic substitution with alcoholates [<1992AGE866, 2001TL6133>](#) and amines [<1961JOC1644>](#), respectively, resulting in the formation of a 5-alkoxy- **86** and 5-amino- **87** derivatives (Scheme 19). Unfortunately, 5-chloro-1,2,3,4-thiadiazole **7** has also been reported to be highly explosive, so alternative ways to prepare these derivatives (see Section 6.09.9 on ring synthesis) should be considered whenever possible. Nucleophilic substitution with azide anion gives rise to a product, presumed to be the 5-azido-1,2,3,4-thiadiazole **8**, detonating as a suspension in water [<1961JOC1644>](#).

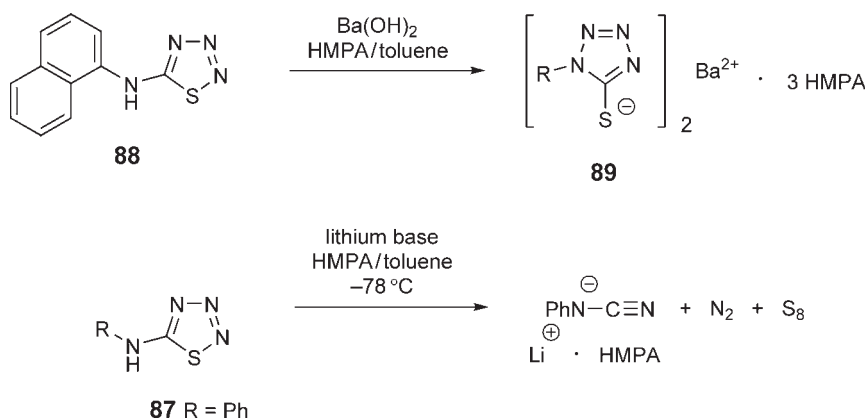


Scheme 19

6.09.7.1.2 5-Amino-1,2,3,4-thiadiazoles

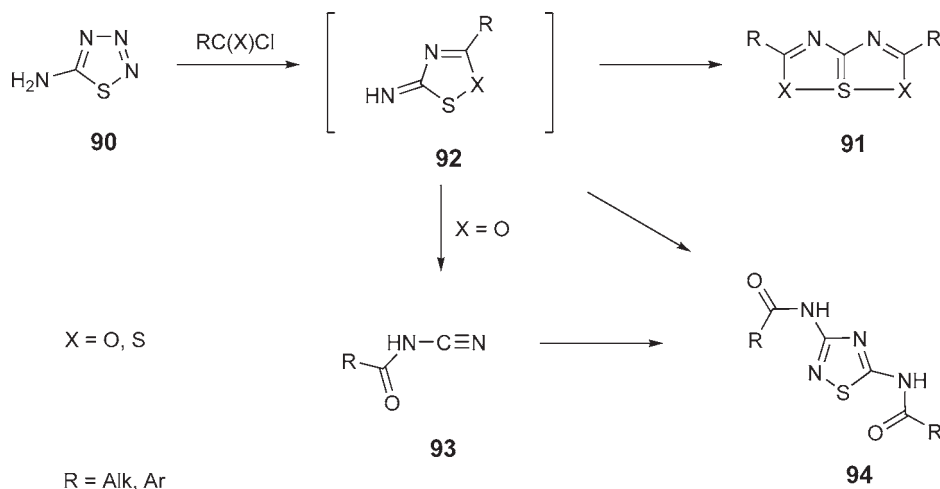
5-Amino-1,2,3,4-thiadiazoles are readily available starting materials and can be transformed into a number of N,S-containing heterocycles.

The Dimroth rearrangement of 5-aminothiadiazoles in the presence of a base gives rise to the formation of tetrazole-5-thiolates, although partial cycloreversion to azide anion and isothiocyanate can also occur. The most recent reports on this reaction were by Snaith and co-workers [<1992CC1152, 1993AG1801>](#). 5-Naphthylamino-1,2,3,4-thiadiazole **88** was treated with 1 equiv of barium hydroxide in the presence of hexamethylphosphoramide (HMPA) as a cosolvent. The corresponding barium 1,2,3,4-tetrazole-5-thiolate **89** crystallized as a complex with three molecules of HMPA, and an X-ray structure was obtained in this case. On the other hand, when the 5-phenylamino derivative **87** ($\text{R} = \text{Ph}$) was treated with lithium bases (LiOH , LiOMe , LiNH_2 , Pr_2NLi , or BuLi) at low temperature in toluene, the lithium salt of phenylaminonitrile was obtained as a HMPA solvate, after base-induced extrusion of molecular nitrogen and sulfur (Scheme 20) [<1993AG1801>](#).



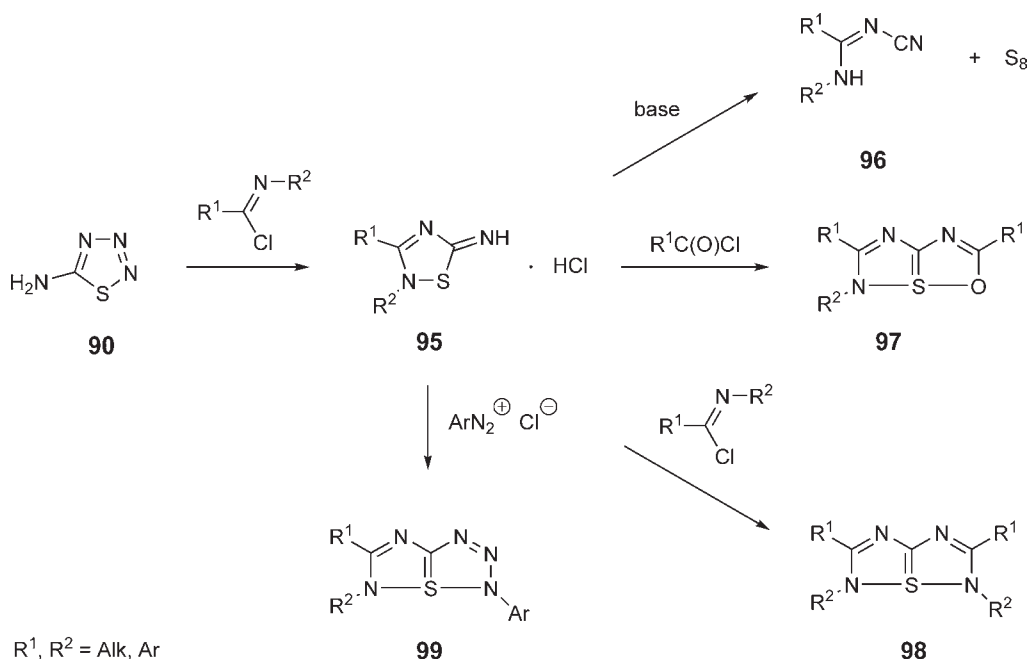
Scheme 20

The parent 5-amino-1,2,3,4-thiadiazole **90** reacts with different electrophiles, affording interesting new heterocycles. For instance, reaction of compound **90** with acid chlorides in the presence of a weak base, such as pyridine or triethylamine, yields dioxathiadiazapentalenes **91** (X = O) with hypervalent sulfur [\[1977AG420, 1977CC143\]](#). In a similar manner, thiobenzoyl chloride in combination with compound **90** affords trithiadiazapentalenes **91** (X = S), albeit in lower yields [\[1981BSB89\]](#). With some acid chlorides or in the absence of base, the bisamide derivatives **94** of 1,2,4-thiadiazole-3,5-diamine may be formed as the by-products [\[1981BSB89\]](#), or as the only product [\[1977CC143\]](#). It has been proposed that the intermediate oxathiazolimine **92** could decompose to cyanamide **93** before the second acylation on its exocyclic nitrogen, and then masked 1,3-dipolar cycloaddition of compound **93** with a second equivalent of oxathiazole derivative **92** (X = O) may give the 1,2,4-thiadiazole **94** (Scheme 21) [\[1981BSB89\]](#).



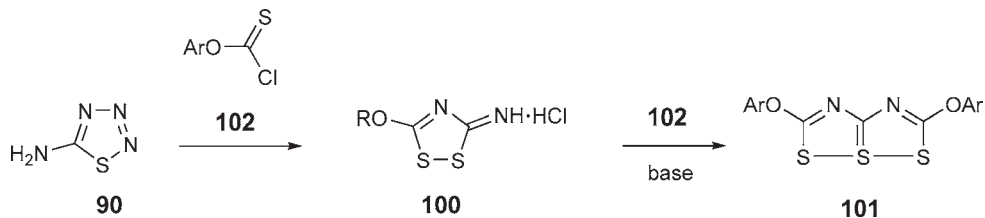
Scheme 21

The reaction of compound **90** with imidoyl halides without added base gives the hydrochloride salts of 1,2,4-thiadiazol-5-imines **95**. The corresponding free bases can be liberated from the salts **95** with weak bases such as bicarbonate, but these imines are labile and decompose readily to form the *N*-cyanamide **96** and sulfur. The free base can be treated *in situ* with a second electrophile, such as an acid chloride, imidoyl chloride, or aryldiazonium salt, affording pentalene derivatives **97–99**. It should be noted that the compound **98** cannot be prepared in a one-pot procedure from compound **90** and 2 equiv of imidoyl chloride in the presence of base, in contrast to the corresponding dioxo compound **91** (Scheme 22) [\[1981BSB89, 1992JHC1317\]](#).



Scheme 22

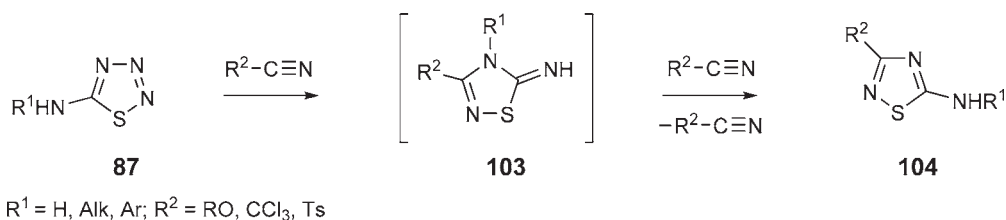
Graubaum and co-workers described the reactions of chlorothioformates **102** with 5-aminothiadiazole **90**. Depending on the reaction conditions different products are formed. In the presence of a base, the main product is the trithiadiazapentalene **101**, but in the absence of a base the dithiazolinimine hydrochlorides **100** are obtained (Scheme 23) <1989M997, 1990JPR208>. Thus, the reactivity of chlorothioformates is intermediate between that of acid chlorides and imidoyl chlorides.



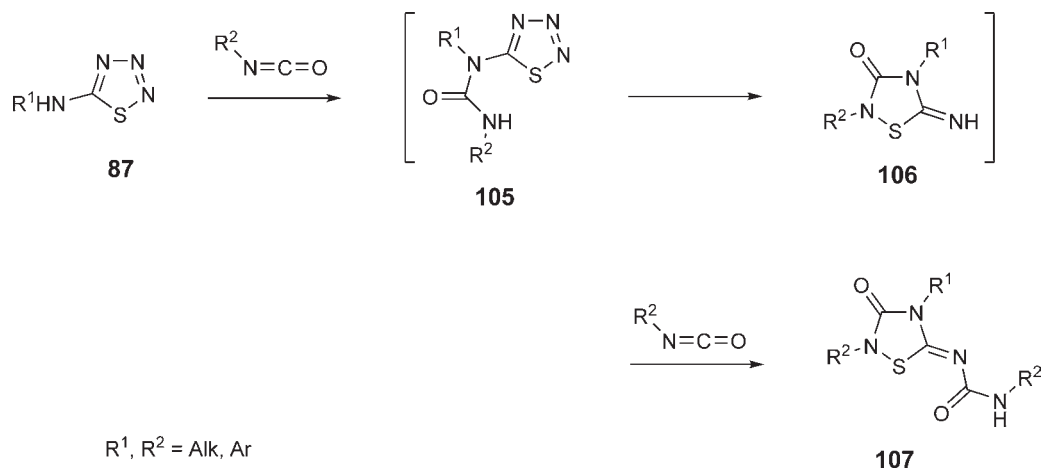
Scheme 23

Electron-poor nitriles react with compound **87** and its derivatives to form the 5-amino-1,2,4-thiadiazole derivatives **104** <1985JOC1295>. Therefore, the formation of product **94** (see Scheme 21) may be explained alternatively by the addition of amidonitrile **93** to compound **90**. The mechanism of the formation of product **104** was discussed in detail in CHEC-II(1996) <1996CHEC-II(4)691> but most probably the steps involved are: (1) reaction of the electrophilic nitrile with the exocyclic nitrogen of compound **87** or its derivatives; (2) loss of nitrogen similarly to the previous reactions and formation of an imine **103**; (3) masked 1,3-dipolar cycloaddition/elimination reaction of the nitrile to the imine **103**. Since the same nitrile is expelled in the elimination step, only 1 equiv of reagent is needed (Scheme 24).

The reaction of 5-amino-1,2,3,4-thiadiazoles **87** with isocyanates gives a 1:2 adduct to which structure **107** was assigned. The reaction is catalyzed by triethylamine. Again, the addition to the exocyclic nitrogen (product **105**), the imine **106** formation, and the addition of a second equivalent of reagent are involved (Scheme 25) <1979JOC3840, 1991JHC1619, 1992JOC1671>.

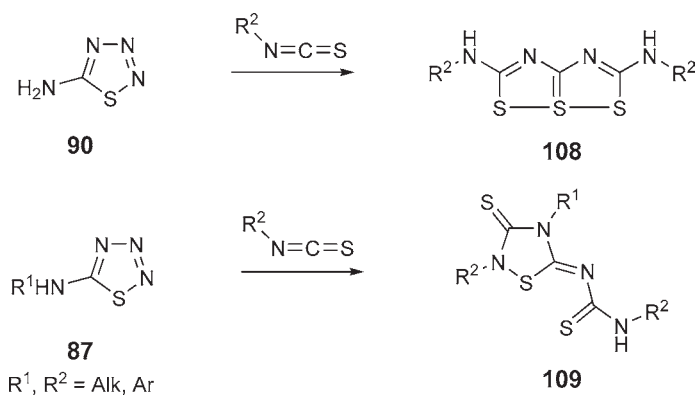


Scheme 24



Scheme 25

Isothiocyanates react much slower with aminothiatriazoles **87** and require the presence of 4-dimethylaminopyridine (DMAP) as a basic catalyst [\[1989JPR115, 1992JOC1671\]](#). In the case of the parent compound **90**, trithiadiazapentalenes **108** are formed. The substituted 5-aminothiatriazoles ($R = \text{alkyl or aryl}$) **87** are more reactive and afford thiourea derivatives **109** in the reaction with 2 equiv of isothiocyanates ([Scheme 26](#)).

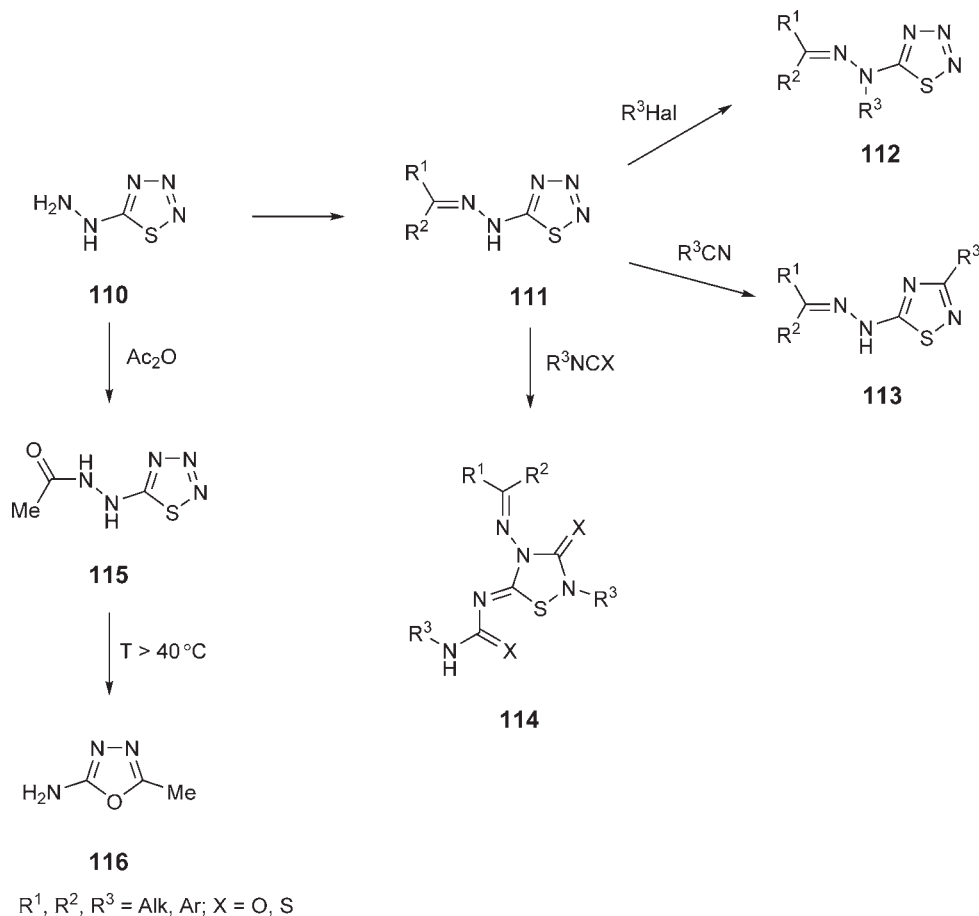


Scheme 26

Other reactions of 5-amino-1,2,3,4-thiatriazoles have been described in CHEC(1984) and CHEC-II(1996) [\[1984CHEC\(6\)579, 1996CHEC-II\(4\)691\]](#).

6.09.7.1.3 5-Hydrazino-1,2,3,4-thiatriazoles

Fairly stable hydrazones **111** are formed from 5-hydrazino-1,2,3,4-thiatriazole **110** and ketones or aldehydes. The hydrazones **111** can be alkylated to form compounds **112** or react further with electrophilic nitriles or iso(thio)cyanates in the same fashion as the 5-amino-1,2,3,4-thiatriazole affording derivatives **113** and **114**, respectively. It is noteworthy that all these reactions of the hydrazones occur at the exocyclic nitrogen adjacent to the ring, rather than on N-4 or the other hydrazone nitrogen <1987JPR409, 1989JPR115>. The hydrazine derivative **110** can be acetylated with acetic anhydride at the terminal nitrogen to afford product **115**, which extrudes molecular nitrogen and sulfur on gentle heating above 40 °C forming oxadiazole derivative **116** (Scheme 27) <1985ZC136>.



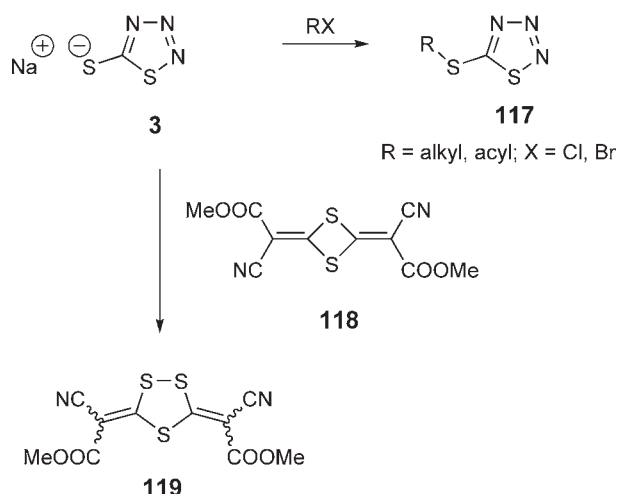
Scheme 27

6.09.7.1.4 1,2,3,4-Thiatriazole-5-thiol and its derivatives

In earlier work <1984CHEC(6)579, 1996CHEC-II(4)691> there has been a discussion about the structure of the alkylation and acylation products of 1,2,3,4-thiatriazole-5-thiol **4**. Finally, it was shown by NMR measurements <1974JOC3770> and independent synthesis <1971ACS2015> that in both cases the product **117** is functionalized at sulfur rather than at nitrogen. L'abbé and co-workers used the 1,2,3,4-thiatriazole-5-thiolate anion as a sulfur transfer reagent for the ring expansion of desaurins **118** to trithiolate derivatives **119** (Scheme 28) <1984BSB405>.

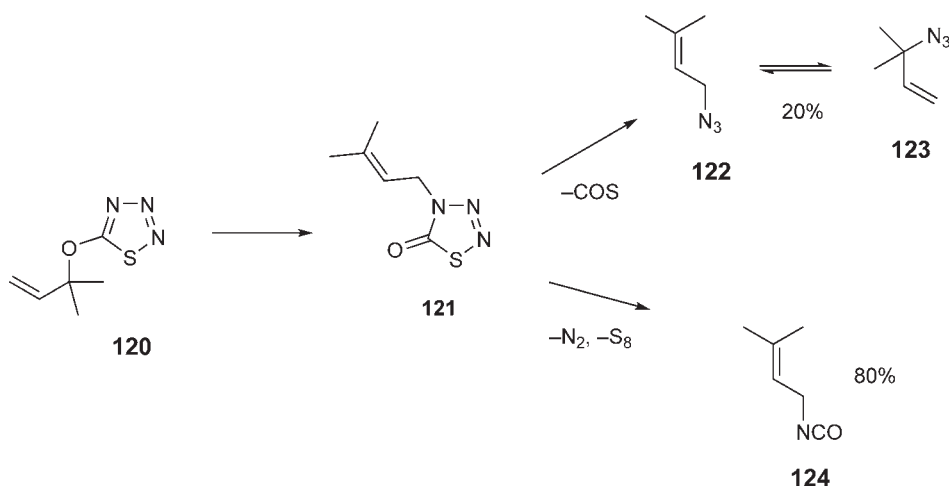
6.09.7.1.5 5-Alkoxy-1,2,3,4-thiatriazoles

The 5-allyloxy-1,2,3,4-thiatriazoles and some analogues can decompose with the formation of intermediate cyanates that undergo [3,3]-sigmatropic rearrangement to isocyanates as described in Section 6.09.5.1. Banert reported that the [3,3]-sigmatropic rearrangement of the dimethylallyloxy derivative **120** could occur before the decomposition,



Scheme 28

affording a relatively stable 1,2,3,4-thiatriazol-5-one **121**. On prolonged heating of compound **121** at 100 °C, the fragmentation products prenyl azide (mixture of isomers **122** and **123**) and prenyl isocyanate **124** were formed in a 4:1 ratio, after the extrusion of carbonyl sulfide or molecular nitrogen and sulfur. Other examples were reported for the reaction of propargyl/allenyl derivatives **120** (Scheme 29) <1992AGE866, 2001TL6133>.

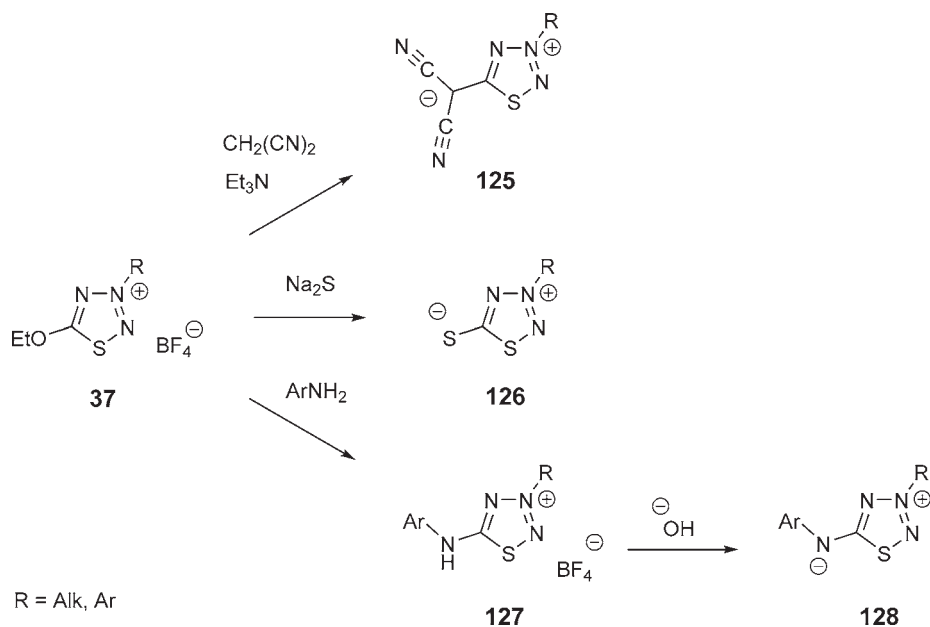


Scheme 29

6.09.7.2 Mesoionic 1,2,3,4-Thiatriazoles

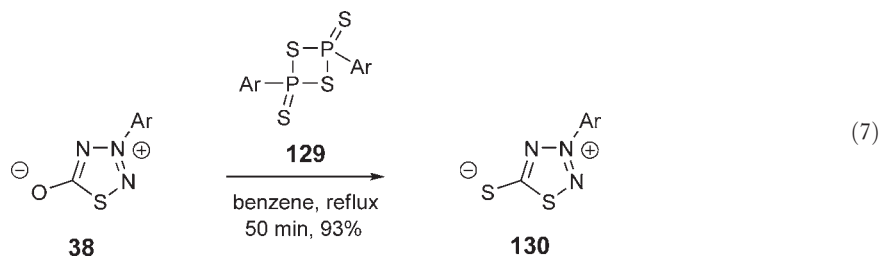
6.09.7.2.1 Reaction with nucleophiles

5-Ethoxy-1,2,3,4-thiatriazolium tetrafluoroborate **37** reacts with malononitrile and triethylamine to give a stable and highly polar (dipole moment 8.8 D) 5-dicyanomethylide **125** by nucleophilic substitution <1979J(P1)744, 1998JMT175>. Other active methylene compounds such as ethyl acetoacetate, dibenzoylmethane, and ethyl cyanoacetate yield similar ylides. The carbonyl-containing analogues of compound **125** have a nearly linear $\text{N}-\text{S}\cdots\text{O}$ angle <1998JMT175>. In the same way, sodium sulfide or anilines can be used as the nucleophile, affording thiatriazolium sulfides **126** <1979J(P1)732> and aminides **128**, respectively. The latter compounds **128** are formed upon treatment of the initially formed salts **127** with a base (Scheme 30) <1979J(P1)741, 1998JMT27, 2000JMT105>.



Scheme 30

Sulfide **130** can be alternatively prepared in 93% yield by treatment of 3-phenyl-1,2,3,4-thiatriazolium-5-olates **38** with Lawesson's reagent (2,4-bis(4-methoxyphenyl)-1,3-dithiaphosphetane-2,4-disulfide) **129** (Equation 7) <1988BCJ2977>.

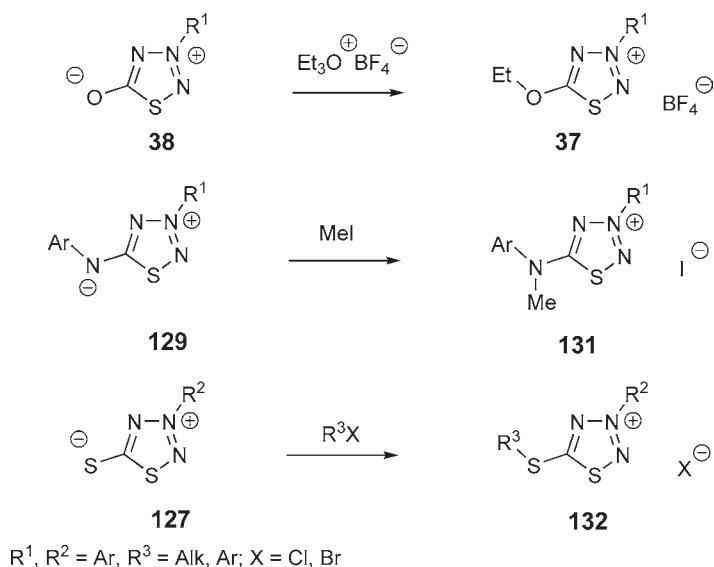


6.09.7.2.2 Reaction with electrophiles

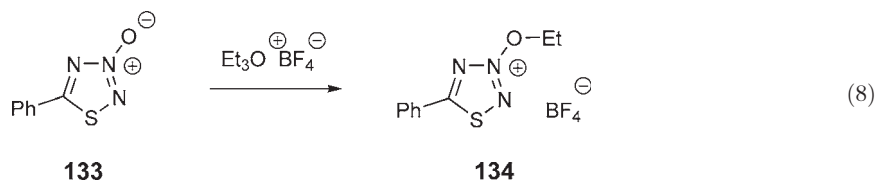
Alkylation of 3-aryl-1,2,3,4-thiatriazolium-5-olates **38** with triethyloxonium tetrafluoroborate leads to 5-ethoxy substituted thiatriazolium salts **37** (R = Ar) <1975T1783>. In the same manner, the aminides **129** react with iodo-methane to afford the thiatriazolium salts **131** with disubstitution at the exocyclic nitrogen (Scheme 31) <1998JMT27>. Also the mesoionic compounds **127** are readily alkylated with different alkylating agents <1997MRC124>.

6.09.8 Reactivity of Substituents Attached to Ring Heteroatoms

Only a few reports in the literature are relevant to this section. Notable is the *O*-alkylation reaction of the 3-oxide of 5-phenyl-1,2,3,4-thiatriazole **133** yielding the 3-ethoxy-1,2,3,4-thiatriazolium salt **134** (Equation 8). The 3-oxide **133** can be regenerated by treatment of salt **134** with nucleophiles. 5-Phenyl-1,2,3,4-thiatriazole is formed as the side product in this reaction <1975JOC431>. In a similar way, 3-substituted 5-phenyl-1,2,3,4-thiatriazolium salts regenerate the 5-phenyl-1,2,3,4-thiatriazole on treatment with alkali hydroxide <1975JOC431>.



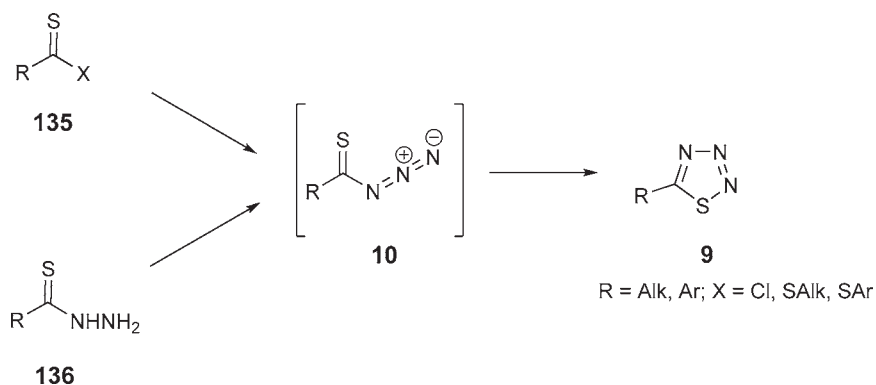
Scheme 31



6.09.9 Ring Synthesis of 1,2,3,4-Thiatriazoles Classified by Number of Ring Atoms in Each Component

6.09.9.1 One Bond

The generation of intermediate azidothiocarbonyl compounds **10** followed by 1,5-electrocyclic reaction leads to 5-substituted 1,2,3,4-thiatriazoles **9**. This mechanism has been proposed in reactions of various derivatives of thiohydrazides **136** with either nitrous acid or arenediazonium salts, and in reactions of thiophosgene (or dithiocarboxylates) **135** ($\text{X} = \text{Cl}, \text{SR}$) with either sodium or trimethylsilyl azide (Scheme 32) <1984CHEC(6)579, 1996CHEC-II(4)691,



Scheme 32

2002TL7601>. The intermediate compound **10** has never been isolated and it is not possible to completely exclude alternative pathways. Therefore, this group of reactions will be considered from a retrosynthetic point of view in Sections 6.09.9.2.1 and 6.09.9.2.2.

6.09.9.2 Two Bonds

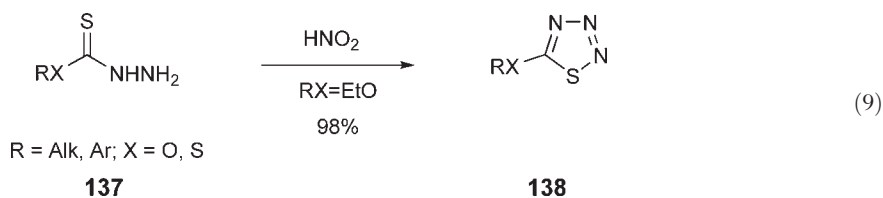
The synthetic methods leading to the 1,2,3,4-thiadiazole ring system are classified here into two main groups where the formation of either S–N and N–N or C–N and S–N bonds takes place.

6.09.9.2.1 From [4+1] fragments: S–C–N–N + N

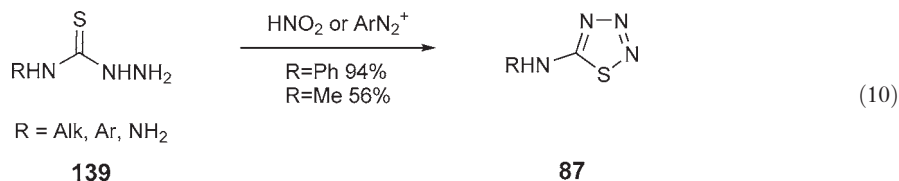
Thiohydrazides **136** react with nitrous acid or aryldiazonium salts to give 5-substituted 1,2,3,4-thiadiazoles **9** <1984CHEC(6)579, 1996CHEC-II(4)691, 2004HOU833>.

Thiadiazoles **9** with an aromatic or heteroaromatic substituent in the position 5 of the ring are rather stable and may thus be easily prepared from thiohydrazides and nitrous acid. The very unstable 5-*tert*-butyl- and 5-cyclohexyl-1,2,3,4-thiadiazoles can also be prepared by this reaction, but this method is not generally applicable because of difficulties in obtaining the starting thiohydrazides <1961ACS1104, 1961JOC5221>.

5-Alkoxy- and 5-aryloxy-1,2,3,4-thiadiazoles of type **138** (X = O) can be prepared in almost quantitative yield from alkoxy- or aryloxyhydrazinecarbothioates **137** (X = O) by treatment with sodium nitrite in the presence of aqueous hydrochloric acid <1964ACS825, 1964TL2829, 1965ACS438, 1965CB2059, 1966ACS2107, 1969ACS1567, 1970ACS1512, 1971JIC843, 1964AGE311, 1967BSF422>. The nitrosation of hydrazinecarbothioates **137** (X = S) produces the sulfur analogues, 5-(alkylsulfanyl)-1,2,3,4-thiadiazoles **138** (X = S) in very good yields (Equation 9) <1971JIC843, 1971JOC2015>.



5-Amino-substituted 1,2,3,4-thiadiazoles **87** were first prepared by a similar reaction starting from the readily available thiosemicarbazides <1895CB74>. In subsequent work this method has been widely used to prepare a variety of derivatives <1981JIC1087>. A modification of this method is to use the aza transfer reaction between aryl diazonium salts and 4-substituted thiosemicarbazide **139** (Equation 10) <1978OPP59>.

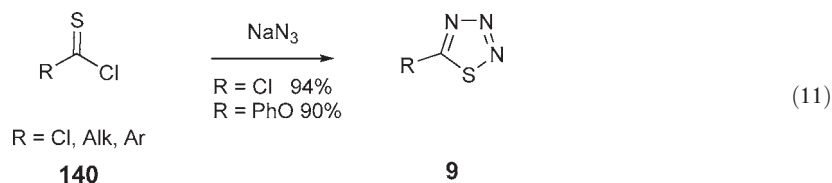


The rather unstable 5-hydrazino-1,2,3,4-thiadiazole **87** (R = NH₂) can be prepared by reaction of thiocarbazide with nitrous acid at 0 °C in moderate yield <1985ZC136, 1989JPR115>.

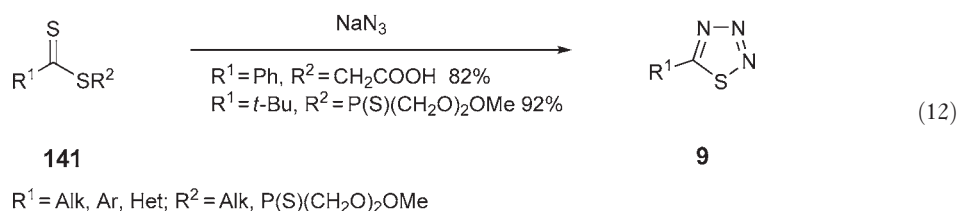
6.09.9.2.2 From [3+2] fragments: N–N–N + S–C

This method is based on the reaction of various thiocarbonyl compounds with azide anion, usually in the form of sodium azide. Trimethylsilyl azide has been described as an alternative reagent for this reaction. Various mechanisms are possible for this reaction. From the retrosynthetic point of view, it is important to note that this is a [3+2] addition where the formation of the thiadiazole ring takes place involving three atoms of the azide and two atoms of the thiocarbonyl compound.

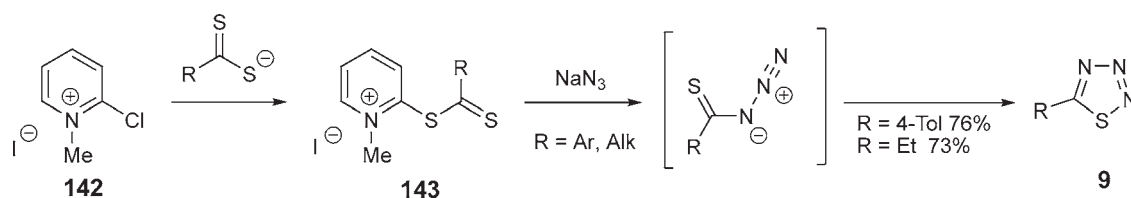
5-Chloro-, 5-alkoxy-, and 5-aryloxy-1,2,3,4-thiatriazoles **9** have been prepared in very high yields from thiophosgene **140** ($R = \text{Cl}$), *O*-alkyl or *O*-aryl chlorothioformates **140** ($R = \text{OAlk}$, OAr) with sodium azide (Equation 11) <1964ACS825, 1964AGE311, 1964CB2689, 1964TL2829, 1965CB2059, 1965CB2063, 1967BSF422, 1970ACS1512, 1971JIC843, 1990S415>. It should be noted that the toxicity and explosive properties of sodium azide and 5-chloro-1,2,3,4-thiatriazole **9** ($R = \text{Cl}$) are serious drawbacks of this synthetic method.



5-Aryl- and 5-heteroaryl-1,2,3,4-thiatriazoles **9** are quite stable and can also be prepared by the reaction of aromatic (respectively heteroaromatic) carbodithioates <1961ACS1104> or *S*-thioacyl dithiophosphates **141** <2002J(P1)1271> with sodium azide (Equation 12).

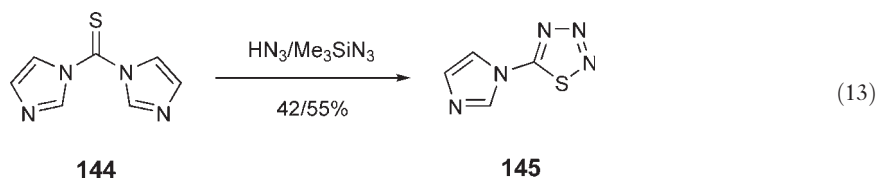


This method is not general and only a limited number of 5-alkyl-1,2,3,4-thiatriazoles were prepared by this reaction. Ikeda and co-workers have described a convenient method for the synthesis of both 5-alkyl- and 5-aryl-1,2,3,4-thiatriazoles **9** by reaction of 1-methyl-2-thioacylpyridinium salts **143** with sodium azide (Scheme 33). Compound **143** can be prepared from pyridinium salt **142** by reaction with dithiocarboxylic acid derivatives. The synthesis can conveniently be carried out as a one-pot reaction from 2-chloro-1-pyridinium salt **142** and carbodithioate leading to final compounds **9** in high yields. The 5-alkyl-1,2,3,4-thiatriazoles **9** were isolated as oils <1990S415, 1990ZC67>.

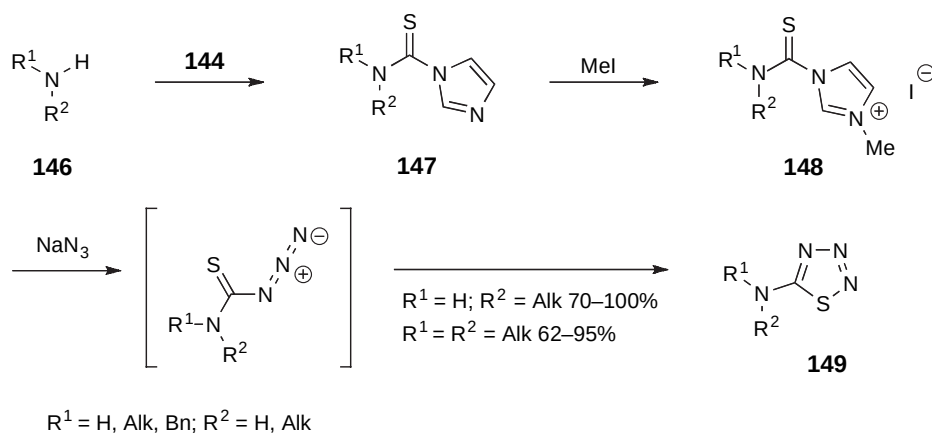


Scheme 33

Thiocarbonyldiimidazole **144** also reacts with hydrazoic acid and trimethylsilyl azide to form 5-(1-imidazolyl)-1,2,3,4-thiatriazole **145** in moderate yields (Equation 13) <1978T453>.



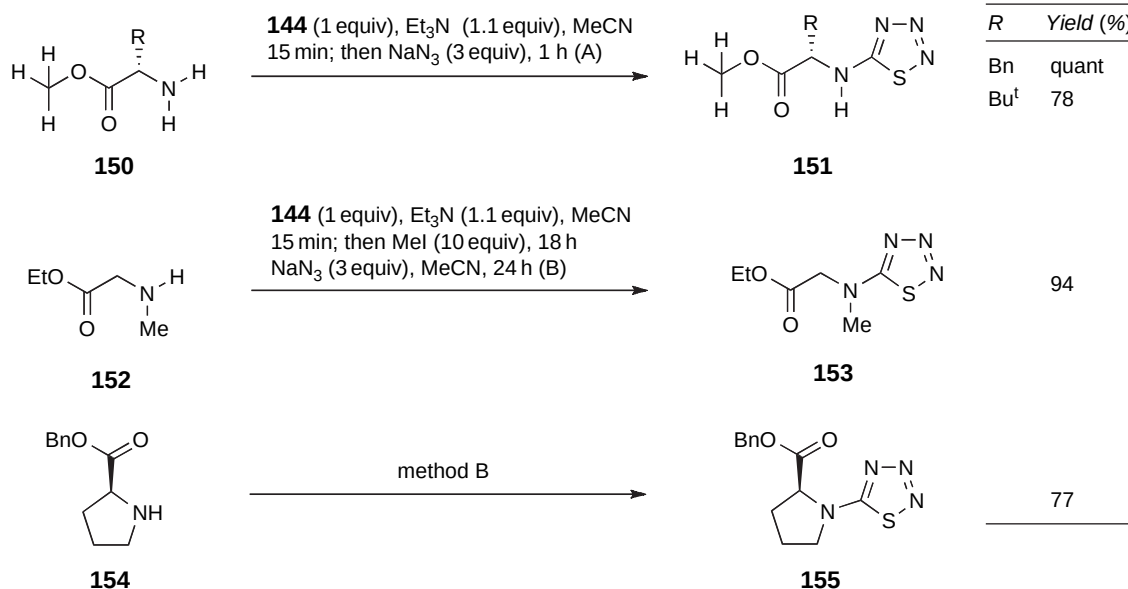
A new and very efficient approach to the mono- and disubstituted 5-amino-1,2,3,4-thiatriazoles was elaborated by Ponzo and co-workers based on the reaction of 1-thiocarbamoylimidazolium salts **148** with sodium azide <2002TL7601>. The displacement of *N*-methylimidazole by azide anion results in the formation of the intermediate thiocarbamoyl azide, which can then undergo rapid 1,5-electrocyclization at room temperature to give the final compounds **149**. Primary and secondary amines **146** reacted with thiocarbonyldiimidazole (TCDI) **144** to afford thiocarbamoyl imidazoles **147**. Reaction of compounds **147** with excess of methyl iodide during 18–24 h at room temperature produced the imidazolium salts **148**. Finally, treatment of salts **148** with sodium azide in acetonitrile affords 5-amino-1,2,3,4-thiatriazoles **149** in 70–100% yields. All monosubstituted thiatriazoles were prepared within 2 days. This method of synthesis of 5-aminosubstituted-1,2,3,4-thiatriazoles **149** ($R^2 = \text{H}$) avoids the use of harsh reaction conditions, unpleasant reagents or extreme pH. Thiocarbamoyl imidazoles **148** derived from secondary amines are less reactive. The time of their reaction with sodium azide is around 48 h, which is considerably longer in comparison with the monosubstituted derivatives that need 3–18 h for the reaction to complete. As a consequence, the yields of *N,N*-disubstituted 5-amino-1,2,3,4-thiatriazoles (62–95%) are generally lower than those for the *N*-monosubstituted compounds (70–100%) (Scheme 34).



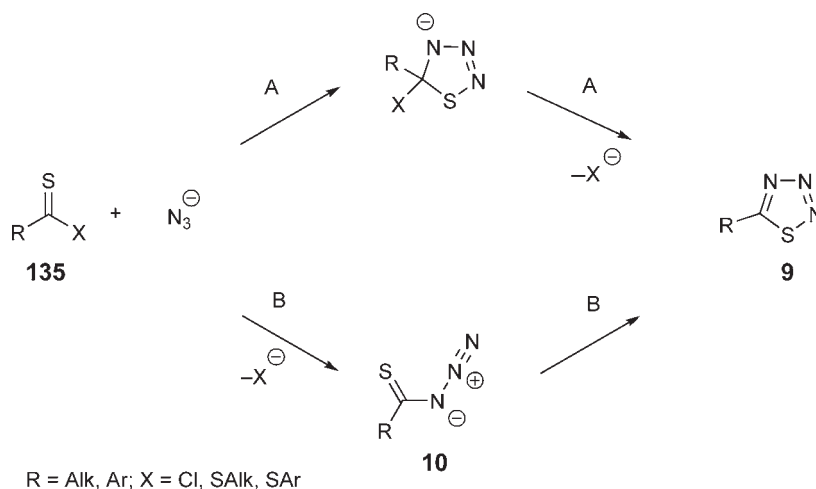
Scheme 34

It has been shown also that both thiocarbamoylimidazoles **147** and **148** can react with sodium azide. These compounds were successfully used to prepare heterocycle–peptide conjugates as peptidomimetics. *N*-Terminal aminothiatriazole modified amino acids have been synthesized using two methods (Scheme 35). To prepare monosubstituted aminothiatriazoles **151** the amino acid derivatives were converted into the thiocarbamoyl imidazoles of type **147** that can react with azide ion to form the thiatriazole ring. On the other hand, for the synthesis of disubstituted amino acid derivatives of 1,2,3,4-thiatriazoles **153** and **155** the activation of the thiocarbonyl group via a salt of type **148** was required. The reaction conditions and the yields of thiatriazoles **151**, **153**, and **154** prepared by this approach are shown in Scheme 35.

Although the generation of azidothiocarbonyl compounds followed by 1,5-electrocyclic ring closure to 1,2,3,4-thiatriazoles is postulated in the reaction of thiocarbonyl compounds with azides, it should be pointed out that an alternative mechanism involving a concerted [3+2] cycloaddition reaction could also take place. It has been shown theoretically that thiocarboxylic acids can react with azides via two pathways depending on the electronic character of the azide component <2006JA5695>. Relatively electron-rich azides undergo a bimolecular coupling reaction with thiocarboxylates via an anion-accelerated [3+2] cycloaddition to give a thiatriazoline. Highly electron-poor azides couple via the bimolecular interaction of the terminal nitrogen of the azide with the sulfur of the thiocarboxylate to give the acyclic adduct. Cyclization of this intermediate gives a thiatriazoline <2006JA5695>. By analogy with these results we can propose that 1,2,3,4-thiatriazole **9** formation from thiocarbonyl compounds **135** and sodium azide can take place via both pathway A, involving a [3+2] cycloaddition and via pathway B where an 1,5-electrocyclic reaction is the key step, depending on the electronic character of the thiocarbonyl component. An increase of electron deficiency of the central carbon, which happens when X is an electron-accepting group, could shift the reaction in favor of mechanism B (Scheme 36). Further theoretical work is needed to answer this question.



Scheme 35

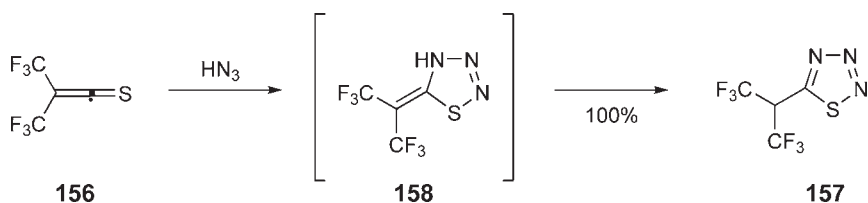


Scheme 36

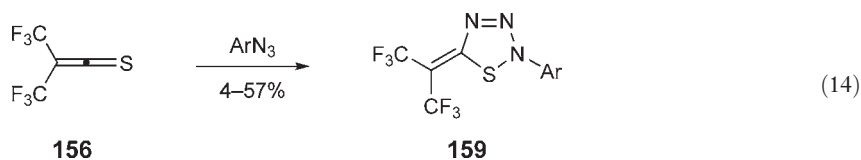
It has been shown that thioketenes, isothiocyanates, and carbon disulfide can react with hydrazoic acid to form 5-alkyl-, 5-amino-, and 5-thiosubstituted-1,2,3,4-thiatriazoles <1996CHEC-II(4)691>. Most probably these reactions proceed via [3+2] cycloaddition of azide anion to C=S bond.

Thus, bis(trifluoromethyl)thioketene **156** reacts with hydrazoic acid to afford the 5-hexafluoropropyl-2-ene derivative that tautomerizes to hexafluoroisopropyl-1,2,3,4-thiatriazole **157**. In contrast to other 5-alkylderivatives of 1,2,3,4-thiatriazole this compound was reported to be stable at room temperature (Scheme 37) <1970JOC3470>.

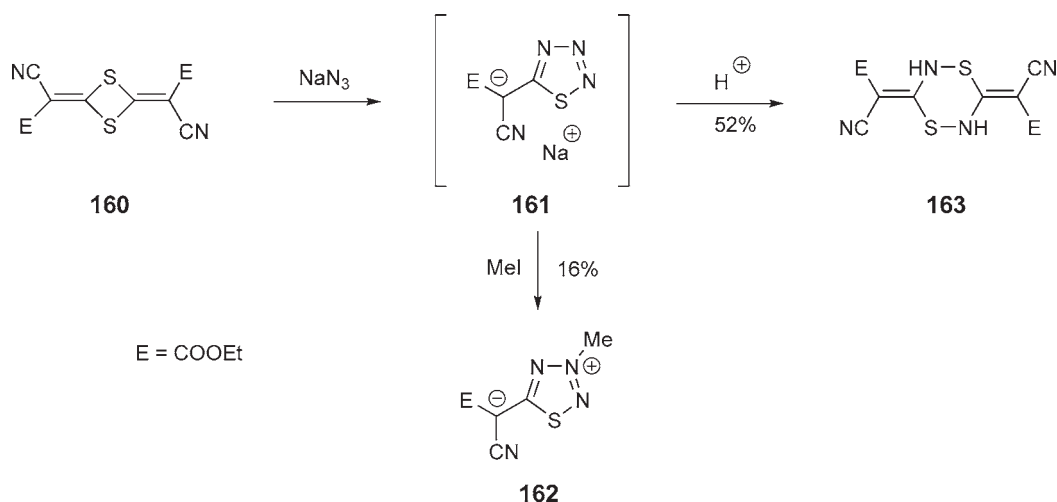
It is known that aryl azides undergo 1,3-dipolar cycloaddition reaction with bis(trifluoromethyl)thioketene **156** to form the yellow Δ^3 -1,2,3,4-thiatriazolines **159** in very low to fair yield supporting the mechanism of reaction of this thioketene with hydrazoic acid (Equation 14) <1978JOC2500>.



Scheme 37



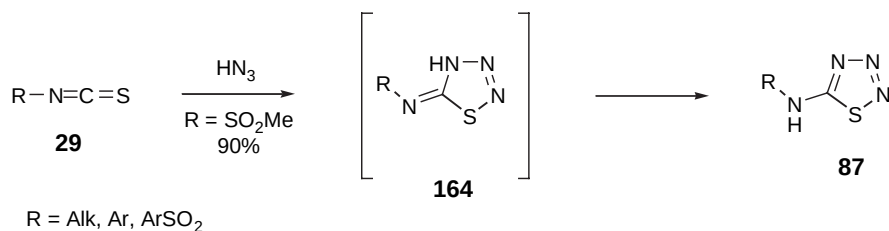
The reaction of desaurines **160** with sodium azide gives an access to the anionic salt of 5-(α -cyanoethoxycarbonyl)thiadiazoles **161** (Scheme 38). This salt could be methylated to form the 3,5-disubstituted ylide **162**.



Scheme 38

In the absence of an alkylating agent, a dithiadiazine **163** is formed on protonation <1984BSB405>. Since desaurine is a dimer of a thioketene, we can classify this reaction in this section. Alternatively, this could be seen as a ring transformation.

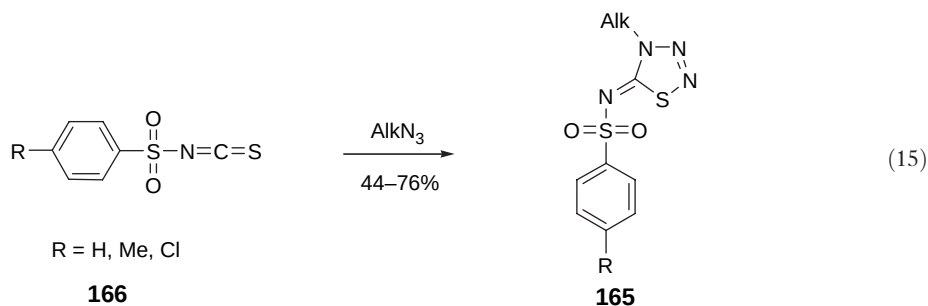
Isothiocyanates **29** can also react with hydrazoic acid to produce 5-amino-1,2,3,4-thiadiazoles **87** (Scheme 39) <1977CCC1557, 1975S52, 1977CCC1557, 1978T453, 1959CJC101, 1930JPR261, 1932JPR60, 1930CB670>. The method involves the use of hazardous hydrazoic acid and this is disadvantageous in comparison with the alternative method of preparation of 5-aminosubstituted 1,2,3,4-thiadiazoles by nitrosation of thiosemicarbazides. In the case of



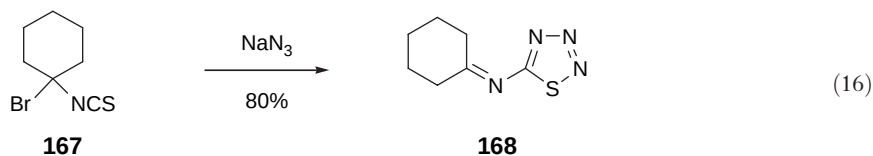
Scheme 39

activated isothiocyanates such as phenylsulfonyl and pyridyl isothiocyanates, in spite of the enhanced reactivity, the reaction results in the addition at the C=S rather than at the C=N bond which would have given rise to tetrazoles <1980CCC2329>. Floch and co-workers have found that the replacement of hydrazoic acid with trimethylsilyl azide considerably increases the rate of this reaction <1977CCC1557>.

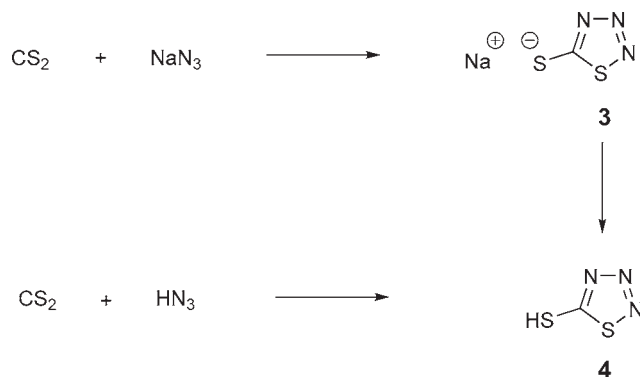
L'abbé and co-workers have found that 4-alkyl-5-sulfonylimino- Δ^2 -1,2,3,4-thiatriazolines **165** can be easily prepared by reaction of the highly reactive arylsulfonyl isothiocyanates **166** with alkyl azides (Equation 15). Kinetic experiments indicate that the reaction between picryl isothiocyanate and alkyl azides is probably concerted since no significant solvent effect has been observed <1973JOC2916, 1974JA3973>. This is in support of the postulated mechanism involving the intermediate 5-imino- Δ^2 -1,2,3,4-thiatriazolines **164** in the reaction of isothiocyanates with hydrazoic acid.



α -Bromoalkylisothiocyanates **167** react with sodium azide resulting in *N*-(alkylidene)thiatriazol-5-amines **168** (Equation 16). In this reaction azide ion reacts both as the source of three nitrogen atoms of the 1,2,3,4-thiatriazole ring and as a base to eliminate bromide ion <1979CB1102, 1979CB1956>.



1,2,3,4-Thiatriazole-5-thiol **4** and its salts **3** can be readily prepared from the water-soluble azide salts with carbon disulfide at 40 °C. These salts should be handled with care. For instance, the slightly soluble heavy-metal salts of 1,2,3,4-thiatriazole-5-thiol are very shock sensitive, even under water. The free acid **4** is obtained by addition of hydrochloric acid to a cooled solution of the sodium salt **3** and can also be prepared from hydrazoic acid and carbon disulfide (Scheme 40) <1964AHC263>.



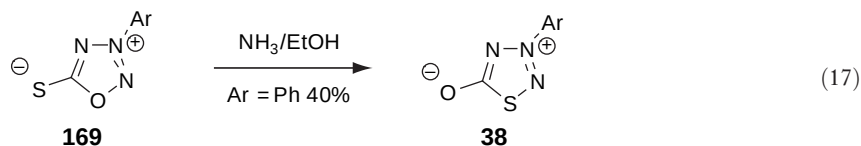
Scheme 40

Some derivatives of 1,2,3,4-thiatriazole-5-thiol were recently reported by Klapötke and co-workers <2004IC1370>.

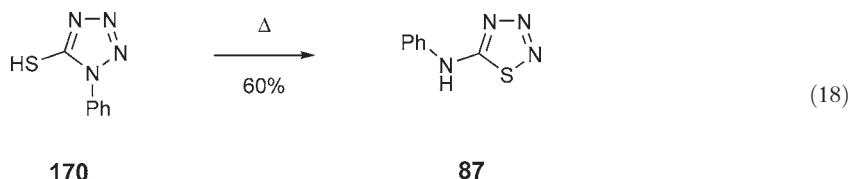
6.09.10 Ring Synthesis of 1,2,3,4-Thiatriazoles by Transformation of Another Ring

The synthesis of 1,2,3,4-thiatriazoles can be carried out by rearrangements of other heterocyclic compounds, but the yields in these reactions are usually poor. Therefore, this synthetic method has theoretical rather than practical importance.

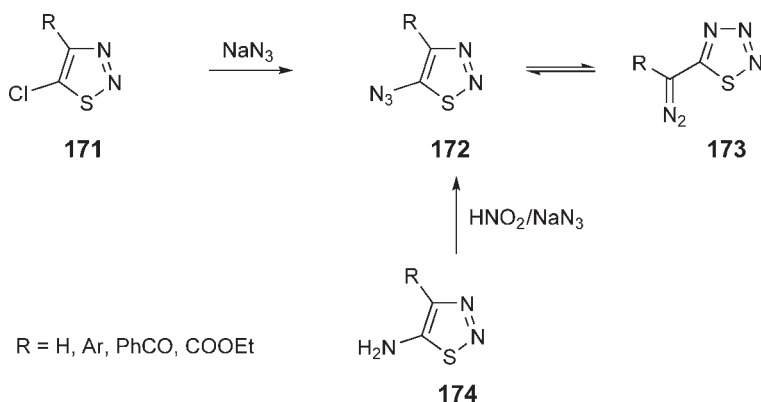
1,2,3,4-Oxatriazol-3-ium-5-thiolates **169** are less stable than the isomeric mesoionic 1,2,3,4-thiatriazol-3-ium-5-olates **24** and can be converted to the latter in moderate yield by treatment with ammonia in ethanol (Equation 17) <1979J(P1)732>.



5-Phenylamino-1,2,3,4-thiatriazole **87** in principle can be prepared by heating of isomeric 1-phenyltetrazole-5-thiol **170** (Equation 18) <1967JOC3580>. The formation of the thiatriazole **87** is accompanied by significant formation of phenylaminonitrile. Therefore, we recommend the use of other synthetic methods (see Section 6.09.8), for instance, the nitrosation of 4-phenyl-3-thiosemicarbazide <1971JIC843, 1981JIC1087>.

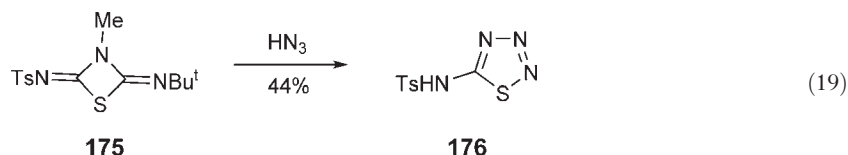


Attempts to prepare 5-azido-1,2,3-thiadiazole **172** by reacting 4-ethoxycarbonyl- or 4-benzoyl-5-chloro-1,2,3-thiadiazoles **171** with sodium azide or by diazotation of 4-ethoxycarbonyl- or 4-benzoyl-5-amino-1,2,3-thiadiazoles **174** with nitrous acid followed by treatment with sodium azide result in formation of the products of rearrangements, 5-diazomethyl-1,2,3,4-thiatriazoles **173** (Scheme 41) <1982TL1103, 1988BSB163>. The rearrangement does not occur for the derivative **172** (R = H). On the other hand, a mixture of thiadiazole **172** and thiatriazole **173** (53–76% combined yield) was obtained from the diazotation reaction of 5-amino-4-aryl-1,2,3-thiadiazoles **174** (R = Ph) followed by treatment with azide anion. The ratio of 1,2,3-thiadiazole and 1,2,3,4-thiatriazole is governed by the electronic character of 4-substituents. Electron-withdrawing substituents promote the formation of the thiatriazole ring by stabilization of the diazo function.

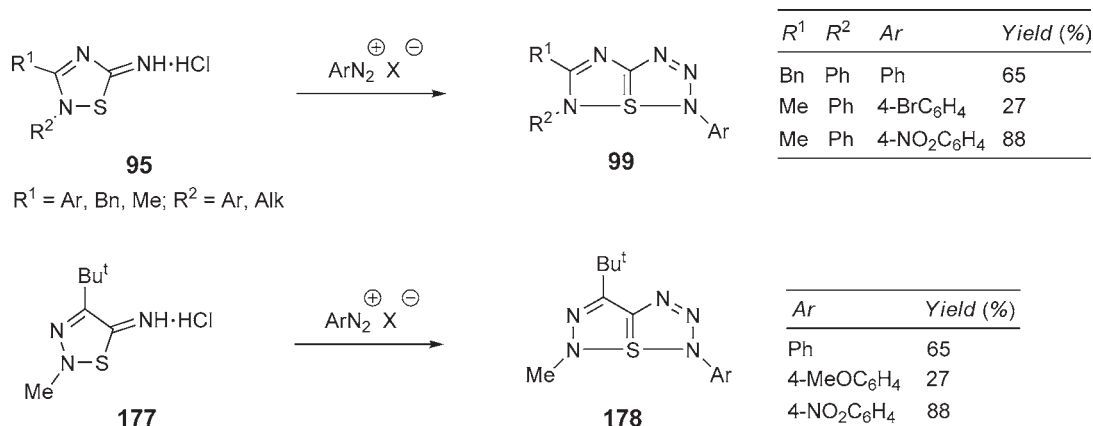


Scheme 41

1,3-Thiazetidine-2,4-diimine **175** reacts with hydrazoic acid to give a substituted 1,2,3,4-thiatriazole **176** (Equation 19). The starting materials can be prepared by reaction of carbodiimides with tosylisothiocyanate. It has been noted that this method has no general synthetic application <1981BSB63>.



Starting from the salts of the isomeric 1,2,4- and 1,2,3-thiadiazol-5-imines, addition of aryldiazonium salts and base affords respectively fused thiapentaazapentalenes **99** and **178** that contain a 1,2,3,4-thiadiazole ring (Scheme 42) (see also Section 6.09.7.2) <1993JHC349, 1994J(P1)2895>.

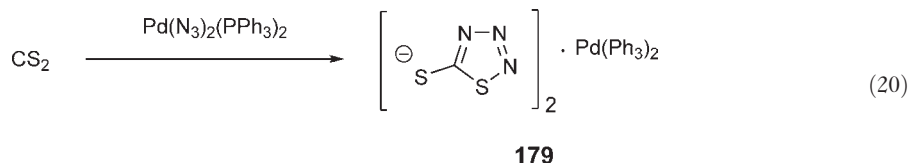


Scheme 42

6.09.11 Synthesis of Particular Classes of Compounds

6.09.11.1 Formation of Complexes of 1,2,3,4-Thiadiazoles

The formation of complexes of 1,2,3,4-thiadiazole-5-thiol has been well described in CHEC-II(1996): 1,2,3,4-thiadiazole-5-thiol can form complexes with various metals such as palladium, nickel, platinum, cobalt, zinc, etc. <1996CHEC-II(4)691>. These complexes can be prepared either by cycloaddition reactions of carbon disulfide with metal complexes of azide anion (Equation 20) or directly from the sodium salt of 1,2,3,4-thiadiazole-5-thiol with metal salts. For instance, the palladium–thiadiazole complex **179** can be obtained as shown in Equation (20) or it may be formed from palladium(II) nitrate, triphenylphosphine, and sodium thiadiazolate-5-thiolate. It should be noted that complexes of azide ion react with carbon disulfide much faster than sodium azide itself.



The copper(I) azide derivatives (PPh₃)(phen)CuN₃ and (PPh₃)(TMP)CuN₃ (phen = 1,10-phenanthroline and TMP = 3,4,7,8-tetramethyl-1,10-phenanthroline) react with CS₂ to give yellow thiadiazolato-copper(I) complexes <1984JOM263>. The complexes are formed only if free triphenylphosphine is present in the reaction medium, otherwise isothiocyanate complexes are formed instead. The kinetics of the reaction of Ru(II) tetraamines with CS₂N₃[−] were studied spectrophotometrically and rate constants for the formation *trans*-[Ru(NH₃)₄L(CS₂N₃)] were determined <1986POL1503>. 1,3-Dipolar cycloaddition of carbon disulfide to bridged coordinate azide in [Pd(benzylideneaniline)(μ-N₃)]₂ was carefully investigated <2001JCR163>. The resulting complex di(μ-N,S-1,2,3,4-thiadiazole-5-thiolate)bis(benzylideneaniline)palladium(II) was characterized by IR and X-ray diffraction. This complex is a dimer containing two [Pd(benzylideneaniline)] moieties connected by two vicinal bridging

N,S-1,2,3,4-thiatriazole-5-thiolate anions in a square-planar coordination geometry for the palladium atoms. The use of 1,2,3,4-thiatriazole complexes in analytical chemistry to determine the sulfite ion concentration was also reported <1996CHEC-II(4)691>.

The copper complex of 3-phenyl-1,2,3,4-thiatriazolium-5-thiolate was patented to form the metal layer adhering to a resin layer <2002EP1253813>.

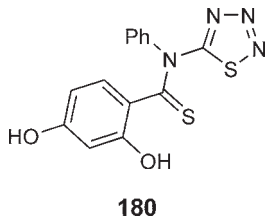
As it was shown by Jazwinski, 2-hydroxyphenyl and 2-carboxyphenyl derivatives of mesoionic 1,2,3,4-thiatriazolium-5-aminide interact strongly with metal cations. The interaction of these compounds with Pb(II), Fe(II), Fe(III), Cu(II), and Cd(II) cations was studied by UV-visible spectroscopy, ^1H and ^{113}Cd NMR spectroscopy <1999PJC199>. The reactions of some 3-phenyl-1,2,3,4-thiatriazolium-5-aminide derivatives with CoCl_2 , $\text{Ni}(\text{ClO}_4)_2$, and $\text{Cu}(\text{OAc})_2$ were also studied by VIS electronic spectroscopy <2000JMT105>. Usually, the presence of different species in equilibrium has been detected in the mixture of a given ligand with a given cation. However, sometimes the formation of well-defined adducts has been observed.

The study of the complexes of 5-anilino-1,2,3,4-thiatriazolate with transition metals was preliminary reported by Vohs and co-workers <2004MI1>.

6.09.12 Applications

Monosubstituted 5-amino-1,2,3,4-thiatriazoles have been reported to possess a range of interesting biological properties, including antihypertensive <1973JME1157>, fungicidal <1976ABC759>, antitubercular <1978MI107>, antiviral <1967BJP1>, anticancer <1979AF728>, and central nervous system muscle stimulant activity <1986MI162>.

It was reported that *N,N*-phenyl-1,2,3,4-thiatriazole-5-yl-2,4- β -resorcylcarbothioamide **180** exhibited *in vitro* antifungal activity <2003AF668>. This compound was found to inhibit the enzymatic activity of selected hydrolases of *C. albicans* and non-*Candida* species strains. 5-Aminosubstituted-1,2,3,4-thiatriazoles have been found to be super-sensitizers in the red region of the electromagnetic spectrum <1994USP5306612>.



The refractive indices before and after photoirradiation were measured for a series of mesoionic compounds including 3-phenyl-1,2,3,4-thiatriazolium-5-thiolate. The knowledge of these data allows controlling the optical properties of polymers. The results obtained in <2002MI2290> suggest the applicability of photoelimination of 3-phenyl-1,2,3,4-thiatriazolium-5-thiolate to make various refractive index patterns for polymeric film. It has also been shown that the refractive index changes of mesoionic compounds are proportional to the number of sulfur atoms in the mesoionic skeletons.

The application of mesoionic compounds, including 3-phenyl-1,2,3,4-thiatriazolium-5-olate, was found to increase the conductivity of DMF based gels <2001PCB9686>.

6.09.13 Further Developments

A topological study of the 1,2,4-thiatriazole-5-thiolate anion and some covalent derivatives has been undertaken <2006MI1, 2006JMS(770)13>. In a recent review article, the CHIH-DFT determination of the molecular structure and infrared and ultraviolet spectra of azathiophenes, including 1,2,3,4-thiatriazoles, is discussed <2007MI1>.

The thermal decomposition of 5-morpholino-1,2,3,4-thiatriazole leads to the extrusion of an active form of sulfur, that is intercepted by thioketones, leading to 1,2,4-trithiolanes in a regioselective manner <2007HCA594>.

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 1930CB670
 1930JPR261
 1932JPR60
 1959CJC101
 1961ACS1104
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 1964CB2689
 1964TL2829
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 1965CB2063
 1966ACS107
 1967BJP1
 1967BSF422
 1967JOC3580
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 1970ACS1512
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 1971AP687
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 1975JA6197
 1975JOC431
 1975T1783
 1975SS52
 1976ABC759
 1976ACA351
 1976ACA997
 1976AG510
 1976AHC145
 1977AG420
 1977CC143
 1977CCC1557
 1977JHC1417
 1977JOC1159
 1978JOC2500
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 1978J(P1)600
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Biographical Sketch



Vasiliy Bakulev was born in Ekaterinburg, Russia. He obtained his Ph.D. in 1979, under the guidance of Prof. Vladimir Mokrushin, on the synthesis of imidazole derivatives. Then he studied electrocyclic reactions of diazocompounds and azomethyne ylides and, in 1990, defended the second thesis of Doctor of Science (similar to Habilitation Degree) at Moscow State University. He received a diploma of Professor in 1998. Jointly with Wim Dehaen, he published a book on the chemistry of 1,2,3-thiadiazoles in 2004. He is currently professor at the Organic Synthesis and Technology Department of the Urals State Technical University (Ekaterinburg, Russia).



Wim Dehaen was born in Kortrijk, Belgium. He obtained his Ph.D. in 1988 under the guidance of Prof. Gerrit L'abbé on a study concerning the rearrangements of 5-diazoalkyl-1,2,3-triazole derivatives. After postdoctoral stays in Israel (1988–90), Denmark (3 months in 1990), the UK (3 months in 1994), and Belgium (most of 1990–98), he was appointed associated professor at the University of Leuven (Belgium) in 1998, becoming a full professor at the same university in 2004. Up to now, 220 publications have appeared in international journals about his work on heterocyclic and supramolecular chemistry, with more than 20 in co-authorship with Vasiliy Bakulev.

6.10

1,2,3,5-Thiatriazoles

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6.10.1	Introduction	486
6.10.2	Theoretical Methods	486
6.10.2.1	Molecular Orbital Calculations	486
6.10.2.2	Aromaticity	487
6.10.3	Experimental Structural Methods	487
6.10.3.1	X-Ray Crystallography	487
6.10.3.2	UV Spectroscopy	489
6.10.3.3	ESR, ENDOR, General Triple Resonance NMR Spectroscopy	489
6.10.3.3.1	NMR spectroscopy data	489
6.10.3.4	1,2,3,5-Thiatriazolines	489
6.10.3.5	1,2,3,5-Thiatriazole Heteropentalenes	489
6.10.4	Thermodynamic Aspects	490
6.10.5	Reactivity of Fully Conjugated Rings	490
6.10.5.1	Thermal Reactions	490
6.10.5.2	Reduction of 1,2,3,5-Thiatriazolium Salts with Metals	490
6.10.6	Reactivity of Nonconjugated Rings	490
6.10.6.1	Thermal Reactions	490
6.10.6.2	Electrophilic Reactions	491
6.10.7	Reactivity of Substituents Attached to Ring Carbon Atoms	491
6.10.8	Reactivity of Substituents Attached to Ring Heteroatoms	491
6.10.8.1	Electrophilic Attack at S-Oxides	491
6.10.9	Ring Synthesis of 1,2,3,5-Thiatriazoles from Acyclic Compounds Classified by Number of Ring Atoms in Each Component	491
6.10.9.1	One Bond	491
6.10.9.2	Two Bonds	492
6.10.9.2.1	From [4+1] fragments: N-C-N-N + S	492
6.10.9.2.2	From [3+2] fragments: C-N-N + S-N	494
6.10.9.2.3	From [3+2] fragments: C-N-S + N-N	494
6.10.10	Ring Synthesis of 1,2,3,5-Thiatriazoles by Transformation of Another Ring	495
6.10.11	Synthesis of Particular Classes of Compounds	496
6.10.11.1	4-Dialkylamino-2,3-dihydro-1,2,3,5-thiatriazole-1,1-dioxides	496
6.10.12	Applications	497
6.10.13	Further Developments	497
	References	497

6.10.1 Introduction

The chemistry of 1,2,3,5-thiadiazoles was covered previously in CHEC(1984) <1984CHEC(6)579> together with data on 1,2,3,4-oxa- and thiadiazoles, and in CHEC-II(1996) <1996CHEC-II(4)733>. Older reviews were cited in the introductions to these texts. Synthetic aspects of 1,2,3,5-thiadiazole derivatives and the isomeric 1,2,3,4-thiadiazoles were recently reviewed by Begtrup <2004HOU833>.

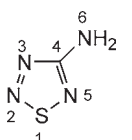
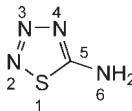
1,2,3,5-Thiadiazole is a rare heterocyclic system. In this chapter, we have compared the data abstracted from a few recent publications with an overview of previous work. Thus, the previous chapters in CHEC(1984) and CHEC-II(1996) should be read together with this chapter in order to obtain a comprehensive view of the field.

6.10.2 Theoretical Methods

6.10.2.1 Molecular Orbital Calculations

Only two papers on molecular orbital (MO) calculations of a 1,2,3,5-thiadiazole have been published, namely of 4-amino-1,2,3,5-thiadiazole (4AT) <2004JMT83, 2005JMT61>. Density functional calculations have been performed with 3-21G* and 6-31G(d,p) basis sets to determine the molecular structure, dipole moment, energy of frontier orbitals, atom charges, Fukui indexes, electronegativity, global and local hardness of 4-amino-1,2,3,5-thiadiazole. Furthermore, the authors applied the new CHIH-DFT model (Chihuahua heterocycles density functional theory) that works well with heterocyclic compounds. They used the modified version of a hybrid density function implying a mix where 25% of Hartree–Fock (HF) exchange and 75% of Perdew–Burke–Ernzerhof (PBE) density functional exchange were used <2004JMT83, 2005JMT61>. The data compared to those for the isomeric 5-amino-1,2,3,4-thiadiazole (5AT) are shown in Table 1.

Table 1 HOMO, LUMO energies, dipole moments, and charges of 4-amino-1,2,3,5-thiadiazole and 5-amino-1,2,3,4-thiadiazole

Structure	E_{HOMO} (eV)	E_{LUMO} (eV)	$\Delta E(\text{LUMO} - \text{HOMO})$ (eV)	Charges, e (atom)	Dipole moment, $\mu(\text{D})$
	−7.2271	−2.0321	5.1949	0.4677 (4C); 0.7976 (1S); −0.6872 (3N); −0.2527 (4N); −0.3438 (5N); −0.8708 (6N)	2.475
	−7.7455	−1.4482	6.2973	0.1611 (5C); 0.4898 (1S); 0.0099 (3N); −0.3472 (4N); −0.3603 (5N); −0.8532 (6N)	5.5846

HOMO = highest occupied molecular orbital; LUMO = lowest unoccupied molecular orbital.

According to the calculated data, the 4-amino-1,2,3,5-thiadiazole molecule is planar <2004JMT83>. In comparison with the isomeric 5-amino-1,2,3,4-thiadiazole, 4AT is less polar and the dipole moment is only half as large as that of the 5AT isomer <2005JMT61>. The energy gap for 4-amino-1,2,3,5-thiadiazole is less than that for the isomeric thiadiazole. Based on these data, it was concluded that the 1,2,3,5-triazole should be more effective as a corrosion inhibitor <2005JMT61>. One may conclude from these data that 4AT is more prone to react with electrophiles than 5AT and that the aromaticity of 4AT is higher (see Section 6.10.2.2).

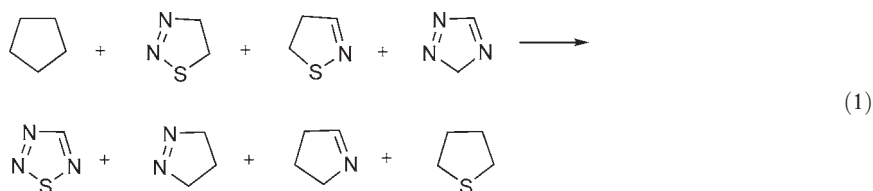
The charges were calculated by the application of a natural population analysis <1988CRV899> with the objective of obtaining a wider knowledge of the reactive properties of the 4-amino-1,2,3,5-thiadiazole system (see Table 1). All nitrogen atoms of the ring of 4-amino-1,2,3,5-thiadiazole are negatively charged, in contrast to the isomeric molecule. This means that 4AT has more propitious sites for the coordination with metallic surfaces, and this has been seen as important to protect metals against corrosion <2005JMT61>. It should be noted that 4AT and other aromatic 1,2,3,5-thiadiazoles have still not been prepared as stable compounds.

The infrared (IR) and ultraviolet–visible (UV–Vis) spectra for 4AT have been predicted according to CHIH (large) model chemistry, and an assignment of the principal peaks has been achieved <2004JMT83>.

6.10.2.2 Aromaticity

For a discussion on aromaticity parameters, see Section 6.09.2.1.1 of Chapter 6.09 and the following references: <B-1994MI1, 1996CHEC-II, B-1997MI1, 2000T1783, 2001CRV1115, 2001CRV1385, 2002JOC1333, 2003T1657>.

The aromatic stabilization energy (ASE) for 1,2,3,5-thiatriazole was calculated according to Equation (1) based on an *ab initio* optimized geometry at B3LYP/6-311+G** and MP2-(fc)/6-311+G** levels of the theory. A homo-desmotic reaction scheme was applied <2002JOC1333, 2003T1657>. The systems with strongly positive ASEs are aromatic, while those with strongly negative values are antiaromatic.



The magnetic susceptibility exaltations (Λ , defined as a difference between the magnetic susceptibility of a given system and a reference one, without cyclic delocalization) are also based on Equation (1). Systems with strongly negative values of Λ are qualified as aromatic.

Nucleus-independent chemical shift (NICS) is the negative value of absolute magnetic shielding calculated at revealing points in or near an aromatic system. Rings with negative NICS and NICS(1) values qualify as aromatic, and the more negative the NICS, the more aromatic the rings are. Consequently, antiaromatic systems have strongly positive values of NICS. The NICS(1) values computed 1 Å above the ring are considered to better reflect the π -electron effects <1997JA12669>.

The calculated data on thiophene, 1,2,3,4-thiatriazole, and 1,2,3,5-thiatriazole are placed in Table 2.

Table 2 Calculated ASE (kcal mol⁻¹), exaltations of the magnetic susceptibility Λ , NICS, NICS 1 Å above the ring centers (ppm)

Structure	ASE	Λ	NICS	NICS(1)
	18.57	-7.00	-13.80	-10.79
	14.72	-6.57	-15.18	-14.65
	21.62	-7.85	-15.49	-14.96

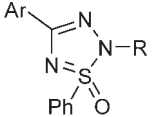
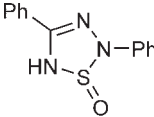
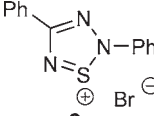
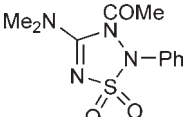
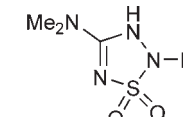
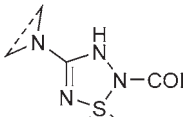
According to the data of Table 2, both energetic and magnetic indexes of aromaticity again advocate that the molecule of 1,2,3,5-thiatriazole is more aromatic than the isomeric 1,2,3,4-thiatriazole and even thiophene. Nevertheless, the parent 1,2,3,5-thiatriazole has not been described in the literature as mentioned before.

6.10.3 Experimental Structural Methods

6.10.3.1 X-Ray Crystallography

Only a few compounds of the 1,2,3,5-thiatriazole series have been subjected to X-ray analysis. The structures of compounds **1** and **3** satisfy the Hückel aromaticity rule. Furthermore, X-ray analysis confirmed their planarity. Crystal structure determination of 2,4-diphenyl-1,2,3,5-thiatriazole clearly revealed a 2,5-dihydro structure <1990J(P2)1619>. The five-membered ring exhibits a shallow envelope form, the sulfur being displaced by 0.49 Å from the least-squares through N-2, N-3, C-4, N-5 which present a perfect planarity. Bond lengths and angles (see Table 3) are closely similar to the corresponding data found in 2*H*-1,2,3,5-thiatriazolo[4,5-*a*]isoquinoline 3-oxide <1970CB1918>. The structure of 2*H*-1,2,3,5-thiatriazolium salts that can be obtained from 2,5-dihydro-1,2,3,5-thiatriazole-1-oxides by

Table 3 X-Ray data for 1,2,3,5-thiatriazoles: bond lengths and bond angles

Formula	Bond length (Å)					Bond angle (deg)					Reference
	S–N(2)	N(2)–N(3)	N(3)–C(4)	C(4)–N(5)	N(5)–S	N(5)–S–N(2)	S–N(2)–N(3)	N(2)–N(3)–C(4)	N(3)–C(4)–N(5)	C(4)–N(5)–S	
 $R = C(Ar) = NSO_2Ph$ 1	1.712	1.402	1.289	1.402	1.545	94	110	107	120	109	1997CJC1188
 2	1.695	1.389	1.281	1.386	1.660	85	114	108	114	112	1990J(P2)1619
 3	1.683	1.306	1.356	1.342	1.583	92	114	108	116	111	1990J(P2)1619
 4	1.736	1.430	1.447	1.319	1.624	97	100	108	115	107	2005AJC332
 5	1.720	1.428	1.392	1.326	1.603	98	104	110	118	107	2005AJC332
$R = 4\text{-chloro-2-methylphenyl}$  6	1.722	1.418	1.401	1.320	1.596	95	109	107	118	111	2005AJC332

reaction with phosphorus pentabromide was also studied by X-ray analysis (Table 3) <1990J(P2)1619>. The five-membered ring was found to be planar. All bonds, except for the N(3)–C(4) bond are shorter than those present in the precursor. X-Ray data on the structures of 2,3-dihydro-1,2,3,5-thiatriazole-1,1-dioxides has been published by Liepa and co-workers <2005AJC332>. Both oxidation of sulfur and acylation at position 3 of the ring leads to a change of bond lengths and angles in the 1,2,3,5-thiatriazole molecule.

6.10.3.2 UV Spectroscopy

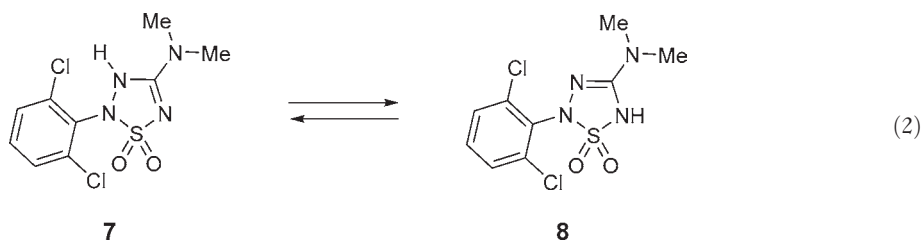
Neugebauer *et al.* reported the UV spectra ($\lambda_{\max}$, nm (log ϵ): 301(4.11); 278(4.03); 345(3.93)) for 2,5-dihydro-2,4-diphenyl-1,2,3,5-thiatriazole-1-oxide, 2,5-dihydro-5-methyl-2,4-diphenyl-1,2,3,5-thiatriazole-1-oxide, and 2,4-diphenyl-2*H*-1,2,3,5-thiatriazol-1-ium chloride, respectively <1990J(P2)1619>.

6.10.3.3 ESR, ENDOR, General Triple Resonance NMR Spectroscopy

The data on electron spin resonance (ESR), electron-nuclear double resonance (ENDOR), and general triple resonance spectroscopy for 2,5-dihydro-1,2,3,5-thiatriazole-5-yl radicals was reviewed by Holm and Larsen <1996CHEC-II(4)733>. There are no new data on this subject.

6.10.3.3.1 NMR spectroscopy data

^1H nuclear magnetic resonance (NMR) spectra were reported for 2,5-dihydro-1,2,3,5-thiatriazole-1-oxide and for 2,5-dihydro-1,2,3,5-thiatriazole-1,1-dioxide <1990J(P2)1619, 2005AJC332>. Although the spectra are of little diagnostic value, they are consistent with the structure of 1,2,3,5-thiatriazole-1-oxide and 1,1-dioxide. The spectra of 2,5-dihydro-1,2,3,5-thiatriazole-1-oxides unsubstituted at position 3 contain a singlet corresponding to the NH protons in the range of 11–12 ppm and the spectra of 2,5-dihydro-1,2,3,5-thiatriazole 1,1-dioxides display broad singlets for NH at 7.7–10.5 ppm. Liepa and co-workers also observed the broadening of other signals in the ^1H and ^{13}C NMR spectra for these compounds <2005AJC332>. The ^1H NMR spectrum for the 2-(2,5-dichlorophenyl) derivative shows a sharpening of the Me_2N signal at higher temperature and resolution into two distinct singlets upon cooling (-13°C). This effect was explained by relatively slow tautomerism due to contribution from zwitterionic resonance structures which restrict free rotation of the substituent at the C-4 position (Equation 2).



^{13}C NMR spectra were reported for 2,5-dihydro-1,2,3,5-thiatriazole-1,1-dioxides in CDCl_3 , including derivatives fused to a pyrazolone ring <2005AJC332>. The C-3 signal shows up in the 156–160 ppm region. The chemical shifts for N-5 and N-3 in the ^{15}N NMR spectra were determined as -243 to -246 and -125 to -129 ppm in 2,5-dihydro-2,4-diphenyl[3,5- $^{15}\text{N}_2$]-1,2,3,5-thiatriazole-1-oxides <1990J(P2)1619>.

6.10.3.4 1,2,3,5-Thiatriazolines

2,5-Dihydro-1,2,3,5-thiatriazoles and 2,3-dihydro-1,2,3,5-thiatriazoles are known as 1-oxides and 1,1-dioxides, respectively. Their structures were carefully studied by ^1H and ^{13}C NMR spectroscopy and X-ray analysis (see Sections 6.10.3.1 and 6.10.3.3).

6.10.3.5 1,2,3,5-Thiatriazole Heteropentalenes

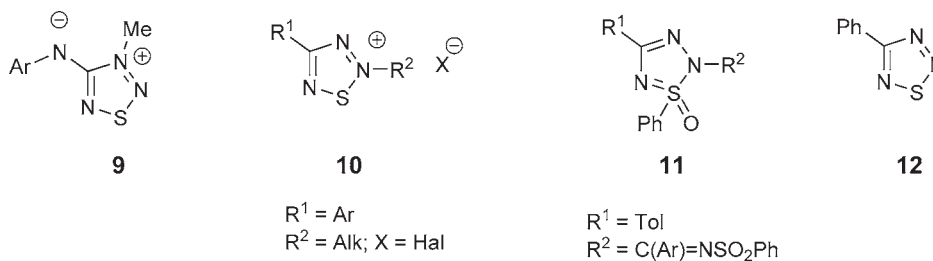
The structures of 1,2,3,5-thiatriazole heteropentalenes were already carefully studied by NMR in 1980 <1996CHEC-II(4)733>. There are no new studies to report.

6.10.4 Thermodynamic Aspects

The parent 1,2,3,5-thiadiazole and its derivatives are even less stable than the isomeric 1,2,3,4-triazoles (see Section 6.09.5). Although according to theoretical calculations the former should be more aromatic than the latter (see Section 6.10.2.2), they are unstable and decompose upon preparation. 1,2,3,5-Thiadiazole-1-oxides and 1,1-dioxides are relatively stable solid compounds with melting points in the range of 100–200 °C <2004HOU833>.

6.10.5 Reactivity of Fully Conjugated Rings

Fully conjugated 1,2,3,5-thiadiazoles have been described in the form of the mesoionic aminides **9** <1988ACB63>, as thiatriazolium salts **10** <1990J(P2)1619> and as compounds with hexavalent sulfur **11** <1997CJC1188>. The parent 1,2,3,5-thiadiazoles of type **12** are described as elusive intermediates in the reaction of amidrazones with thionyl chloride leading to benzonitrile formation <2004HOU833>.

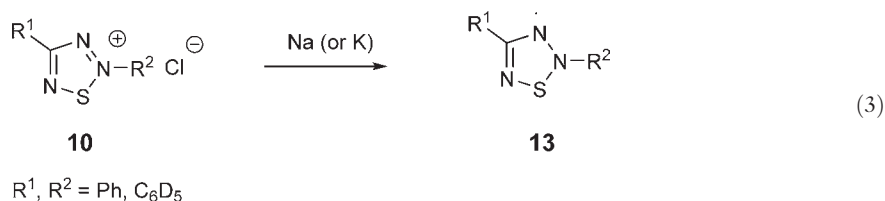


6.10.5.1 Thermal Reactions

In comparison with the isomeric 1,2,3,4-thiadiazole, much less work has been done on the thermal decomposition reaction of the 1,2,3,5-isomers and its mechanism. In contrast to the aromatic 1,2,3,5-thiadiazole **12** that decomposed to benzonitrile, sulfur, and nitrogen during an attempted preparation, aromatic aminides **9**, 1,2,3,5-thiatriazolium salts **10**, and compounds of type **11** are stable and were isolated and identified by spectroscopic methods.

6.10.5.2 Reduction of 1,2,3,5-Thiatriazolium Salts with Metals

Neugebauer and co-workers have found that treatment of dilute solutions of 2*H*-1,2,3,5-thiatriazolium salts **10** in 1,2-dimethoxyethane with sodium or potassium metals leads to the reduction of the N=S bond to generate 2,5-dihydro-1,2,3,5-thiatriazol-5-yl radicals **13** (Equation 3) <1997CJC1188>. ESR, ENDOR, and triple resonance studies in combination with ¹⁵N labeling yielded the magnitude and assignment of all ¹H and ¹⁴N hyperfine coupling (hfc) constants. The radicals have been shown to have a basic five π -electron amidrazon-2-yl structure with highest spin density at N-2.



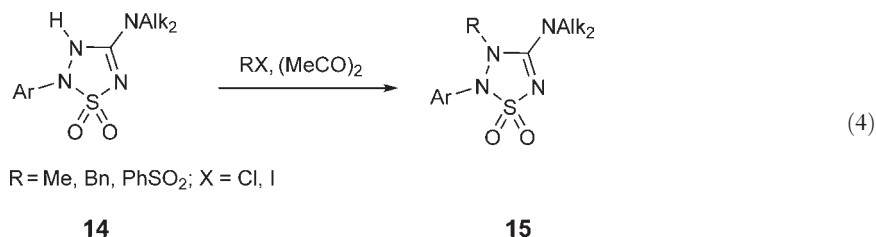
6.10.6 Reactivity of Nonconjugated Rings

6.10.6.1 Thermal Reactions

Thermal decomposition reactions have been described for 1,2,3,5-thiatriazolin-1,1-dioxides and for 1,2,3,5-thiatriazolidine-1-oxides in the previously covered literature <1996CHEC-II(4)733>. No new data have been published.

6.10.6.2 Electrophilic Reactions

2,3-Dihydro-1,2,3,5-thiatriazole-1,1-dioxides **14** with an NH function at position 3 of the ring were shown to have nucleophilic nature and to be capable of reacting with alkyl, acyl, and sulfonyl halides to afford the 3-substituted compounds **15** (see Equation 4) <2005AJC332, 1985M1321>.



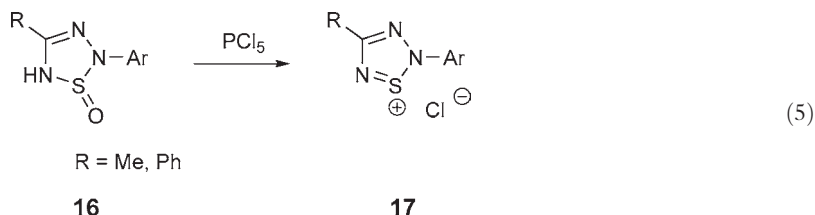
6.10.7 Reactivity of Substituents Attached to Ring Carbon Atoms

There are no data on the reactivity of substituents attached to ring atoms of 1,2,3,5-thiatriazoles since the publication of CHEC-II(1996).

6.10.8 Reactivity of Substituents Attached to Ring Heteroatoms

6.10.8.1 Electrophilic Attack at S-Oxides

The only known reaction related to this subject includes the transformation of 2,5-dihydro-1,2,3,5-thiatriazole-1-oxides **16** to 2*H*-1,2,3,5-thiatriazolium salts **17** upon treatment with phosphorus pentachloride (Equation 5) <1990J(P2)1619>.



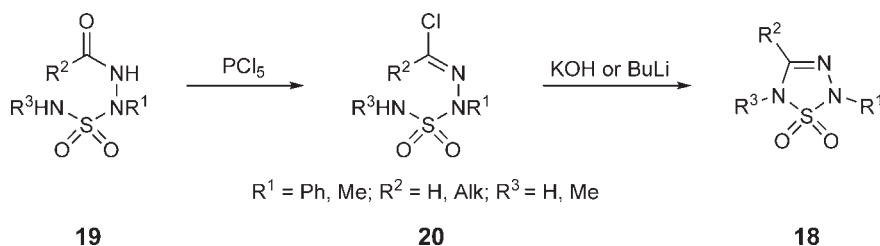
6.10.9 Ring Synthesis of 1,2,3,5-Thiatriazoles from Acyclic Compounds Classified by Number of Ring Atoms in Each Component

6.10.9.1 One Bond

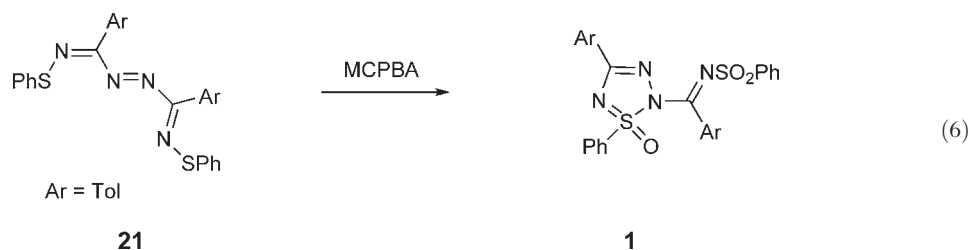
Two types of reaction where the formation of one bond occurs in the cyclization process are known to lead to the 1,2,3,5-thiatriazole ring system <1985M1141, 1997CJC1188>.

Knollmüller and Kosma have elaborated a general method to prepare 2,5-dihydro-1,2,3,5-thiatriazole-1,1-dioxides **18** starting from *N*¹-acylsulfamoylhydrazides **19** by reaction with phosphorus pentachloride followed by treatment of the intermediate *N*²-sulfamoylcarbohydrazonoyl chlorides **20** with KOH or *n*-butyllithium. This reaction was carefully studied. The intermediate compounds **20** were isolated at lower temperature. It has been shown that the compounds **19** (R¹ = Me; R² = Bn; R³ = H, Me) did not afford thiatriazolines **18** when a one-pot reaction was attempted (Scheme 1) <1985M1141>.

The reaction of (*Z,E,Z*)-PhSN=C(Ar)N=NC(Ar)=NSPh (Ar = Tol) **21** with *m*-chloroperbenzoic acid (MCPBA) has been shown to result in ring closure via an intramolecular redox process to give the 1,2,3,5-thiatriazole **1** (Equation 6). The X-ray structural data revealed that thiatriazole **1** contains a planar five-membered CNS(vi)NN ring with *d*(N–N) = 1.402(6) Å (see also Section 6.10.3) <1997CJC1188>.



Scheme 1

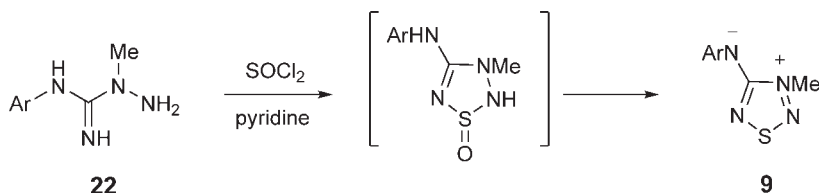


6.10.9.2 Two Bonds

6.10.9.2.1 From [4+1] fragments: N-C-N-N + S

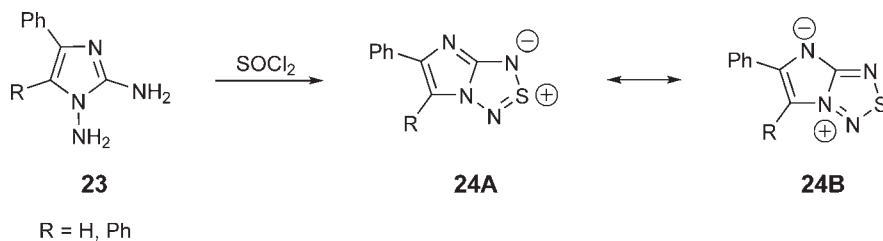
This type of synthesis involves the reactions of amidrazones <1962LA169, 1971CB639, 1980LA1376, 1985M1141, 1989JHC205, 1990J(P2)1619, 1996MI83>, aminoguanidines <1988ACB63>, semicarbazides and thiosemicarbazides <1978ZC336, 1979JHC895> with thionyl chloride and sulfonyl fluoride.

3-Substituted 1,2,3,5-thiadiazolium-4-aminides **9** constitute the only known class of mesoionic 1,2,3,5-thiadiazoles <1988ACB63>. They are formed in the reaction of 1-amino-1,3-disubstituted guanidines with approximately 2 equiv of thionyl chloride in pyridine as the solvent. The mesoionic compounds **9** are sensitive toward acids and bases (Scheme 2) <1988ACB63>.



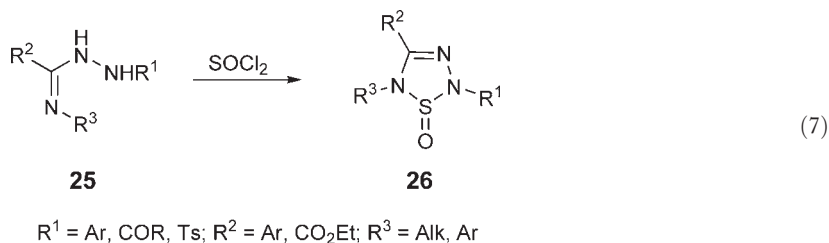
Scheme 2

Mesoionic 1,2,3,5-thiadiazoles **24** that are fused to an imidazole ring were successfully prepared from 1,2-diaminoimidazoles **23** and thionyl chloride (Scheme 3) <1981JOC4065>. The benzimidazo[1,2-*c*]thiadiazole was prepared in an analogous manner.



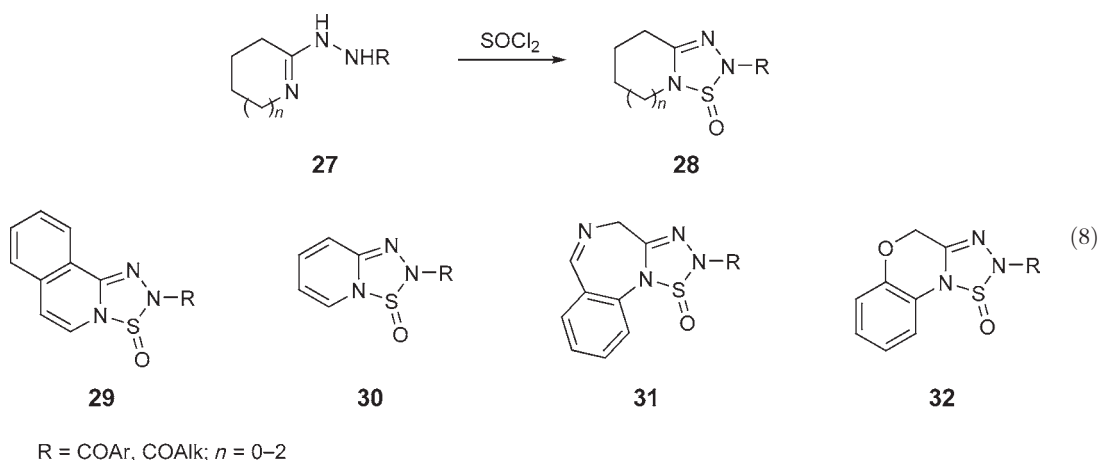
Scheme 3

Amidrazones **25** have been shown to react with thionyl chloride in the presence of a base to give 2,5-dihydro-1,2,3,5-thiatriazole 1-oxides **26** (Equation 7) <1962LA169, 1970CB1934, 1971CB639, 1980LA1376, 1989JHC205, 1990J(P2)1619, 1996MI83>.



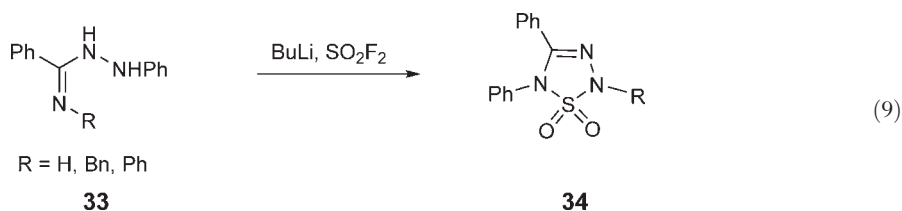
Recently this reaction was expanded to prepare a series of 1,2,3,5-thiatriazoles **26** bearing a tosyl group at the 2-position of the ring <2003PS1433>.

It was demonstrated that this reaction is an efficient method to prepare fused 1,2,3,5-thiatriazoles of type **26** bearing various substituents at the 2-, 4-, 5-positions. The same reaction has also been described for 'masked' or fused amidrazones **27**, where the N-1 atoms of the amidrazones are involved in aromatic or nonaromatic rings. Indeed this method was used to prepare 1,2,3,5-thiatriazoles **28–32** fused to pyridine, isoquinoline, benzodiazepine, and benzoxazine rings (Equation 8).

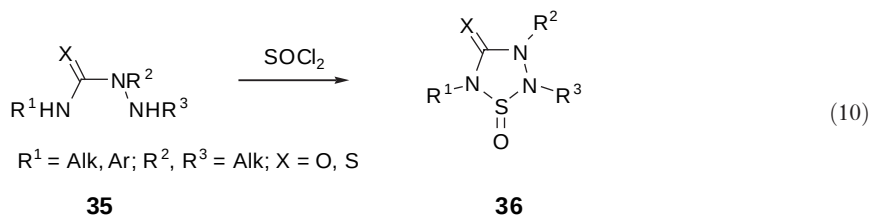


However, this method only allows the preparation of oxide derivatives of 1,2,3,5-thiatriazoles. All attempts to prepare 3-phenyl-1,2,3,5-thiatriazole by the reaction of benzamidrazone with thionyl chloride have failed. The ring degradation products, namely benzonitrile, sulfur, and nitrogen, were detected (see also Section 6.10.5.1) <1988ACB63>.

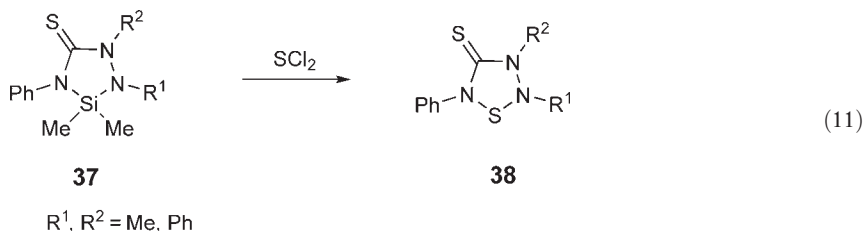
Reaction of amidrazones with sulfuryl fluoride leads to the formation of 1,2,3,5-thiatriazole 1,1-dioxides. Knollmüller and Kosma have found that amidrazones **33** do not react with sulfuryl fluoride in the presence of triethylamine. The use of a stronger base such as butyllithium allowed the preparation of 2,5-dihydro-1,2,3,5-thiatriazole-1,1-dioxides **34** (Equation 9) <1985M1321>.



This general approach to the 1,2,3,5-thiatriazole ring was also used to prepare 1,2,3,5-thiatriazolidine-4-one-1-oxides **36** (X=O) and 1,2,3,5-thiatriazolidine-4-thione-1-oxides **36** (X=S) by the reaction of semicarbazides **35** (X=O) and thiosemicarbazides **35** (X=S), respectively, with thionyl chloride in methylene chloride solution (Equation 10) <1979JHC895>.

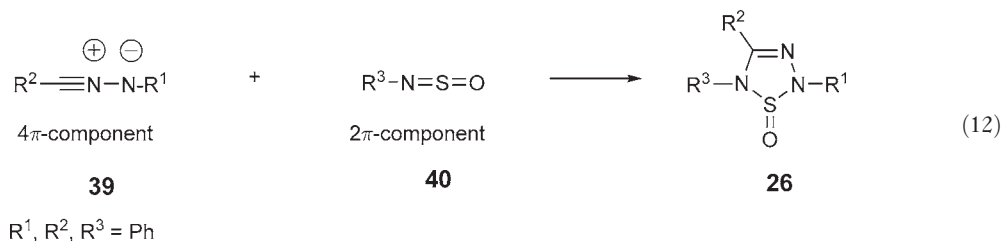


The reaction of 3-sila-1,2,4-triazolidin-5-thiones **37** with sulfur dichloride leads to 1,2,3,5-thiadiazolidine-4-thione **38** in very good yield. Formally, this reaction is a method of ring synthesis by transformation of another ring and will thus be listed in the appropriate section (Equation 11) <1978ZC336>.

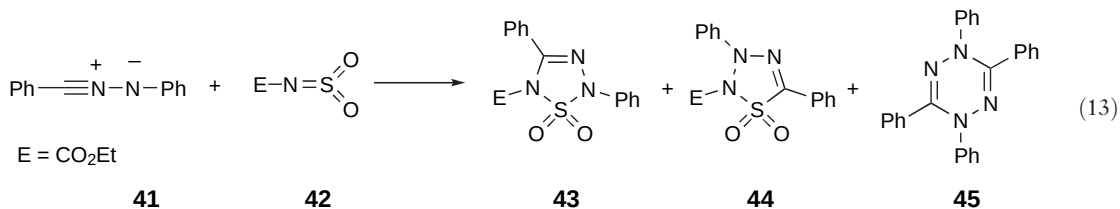


6.10.9.2.2 From [3+2] fragments: C–N–N + S–N

1,3-Dipolar cycloaddition reactions of nitrilimines to the N=S bonds of *N*-thionyl- and *N*-sulfonyl amines were used to prepare 2,5-dihydro-1,2,3,5-thiadiazole-1-oxides and 2,5-dihydro-1,2,3,5-thiadiazole-1,1-dioxides. Thus, nitrilimines **39** generated *in situ* from hydrazonoyl chlorides reacted with *N*-phenyl-*N*-sulfonylamine **40** or with triphenylsilylsulfonylamine in a regioselective manner to give 2,5-dihydro-1,2,3,5-thiadiazoles **26** in very good yield (Equation 12) <1962LA169>.

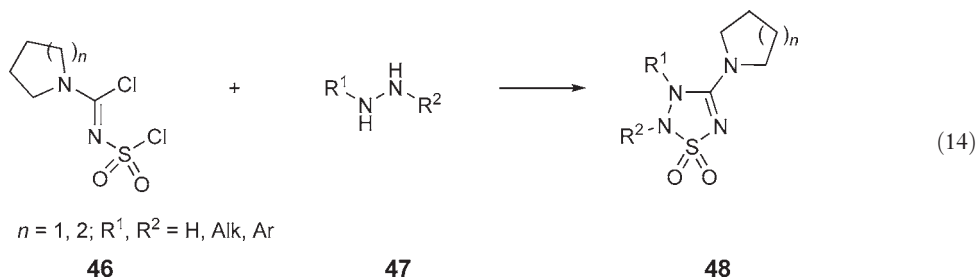


In contrast to the reaction of *N*-thionylaniline, the analogous reaction of *N*-sulfonyl amines **42** with nitrilimines **41** is not regioselective. A mixture of regioisomeric thiadiazoles **43** and **44** is formed in this reaction along with a substantial amount of by-product **45** <1985M1321>. Because of the very low yield of 1,2,3,5-thiadiazoles, this method is not recommended for the preparation of these compounds (Equation 13) <1985M1321>.

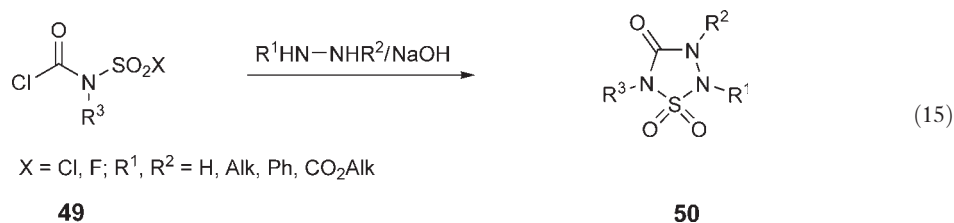


6.10.9.2.3 From [3+2] fragments: C–N–S + N–N

Reaction of *N*-(chlorosulfonyl)chloroformamidine **46** with hydrazines **47** afforded 4-pyrrolidino- and 4-piperidino-1,2,3,5-thiadiazole-1,1-dioxides **48** in good yield <2005AJC332>. Earlier, this reaction was used to prepare the 4-diethylamino derivative of the dioxides **48** (Equation 14) <1977JCM238, 1977JRM2813>.

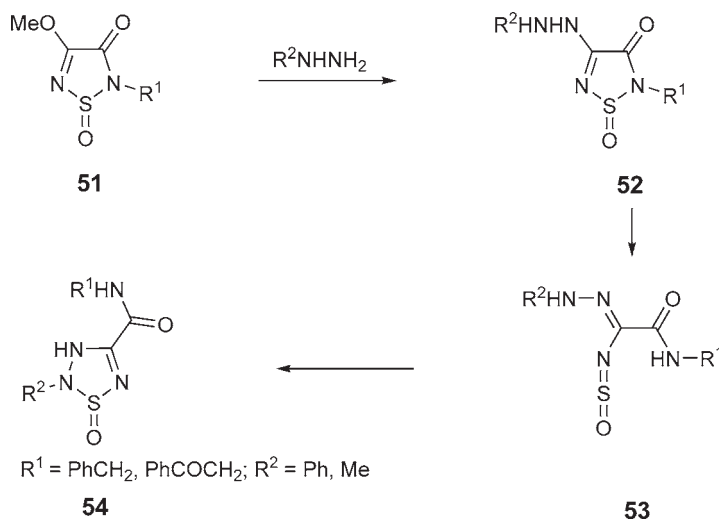


N-(Fluorosulfonyl)- or *N*-(chlorosulfonyl)carbamoyl chlorides **49** react with hydrazines and acylated hydrazines at -50°C to give 1,2,3,5-thiadiazolidine-4-one 1,1-dioxides **50**. Sodium hydroxide was used to neutralize hydrogen halides formed in this reaction (Equation 15) <1977JRM2813, 1977JCM238>.



6.10.10 Ring Synthesis of 1,2,3,5-Thiadiazoles by Transformation of Another Ring

Only two examples are described in the literature where ring transformation reactions were used for the synthesis of 1,2,3,5-thiadiazoles. 4-Methoxy-1,2,5-thiadiazol-3(2*H*)-one 1-oxides **51** readily react with amines to give the corresponding amino derivatives <1985TL6155, 1986H(24)1193>. When hydrazines were used instead of amines the substitution reaction of the methoxy group is followed by rearrangement of intermediate **52** via **53** to give 2,3-dihydro-1,2,3,5-thiadiazol-1-oxides **54** (Scheme 4). This reaction can be assigned, according to the L'Abbé classification, to the rearrangements where two atoms of the chain take part in the ring transformation process (Scheme 4) <1984JHC627>.



Scheme 4

The transformation of 3-sila-1,2,4-triazolidin-5-thiones **37** to 1,2,3,5-thiadiazolidine-4-thiones **38** takes place when the former is treated with sulfur dichloride (Equation 11) <1978ZC336>. This method is discussed in Section 6.10.9.2.1.

6.10.11 Synthesis of Particular Classes of Compounds

6.10.11.1 4-Dialkylamino-2,3-dihydro-1,2,3,5-thiadiazole-1,1-dioxides

The synthesis of novel heterocyclic compounds of low molecular weight is of interest for medicinal chemistry as a tool to create new biologically active compounds. Reaction of *N,N*-dialkyl (*N'*-chlorosulfonyl)chloroformamidines **55** with hydrazines **56** has been recently shown to be a versatile and efficient method for the synthesis of a variety of 4-dialkylamino-2,3-dihydro-1,2,3,5-thiadiazole-1,1-dioxides **57** (Equation 16) <2005AJC332>. First, this method has been described for the simple condensation products from the reaction of compound **55** with hydrazine, *N*-methylhydrazine, and 1,2-dimethylhydrazine <1985M1321>. Reaction of precursor **55** with methylhydrazine **56** ($R^2 = \text{Me}$, $R^1 = \text{H}$) has been shown to take place in a regioselective manner to afford thiadiazole **57** ($R^2 = \text{Me}$, $R^3 = \text{H}$) as the major product. The isomeric product **57** ($R^2 = \text{H}$, $R^3 = \text{Me}$) was obtained in only 4% yield. The reactions of compound **55** with aryl and acyl hydrazines afford 2-substituted thiadiazoles **57** as exclusive products in modest yields <2005AJC332>. The structures of the products obtained were confirmed by X-ray crystallographic analysis for compounds **57** ($R^2 = 5\text{-Cl}$, $2\text{-MeC}_6\text{H}_3$; $R^3 = \text{H}$ and $R^2 = 2\text{-thienoyl}$; $R^3 = \text{H}$). The conclusion was made that unsubstituted nitrogen atom of hydrazines **56** ($R^3 = \text{H}$) reacted with the amidine carbon atom of compound **55** while the substituted nitrogen atom reacted intramolecularly with the sulfonyl chloride moiety <2005AJC332>. 3-Substituted 1,2,3,5-thiadiazole-1,1-dioxides **57** were prepared by alkylation and acylation of 3-unsubstituted compounds **57** <1985M1321, 2005AJC332>. The structures of 4-dialkylamino-2,3-dihydro-1,2,3,5-thiadiazole-1,1-dioxides **57** together with the yield of the compounds prepared are shown in Table 4.

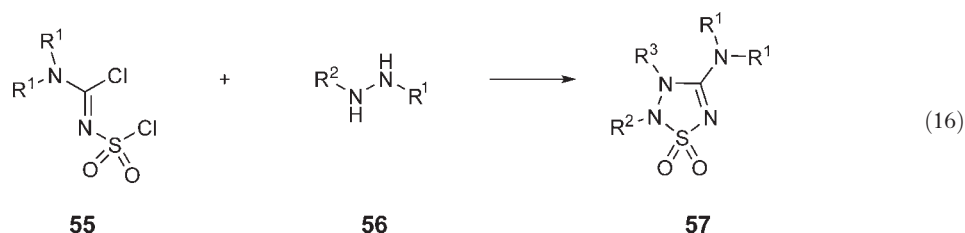


Table 4 4-Dialkylamino-2,3-dihydro-1,2,3,5-thiadiazole-1,1-dioxides **57** (Equation 16)

NR^1R^1	R^2	R^3	Yield (%)	Reference
Me_2N	<i>tert</i> -Butoxycarbonyl	H	50	2005AJC332
Me_2N	4-Cl-3- MeC_6H_3	H	85	2005AJC332
Me_2N	4- ClC_6H_4	H	23	2005AJC332
Me_2N	2,6-Dichlorophenyl	H	50	2005AJC332
Me_2N	Phenyl	Acetyl	41	2005AJC332
Me_2N	4- ClC_6H_4	Acetyl	79	2005AJC332
Me_2N	2,6-Dichlorophenyl	4- $\text{FC}_6\text{H}_4\text{CH}_2$	67	2005AJC332
Me_2N			59	2006AXE3170
$R^2 + R^3 =$				
Et_2N	H	H	46	1985M1321
Et_2N	Me	Me	68	1985M1321
Et_2N	H	Me	4	1985M1321
Et_2N	Me	H	63	1985M1321
Et_2N	3-Chloropyridazin-5-yl	H	61	2005AJC332
Piperidin-1-yl	2-Thiophenecarbonyl	H	24	2005AJC332
Piperidin-1-yl	4-Methylbenzoyl	H	44	2005AJC332
Piperidin-1-yl	Phenyl	H	41	2005AJC332
Piperidin-1-yl	Ethoxycarbonyl	Ethoxycarbonyl	18	2005AJC332
Piperidin-1-yl	2-Thiophenecarbonyl	Me	45	2005AJC332
Piperidin-1-yl	Phenyl	4-Cl- $\text{C}_6\text{H}_4\text{SO}_2$	91	2005AJC332

6.10.12 Applications

Theoretical calculations predict anticorrosion properties for 4-amino-1,2,3,5-thiadiazoles <2005JMT61>.

6.10.13 Further Developments

Two articles have appeared very recently dealing with ring expansion of 1,2,3,5-thiadiazoles to 1,2,4,6-thiadiazines <2007OBC472> and with the transformation of pyranopyrimidines to 1,2,3,5-thiadiazolopyrimidine-1-oxide <2006PS2529>.

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Biographical Sketch



Vasiliy Bakulev was born in Ekaterinburg, Russia. He obtained his Ph.D. in 1979, under the guidance of Professor Vladimir Mokrushin, on the synthesis of imidazole derivatives. He then studied electrocyclic reactions of diazocompounds and azomethyne ylides and in 1990 defended the second thesis of Doctor of Science (similar to Habilitation Degree) at Moscow State University. He received a diploma of Professor in 1998. Jointly with Wim Dehaen, he published a book on the chemistry of 1,2,3-thiadiazoles in 2004. He is currently professor at the Organic Synthesis and Technology Department of the Urals State Technical University (Ekaterinburg, Russia).



Wim Dehaen was born in Kortrijk, Belgium. He obtained his Ph.D. in 1988 under the guidance of Professor Gerrit L'Abbé on a study concerning the rearrangements of 5-diazoalkyl-1,2,3-triazole derivatives. After postdoctoral research in Israel (1988–90), Denmark (three months in 1990), the United Kingdom (three months in 1994), and Belgium (most of 1990–98), he was appointed as an associate professor at the University of Leuven (Belgium) in 1998, becoming a full professor at the same university in 2004. Until now, 220 publications have appeared in international journals about his work on heterocyclic and supramolecular chemistry, with more than 20 in co-authorship with Vasiliy Bakulev.

6.11

1,2,3,5-Dithiadiazoles and 1,3,2,4-Dithiadiazoles

R. J. Pearson

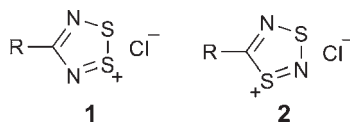
Keele University, Keele, UK

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6.11.1	Introduction	500
6.11.2	Theoretical Methods	500
6.11.2.1	1,2,3,5-Dithiadiazolium-4-Thiolate	500
6.11.2.2	Concerted Rearrangement of 1,3,2,4-Dithiadiazole	501
6.11.2.3	<i>Ab Initio</i> Calculations	501
6.11.3	Experimental Structural Methods	502
6.11.3.1	NMR Spectroscopy	502
6.11.3.2	IR Spectroscopy	503
6.11.3.3	UV Spectroscopy	503
6.11.3.4	Mass Spectrometry	503
6.11.3.5	ESR Spectroscopy	504
6.11.3.6	X-Ray Crystallography	504
6.11.4	Thermodynamic Aspects	505
6.11.4.1	Isomerism	505
6.11.4.2	Dimerisation	506
6.11.5	Reactivity of Fully Conjugated Rings	506
6.11.6	Reactivity of Substituents Attached to Ring Carbon Atoms	507
6.11.7	Reactivity of Substituents Attached to Ring Heteroatoms	507
6.11.8	Ring Synthesis from Acyclic Compounds	507
6.11.8.1	1,2,3,5-Dithiadiazoles	507
6.11.8.1.1	Synthesis from amidines	507
6.11.8.1.2	Synthesis from amidinium salts	508
6.11.8.1.3	Synthesis from amidoximes	509
6.11.8.1.4	Synthesis from nitriles	509
6.11.8.1.5	Synthesis from benzyl halide	509
6.11.8.1.6	Synthesis from alkenes	510
6.11.8.2	1,3,2,4-Dithiadiazoles	510
6.11.8.2.1	Synthesis from nitriles	510
6.11.8.2.2	Synthesis of 5-oxo-1,3 λ^4 ,2,4-dithiadiazole	511
6.11.9	Ring Synthesis by Transformations of Another Ring	512
6.11.10	Synthesis of Particular Classes of Compounds	512
6.11.10.1	Formation of Dithiatetrazocines	512
6.11.10.2	Formation of Metal Complexes	513
6.11.11	Important Compounds and Applications	513
	References	513

6.11.1 Introduction

In this chapter the dithiadiazole family is reported for the very first time. Since these fascinating five-membered heterocyclic cations, radicals, and dimers were not covered in CHEC-I(1984) and CHEC-II(1996), the discussion encompasses all available literature rather than focusing solely on publications post-1995. Before any further discussion, an appreciation of the two isomeric forms and the nomenclature associated with each is essential. The 6 π cyclic systems of 1,2,3,5-dithiadiazolium chloride **1** and 1,3,2,4-dithiadiazolium chloride **2** are shown below. As this chapter demonstrates, the 1,2,3,5-isomeric form dominates the literature in this field, reflecting the wider synthetic opportunity and stability associated with it.

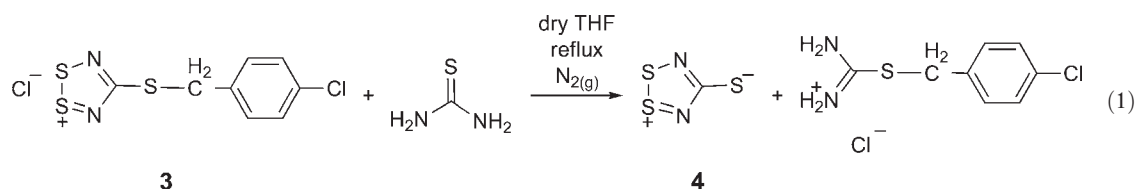


In the absence of the strict publication window adopted by the established chapters, we report herein the major highlights from a vast and varied array of key experimental findings. The majority of the described work was conducted over the last four decades and provides a real flavor and insight into the historical, recent, and ongoing areas of interest for these colorful and frequently crystalline compounds. Although this chapter does cover a broad sweep of the dithiadiazole literature, the material predominantly originates from the scientific contributions made by the Banister, Cordes, Oakley, Passmore, and Rees laboratories.

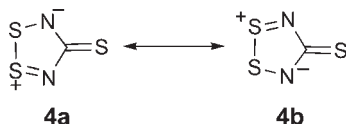
6.11.2 Theoretical Methods

6.11.2.1 1,2,3,5-Dithiadiazolium-4-Thiolate

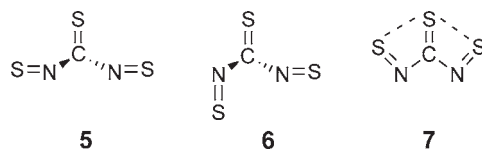
AM1 semi-empirical molecular orbital calculations on meso-ionic 1,2,3,5-dithiadiazolium-4-thiolate **4** suggested it could be a viable local energy minima product for the reaction of *S*-benzyl-1,2,3,5-dithiadiazol-4-ylum chloride **3** with thiourea (Equation 1) <2002ARK224>.



Calculated charge densities predicted very little charge on the exocyclic sulfur atom supporting instead the existence of canonical forms **4a** and **4b**.

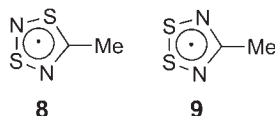


Experimental findings show no evidence in support of compound **4**. It is thought that isomeric structures **5–7** may account for the absence of proposed product **4**. This suggestion is reinforced by molecular orbital calculations that predict all three isomers to exhibit similar stability to that of compound **4**. While the heats of formation of the two acyclic valence tautomers **5** and **6** are 28 and 30 kcal mol⁻¹ higher than compound **4**, there is only 12 kcal mol⁻¹ separating compound **7** from the target compound (thiolate **4**). The equilibrium between compounds **4** and **7**, in which the latter shows further unexplained reactivity, would account for the generation of an unidentifiable brown gum.

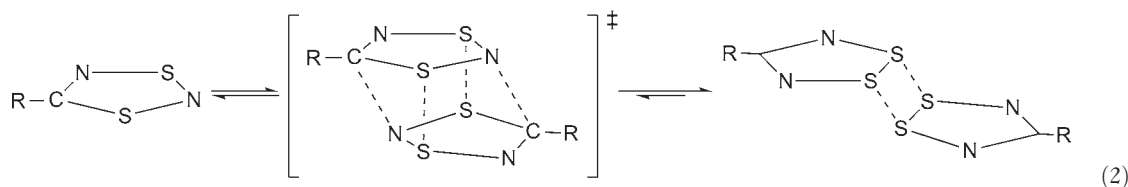


6.11.2.2 Concerted Rearrangement of 1,3,2,4-Dithiadiazole

In addition to meso-ionic examples, molecular orbital (MO) calculations have also been applied to radical work. 5-Methyl-1,3,2,4-dithiadiazolyl radical **8** has been reported to undergo a concerted rearrangement to 4-methyl-1,2,3,5-dithiadiazolyl radical **9** <1986CC140>.



The shape of the singly occupied molecular orbital (SOMO) supports the theory of head-to-tail interactions between two 1,3,2,4-dithiadiazolyl monomers to give the 1,2,3,5-dimer **11** via transition state **10** (Equation 2).



Compound	R
8	Me
12	H

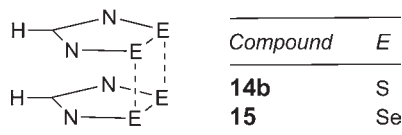
Compound	R
10	Me
13	H

Compound	R
11	Me
14a	H

Further complete neglect of differential overlap (CNDO) methodology in the same laboratory <1996IC1313>, on the simplest possible 1,3,2,4-radical **12**, shows that the concerted dimerization process, to yield compound **14a** via transition state **13** (Equation 2), is a photochemically symmetry allowed rearrangement.

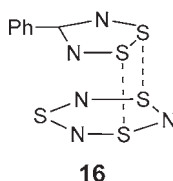
6.11.2.3 *Ab Initio* Calculations

Remaining on an identical theme to that introduced in Section 6.11.2.2, *ab initio* calculations on dimer **14b** were performed to elucidate the effect of replacing both sulfur atoms in the dithiadiazole core with selenium to give dimer **15** <1993JA7232>. Binding energies of 4.0 and 10.0 kcal mol⁻¹ were calculated for compounds **14b** and **15**, respectively. The greater strength associated with dimer **15** is consistent with better van der Waals contacts between selenium atoms (cf. sulfur atoms) of adjacent diselenadiazole rings. Such contacts are attributed to rings aligning 3.0–3.3 Å apart; a prediction that is in good agreement with the reported crystallographic data (Section 6.11.3.6) that shows both dimers to adopt a cofacial geometry.



In a separate example, the 4-phenyl-1,2,3,5-dithiadiazolium cation in the presence of [S₃N₃] gave 4-phenyl-1,2,3,5-dithiadiazolylum-1,3,5,2,4,6-trithiatriazinide **16**. *Ab initio* calculations show that the ionic charges of the two rings are

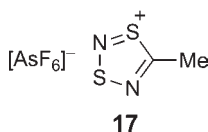
suitably matched for the five- and six-membered rings to align in parallel fashion to form charge-transfer complexes. Isolation of complex **16** showed secondary $S \cdots S$ interactions to be 2.864 and 2.812 Å <1990JCD2793, 1991JCD1099>.



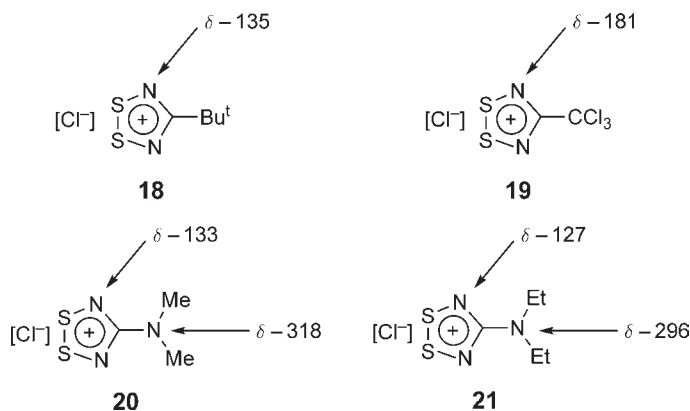
6.11.3 Experimental Structural Methods

6.11.3.1 NMR Spectroscopy

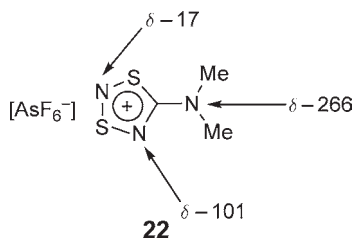
The ^1H NMR of 5-methyl-1,3,2,4-dithiadiazolium hexafluoroarsenate salt **17** exhibits a characteristic singlet at δ 4.82 <1985JCD1405>. However, diagnosis by conventional ^1H and ^{13}C NMR analysis is clearly hampered in many instances involving the dithiadiazoles due to the lack of relevant nuclei. As an alternative, characteristic ^{14}N NMR signals have been reported <1986MRC1080>.



Using ^{14}N NMR spectra, chemically different nitrogen atoms can be adequately distinguished from one another. Based on chemical shift data, ring nitrogens can be easily identified from nitrogen substituents attached to the ring carbon, as exemplified by the symmetrical chloride salts of **18**, **19**, **20**, and **21** <1989CC96>.



Similar chemical shift data are also available for the 1,3,2,4-isomeric form (compound **22**) of compound **20**, though the hexafluoroarsenate anion is the counterion in the example shown here (cf. chloride as counterion in compound **20**). Since the ring nitrogens become chemically inequivalent, we observe an extra signal. Thus, this technique serves as an ideal tool for establishing the proportion of each isomeric form within a given sample <1988IC2749>.



For compound **17** (lacking a side chain nitrogen), the chemical shift difference between the two ring nitrogens is even more pronounced, with the nitrogen flagged by sulfur atoms identified at $\delta -27$ while that adjacent to the ring carbon is reported at $\delta +126$ <1988IC2749>.

In some cases ^{14}N signals are too broad. A suitable alternative is ^{15}N NMR. However, this approach is often disfavored due to the synthetic demands associated with ^{15}N enrichment <1988IC2749>.

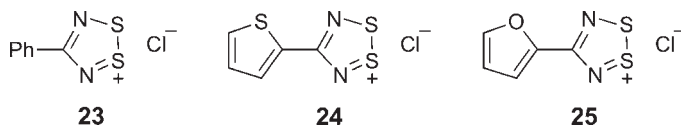
6.11.3.2 IR Spectroscopy

Depending on the side chains, IR data for dithiadiazoles are generally reported between 1600 and 250 cm^{-1} <1991JA582>. Such spectroscopy has been used in conjunction with other analytical techniques to confirm the rearrangement of some 1,3,2,4-dithiadiazoles into their 1,2,3,5 analogues <1992JCD1277>.

Diagnostic signals for hexafluoroarsenate salt **17** (Section 6.11.3.1) include the C–S and S–N stretches. In nujol mull assignments for the ν C–S (595 cm^{-1}), ν_{asym} S–N (1154 cm^{-1}) and ν_{sym} S–N (807 cm^{-1}) stretches are all reported <1985JCD1405>.

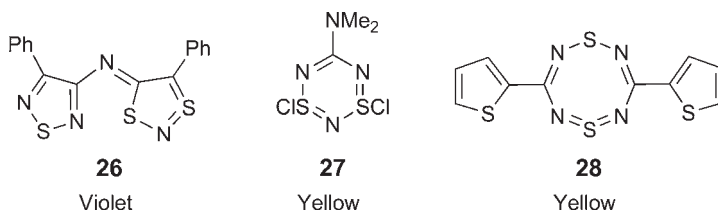
6.11.3.3 UV Spectroscopy

As mentioned in Section 6.11.1, the dithiadiazoles are frequently observed as brightly colored crystals. Examples of orange, purple, yellow, red, and burgundy colored compounds exhibiting UV activity are given by compounds **19**, **21**, **23**, **24**, and **25**, respectively <1989J(P1)2495, 1979J(P1)1192, 1986IC2119>. For compound **21**, $\lambda_{\text{max}} = 530\text{ nm}$.



It has been reported <1992CBR148> that, in general, the softer the anion used, the darker colored the resulting salt will be.

The intensity and array of colors is consistent with similar observations for structural relatives such as the dithiazoles <1989CC1134>, dithiatriazines <1989CC96>, and dithiatetrazocines <1981JA1540, 1989J(P1)2495, 1989CC1137>. Compounds **26–28** represent one example from each family.

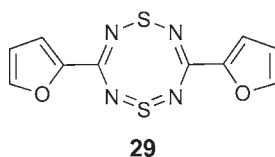


In addition to providing useful characterization data, the UV activity of these compounds has been applied to monitoring the progress of a ring contraction process. Thermolysis of 5-dimethylamino-1,3-dichloro-1,2,3,5-dithiadiazine **27** into 4-dimethylamino-1,2,3,5-dithiadiazole **20** can be tracked by the growth of an absorbance peak at 530 nm, and the concurrent loss of absorbance at 360 nm <1989CC96>.

Characteristic UV wavelengths have also been utilized in the determination of planar and buckled structures <1989J(P1)2495, 1989CC1137>.

6.11.3.4 Mass Spectrometry

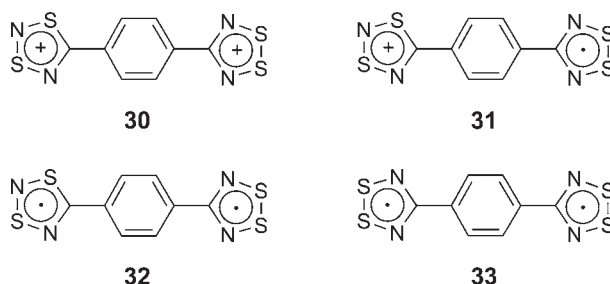
Synthesis of 1,2,3,5-dithiadiazoles from amidines in combination with sulfur dichloride is covered in Section 6.11.8.1.1. Interestingly, product mixtures were obtained when applying such synthetic approaches to yield compounds **24** and **25** from 2-thienylamididine and 2-furylamididine, respectively. Mass spectroscopy showed the mixtures to contain the desired compound as the major product, with strong RCN_2S_2^+ peaks <1979J(P1)1192> along with polychlorinated derivatives and small quantities of the corresponding dithiatetrazocines **28** and **29** <1989J(P1)2495>.



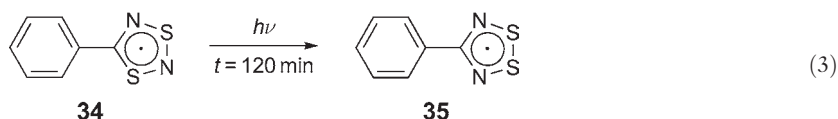
In addition to identifying the molecular ion of the dithiadiazole cation, major fragments corresponding to the loss of NS and NS₂ were also observed. Fragmentations for the dithiatetrazocines see a loss of thiophene-2-carbonitrile or furan-2-carbonitrile, with N, N₂S, and N₂S₂.

6.11.3.5 ESR Spectroscopy

The partial reduction of dication **30** to give radical cation **31** can be monitored in toluene at room temperature by electron spin resonance, as the 1:2:3:2:1 quintet, as described by Banister and co-workers <1993JCD1421>. Further reduction to give the diradical **32** results in a 1:1:1 triplet overlapping with a quintet. Upon stronger heating, rearrangement to diradical **33** was observed.



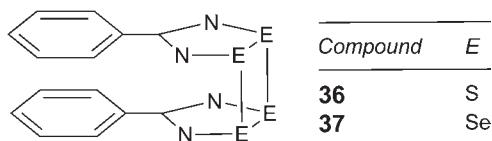
Similar rearrangement patterns have been reported for conversion of the 5-phenyl-1,3,2,4-dithiadiazole radical **34** into 4-phenyl-1,2,3,5-dithiadiazole radical **35** (Equation 3). In this latter example, complete conversion was seen after 120 min under photochemical conditions <1992CBR148>.



These two examples highlight how electron spin resonance (ESR) is a valuable means of monitoring dithiadiazole isomerizations.

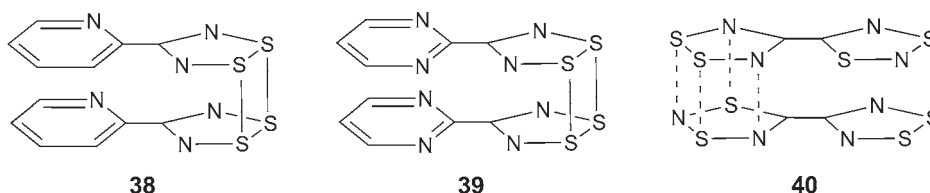
6.11.3.6 X-Ray Crystallography

There is a great wealth of data concerning the crystalline properties of dithiadiazolium cations and their corresponding radicals and dimers. The cofacial dimers for the 4-phenyl-1,2,3,5-dithiadiazolyl and 4-phenyl-1,2,3,5-diselenadiazolyl radicals have both been resolved (dimers **36** and **37**) (see also Section 6.11.2.3). When dimer **37** stacks in the crystalline form, a herringbone arrangement is observed <1989JA9276>. In the sulfur series (dimer **36**), three dimers arrange themselves with intermolecular S · · S interactions ranging from 3.795 to 3.93 Å. Such an arrangement provides channels through the crystal lattice <1989JCD1705>.

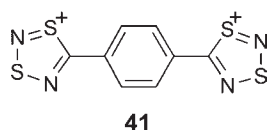


More recent findings show that 4-(2'-pyridyl)-1,2,3,5-dithiadiazolyl dimer **38** and 4-(2'-pyrimidyl)-1,2,3,5-dithiadiazolyl dimer **39** adopt similar coplanar arrangements to those already described (cf. compounds **14b**, **15**, **36**, and **37**).

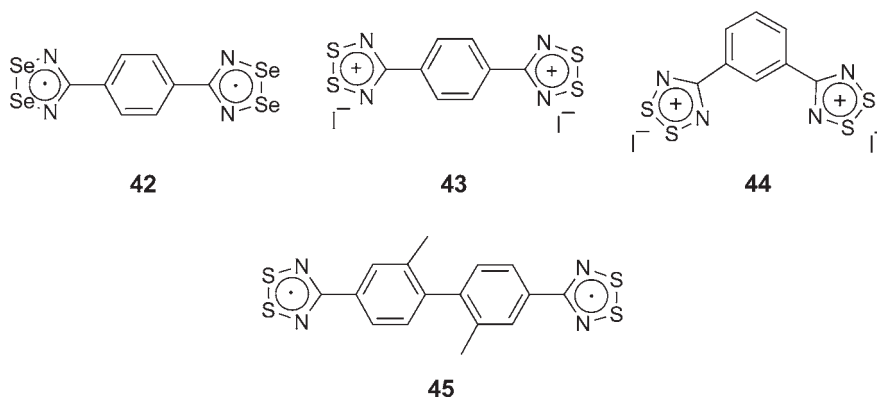
<2004JA9942, 2006CC341>. Likewise, the mixed biradical **40** shows favorable S··S, S··N and N··N interactions consistent with the general model of ring overlap <2005IC2576>.



The incorporation of a spacer unit in compound **40** provides the potential for a whole series of bis-dithiadiazoles. The cationic forms of these compounds tend to readily stack in the solid state. Many of the reported examples center upon the use of a rigid phenyl spacer. For 1,3,2,4-bis(dithiadiazole) dication **41**, the high degree of symmetry has been attributed to the observed molecular stacking. A slipped stacking system ensures that each dithiadiazole ring overlaps with a phenyl ring from the layer immediately above <1991JCD1099>.



Comparable stacking was also observed for the related 1,2,3,5-bis(diselenadiazole) diradical **42** <1991JA582> and 1,2,3,5-bis(dithiadiazole) salts **43** and **44** <1995JA6880>. A further modification looks at the introduction of a conformationally restrained diphenyl spacer, to generate compound **45**. This resulted in structural disorder not reported in the previous diradical systems <1999CC2269>.

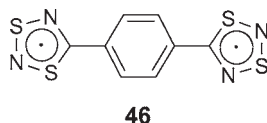


The polymorphic nature of some crystalline forms has also been widely reported <1995CC679, 1996AGE2533, 2002JCD2522, 2005CC4726>.

6.11.4 Thermodynamic Aspects

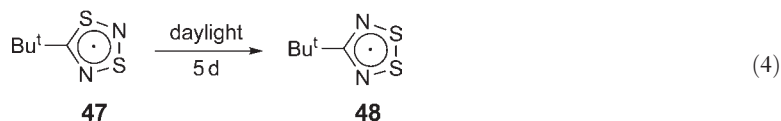
6.11.4.1 Isomerism

In the solid state, diradical **46** can irreversibly rearrange to give diradical **33** when heated at 150 °C <1992JCD1277>. The heat of rearrangement (ΔH_{rearr}) was calculated to be $317 \pm 10 \text{ kJ mol}^{-1}$. In addition to IR and ESR spectroscopy, the rearrangement was confirmed by differential scanning calorimetry and X-ray powder diffraction.



Radical **47** can also undergo a transformation to afford the 1,2,3,5-analogue **48** (Equation 4) <1987CC69>. This isomerism is a photochemically symmetry-allowed process, providing radical **48** in quantitative yield. This controlled

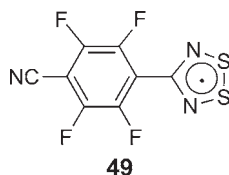
isomerism is thermally forbidden. Melting point values of 0–1 and 20–21 °C for radicals **47** and **48** are uncharacteristically low, but may be explained by the steric bulk of the *tert*-butyl group affecting the crystal packing. When stored in the absence of light, radical **47** shows no isomerism over a 20 h period.



For the corresponding chloride salt of radical **48** (compound **18**), and for other similar dithiadiazoles (compound **19**), ionic character is clearly observed with low solubility in nonpolar solvents <1979J(P1)1192>.

6.11.4.2 Dimerisation

As already addressed in Section 6.11.2.3, secondary interactions will govern the shift between radical and dimer. Since most dimers of this type are formed, from the radical version, by S··S interactions (or the selenium equivalents) of rings lying coplanar <1980JCD1812, 1985CB3781>, the introduction of steric bulk could be considered as a good strategy to promote a stabilized radical. On a similar theme radical **49** was proposed. Here the generation of dimer is subdued by in-plane CN··S interactions and coplanar F··F repulsions <1996AGE2533>.

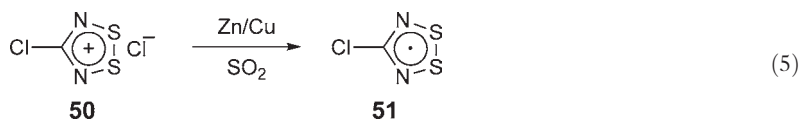


The ability to resolve X-ray crystals of dithiadiazole radicals is significant in emphasizing their stability and furthermore the low-energy barrier between free radical and associated radicals (to give dimer). For the 4-phenyl-1,2,3,5-dithiadiazole dimer **36**, $\Delta H_{\text{dimer}} \approx -35 \text{ kJ mol}^{-1}$ <1986JCD1465, 1989JCD2229, 1996AGE2533>. This weak binding data is comparable to that obtained separately by quantitative ESR spectroscopy <1987CC69> and highlights how the dimer-radical balance can be manipulated by subtle structural modifications as presented for radical **49**.

6.11.5 Reactivity of Fully Conjugated Rings

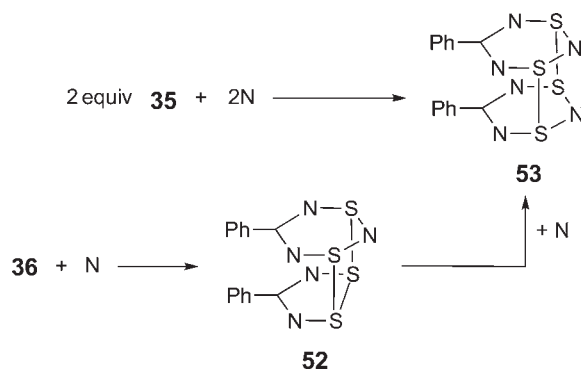
In this section, we can consider many different transformations. Unimolecular, radical, reduction, ring expansion, hydrolysis, and dechlorination reactions can all be described. The first two reactions in this list have already been addressed (Sections 6.11.2.2, 6.11.4.1, and 6.11.4.2).

Reduction of 4-chloro-1,2,3,5-dithiadiazolium chloride **50** to give air-sensitive 4-chloro-1,2,3,5-dithiadiazolyl radical **51** (Equation 5) was achieved with Zn/Cu in liquid SO₂ <1983CB416, 1989JCD1705, 1995CC679, 2002JCD2522>. Other reduction techniques include the use of Ph₃Sb <1993JCD1421>, the use of silver powder in acetonitrile, or the use of sodium dithionite in tetrahydrofuran <1985JCD1405>.



The disulfide bond in radical **35** and dimer **36** can incorporate atomic nitrogen, allowing a ring-expanded dithiatrizine dimer **53** (Scheme 1). Two mechanisms have been proposed for this plasma reaction with one involving the initial formation of compound **52** <1989JCD1705>.

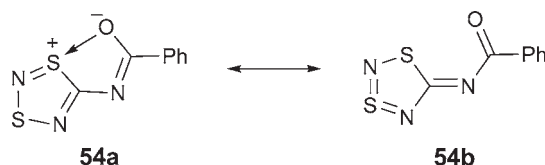
For the dithiadiazolium chloride salts, dechlorination reactions to give the corresponding dimer have also been reported <1989CC351>. This process can be performed electrochemically and is reversed in the presence of sulfur chloride. Such dithiadiazolium salts are also prone to hydrolysis when exposed to the atmosphere, with rapid hydrolysis observed under aqueous conditions <1979J(P1)1192>.



Scheme 1

6.11.6 Reactivity of Substituents Attached to Ring Carbon Atoms

The most relevant example for this section relates to the work involving the meso-ionic 1,2,3,5-dithiadiazolium-4-thiolate **4** (see discussion in [Section 6.11.2.1](#)). In the 1,3,2,4-dithiadiazole series, compound **54** also has two resonance forms, highlighting how the functionality attached to the ring carbon can provide intramolecular stability to the dithiadiazolium core structure [<1978CB698>](#).



6.11.7 Reactivity of Substituents Attached to Ring Heteroatoms

In the related dithiatetrazocine series ([Sections 6.11.3.3 and 6.11.3.4](#)) attempts were made to synthesize the *S*- and *N*-oxide derivatives using either *m*CPBA or N_2O_4 [<1989CC1137, 1989J\(P1\)2495>](#). Such synthetic goals proved to be unsuccessful and may account for a similar lack of compounds relevant for discussion in the dithiadiazole series.

6.11.8 Ring Synthesis from Acyclic Compounds

Over the last 40 years, a number of different synthetic strategies have been employed to yield the dithiadiazole ring structure from a range of acyclic building blocks. Due to a wealth of synthetic approaches, including a number of subtle modifications, the 1,2,3,5- and 1,3,2,4-derivatives are discussed independently in this section in an attempt to improve clarity and highlight the availability of different reagents.

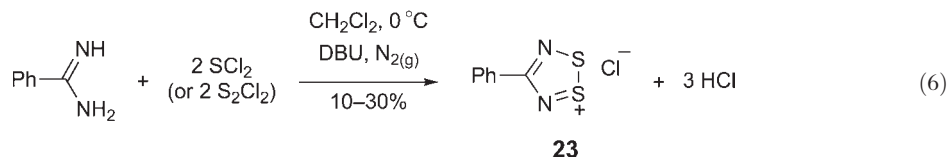
6.11.8.1 1,2,3,5-Dithiadiazoles

Attention will first focus on a variety of successful preparations of 1,2,3,5-dithiadiazoles, since these are reported in the literature to a greater extent than their 1,3,2,4-counterparts. As already described ([Section 6.11.3.3](#)), these compounds tend to be isolated as brightly colored plates or needles.

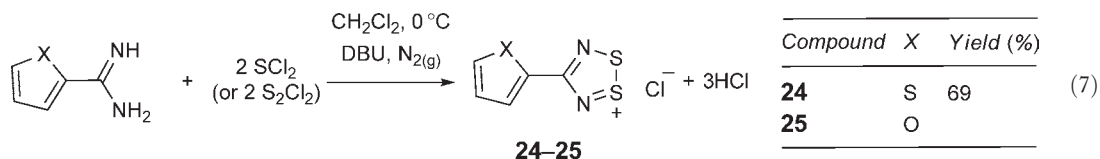
6.11.8.1.1 Synthesis from amidines

Amidines dissolved in dichloromethane at 0°C and under an atmosphere of nitrogen can be combined with sulfur dichloride (SCl_2) or disulfur dichloride (S_2Cl_2) to easily generate the dithiadiazolium chlorides. [Equation \(6\)](#) illustrates the overall transformation to give 4-phenyl-1,2,3,5-dithiadiazolium chloride **23**. Since HCl is generated

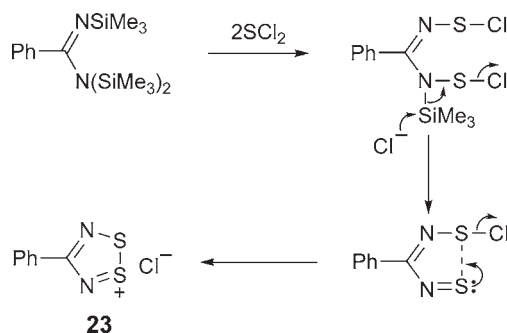
as a by-product, the inclusion of a tertiary base, such as 1,8-diazabicyclo-[5,4,0]-undec-7-ene (DBU), has been shown to enhance the progress of the reaction [<1992CBR148, 1989CC1134>](#).



Using similar reaction conditions to those already described, 4-(2-thienyl)-1,2,3,5-dithiadiazolium chloride **24** and 4-(2-furyl)-1,2,3,5-dithiazolium chloride **25** have been synthesized (Equation 7). Compound **24** is isolated as a red crystalline material in a yield of 69% [<1989J\(P1\)2495>](#).



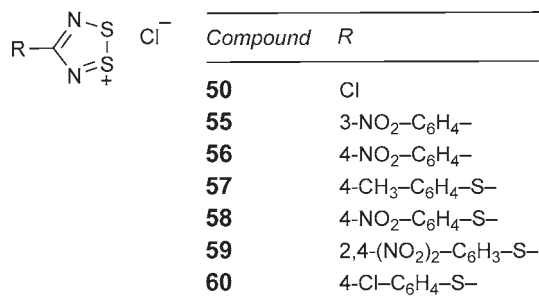
The yellow crystals of compound **23** (Equation 6) are routinely obtained in a yield of 10–30%. However, replacement of benzamidine with *N,N,N'*-tris(trimethylsilyl)benzamidine gives compound **23** in a 60% yield without the requirement for any acid scavengers, thus improving the ease of the purification process [<1989J\(P1\)2495>](#). The mechanism and labile nature of the trimethylsilyl groups is illustrated in Scheme 2 (modified from [<1989J\(P1\)2495>](#)). On the basis of these findings, silylated amidines remain an attractive route to dithiadiazoles.



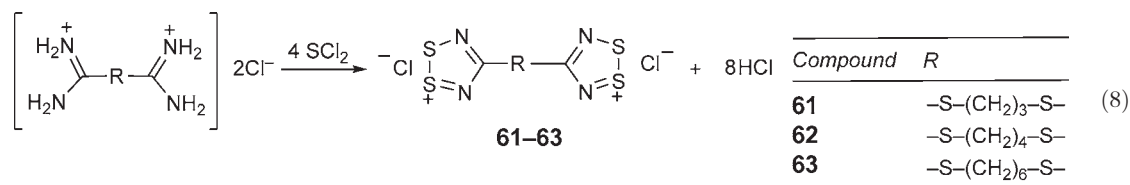
Scheme 2

6.11.8.1.2 Synthesis from amidinium salts

Applying similar methodology to that described previously (Section 6.11.8.1.1), the dithiadiazole ring can also be synthesized starting from the corresponding amidinium salts. Using benzamidinium chloride and 3 equiv of sulfur dichloride in nitrobenzene, heated to 105°C for approximately 5 h, gives a 19% yield of compound **23** [<1979J\(P1\)1192>](#). Rees and co-workers achieved the same material in a 54% yield using SCl₂ in dichloromethane at room temperature in the presence of DBU [<1989J\(P1\)2495>](#). As an extension of the work already described, Tschöpe and co-workers reported the synthesis of compound **50** and six other derivatives (compounds **55–60**) in yields ranging from 60% to 70% [<1994JPR266>](#).

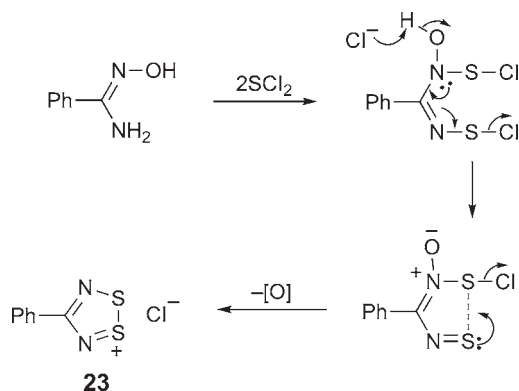


The same research group <1994JPR266> expanded the synthesis to encompass diamidinium salts. Using dithioether spacers between amidine units, three alkyl-dithio-bis(1,2,3,5-dithiadiazolium) salts were synthesized (compounds **61–63**), from the respective diamidine salts (Equation 8), in yields of 90%.



6.11.8.1.3 Synthesis from amidoximes

In similar fashion to the mechanism involving silylated benzamidine (Scheme 2), sulfur dichloride in the presence of benzamidoxime can also lead to the generation of 4-phenyl-1,2,3,5-dithiadiazolium chloride **23**. In the presence of DBU, this reaction is achieved in a yield of 32% <1989J(P1)2495>. Examination of the mechanism (Scheme 3), when compared directly to the analogous reaction involving the amidine (Section 6.11.8.1.1), reveals two major differences. The first involves the generation of an *N*-oxide intermediate and the second shows the need for a deoxygenation process, in the final step, along with the ring closure.



Scheme 3

6.11.8.1.4 Synthesis from nitriles

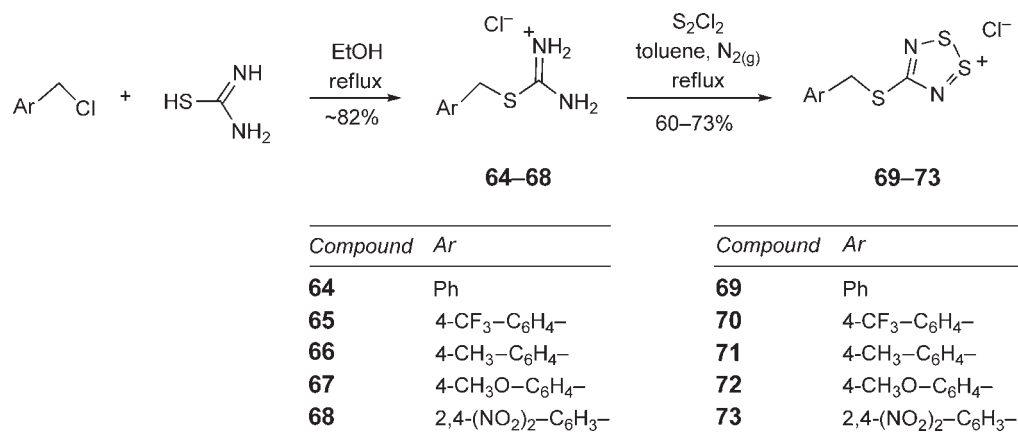
The role of nitriles is pivotal to the synthesis of 1,3,2,4-dithiadiazoles, as outlined later in this chapter (Section 6.11.8.2.1). However, it is also possible to make use of this functionality in the 1,2,3,5-series. 4-Trichloromethyl-1,2,3,5-dithiadiazolium chloride **19**, 4-phenyl-1,2,3,5-dithiadiazolium chloride **23**, and 4-*tert*-butyl-1,2,3,5-dithiadiazolium chloride **18** can all be prepared from the related nitrile building blocks <1979J(P1)1192>.

The synthesis of all three derivatives has been studied by two different methods from within the same laboratory. The first reaction requires trichlorocyclotrithiazene (NSCl)₃ (see Sections 6.11.8.1.6 and 6.11.9) and the introduction of heat, while, the second protocol uses NH₄Cl and SCl₂ with heat again being applied. In the case of the trichloromethyl and phenyl derivatives (compounds **19** and **23**), better yields were observed when the first method was adopted (e.g., 42% vs. 30% and 50% vs. 25% yield, respectively).

For the tertiary butyl derivative (compound **18**), such analysis was difficult due to rapid decomposition. A lack of dithiadiazole product is also observed when attempting these reactions with nitriles containing α-CH bonds. The resulting black sticky solids gave unidentified mixtures; therefore compounds with activated hydrogens should be avoided when following this procedure <1979J(P1)1192>.

6.11.8.1.5 Synthesis from benzyl halide

S-Benzyl derivatives can be formed using the robust synthesis of the appropriately substituted benzyl halide in combination with thiourea (Scheme 4). The tethered thiuronium salts **64–68** are routinely prepared by S_N2



Scheme 4

reactions in 78–82% yield. Since the second synthetic step is analogous to that involving the amidinium salts (Section 6.11.8.1.2), as outlined in Equation (8), a number of derivatives **69–73** can be generated in respectable yields (60–73%) <2002ARK224>. This chemistry clearly relies on the use of thiourea, which is a known carcinogenic reagent. However, when handled correctly there exists a great deal of scope, using this synthetic route, due to the number of alkyl halides commercially available.

6.11.8.1.6 Synthesis from alkenes

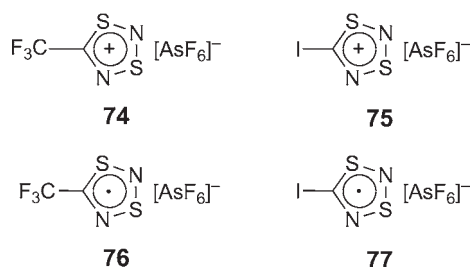
For situations where the amidine, amidinium salt, amidoxime, nitrile, or halide is not a feasible option, the procedure by Banister and co-workers provides yet another route to the desired five-membered ring systems <1979J(P1)1192>. Starting from a suitable alkene and trichlorocyclotrithiazene (NSCl)₃, this colorful reaction can undergo a number of transitions upon heating to 60–80 °C, under nitrogen. When applied to tetrachloroethene, 4-trichloromethyl-1,2,3,5-dithiadiazolium chloride **19** can be obtained in 13% yield, as orange plates, after cooling and recrystallizing from thionyl chloride. While this procedure presents a further route to the desired dithiadiazoles, the longer reaction time (2 days, rather than 1–5 h) and lower yield, relative to the synthesis via the nitrile building block (cf. 30–42%, see Section 6.11.8.1.4) resigns this methodology to situations when the alkene is the only feasible starting material.

6.11.8.2 1,3,2,4-Dithiadiazoles

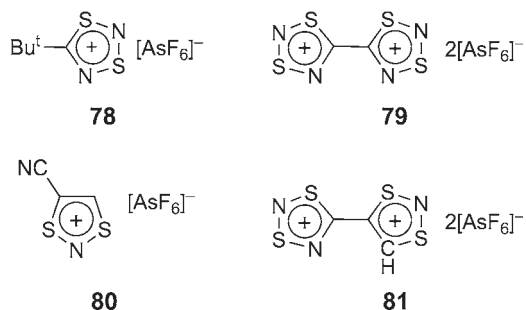
Synthesis of the 1,3,2,4-analogues is confined to SNS⁺ reacting with a nitrile. Fewer synthetic options, coupled with the conversion of the 1,3,2,4-radical to the 1,2,3,5-counterpart, by thermal or photochemical isomerism (Section 6.11.4.1), account for a limited number of examples in this section.

6.11.8.2.1 Synthesis from nitriles

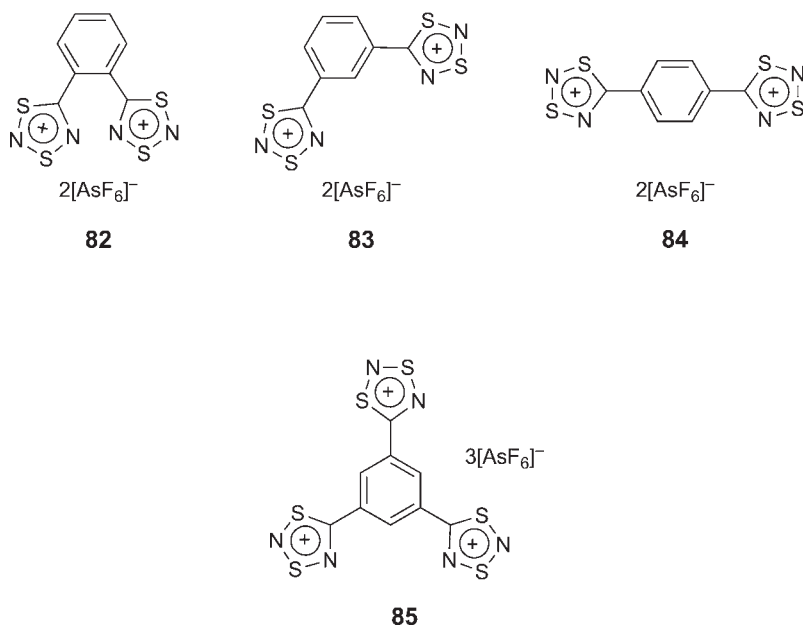
Hexafluoroarsenate salts **74** and **75** are prepared from the relevant nitriles using S₂NAsF₆ as the source of the dithianitronium cation (SNS⁺). Further reaction with 2 equiv of SbPh₃ gives radicals **76** and **77**. Such reactivity can be confirmed by ESR spectroscopy, prior to quantitative isomerism, which takes place at room temperature <1986CC140>.



The same approach was used to synthesize the 5-*tert*-butyl-1,3,2,4-dithiadiazolium salt **78** and radical **47** <1987CC69>, as well as dication **79** <1991CC369>. A yield of 97% was achieved for this latter example, when dicyanogen was heated at 50 °C for 5 days in the presence of SNSAsF₆. A similar yield was also obtained for compound **80** using HCCCN as the starting material. This highlights the greater reactivity of the alkyne over the nitrile. Further reactivity with SNSAsF₆ to give compound **81** is very slow, showing completion only after heating at 50 °C for 10 weeks <1991CC369>.

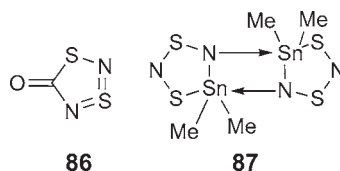


Using the same methodology, from *ortho*, *meta*, and *para* dicyanobenzenes compounds **82**, **83**, and **84** were synthesized in yields of 75%, 85%, and 92% <1991CC369>. As expected, *para* derivative **84** gave the most stable crystal lattice, presumably due to its linear nature. Further work in the same laboratory involved the synthesis of the 5,5',5''-(1,3,5-phenylene)tris(1,3,2,4-dithiadiazolium)tri(hexafluoroarsenate) salt **85** in 80% yield.



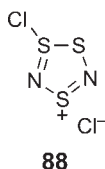
6.11.8.2.2 Synthesis of 5-oxo-1,3λ⁴,2,4-dithiadiazole

Compound **86** highlights a more unusual 1,3,2,4-dithiadiazole <1975AGE498, 2004CPL516, 2005CPL440>. This five-membered heterocyclic ketone, which can be alternatively formulated as a meso-ionic 1,3,2,4-dithiadiazolium-5-olate, is synthesized from tetrasulfur tetranitride and tris(trimethylstannyl)amine to form 5,5-dimethyl-1,3λ⁴,2,4,5-dithiadiazastannole **87**, which upon treatment with COF₂ is converted into compound **86** in 49% yield, with dimethyltin fluoride as the by-product.



6.11.9 Ring Synthesis by Transformations of Another Ring

The use of trichlorocyclotrithiazene as a reactant for nitriles (Section 6.11.8.1.4) and alkenes (Section 6.11.8.1.6) could be considered as a method for forming dithiadiazoles via the transformation of an existing ring structure. While the reaction mechanism remains debatable, cyclic degradation upon heating the trimer to give the monomer (NSCl) is one clearly recognized process. In this sense, the mechanism is best described as a ring degradation event, rather than a ring transformation. 1-Chloro-1,2,4,3,5-cyclotrithiadiazenium chloride **88** provides an alternative source of NSCl.



The formation of compound **88** involves heating ammonium chloride and disulfur dichloride. Since dithiadiazoles can also be synthesized by the procedure already outlined in the nitrile section (Section 6.11.8.1.4) involving heat and the three acyclic reagents, NH_4Cl , SCl_2 , and RCN in a ratio of 1:2:1, the suggestion that NSCl is again generated *in situ* appears valid. By way of clarifying this situation, Banister and co-workers <1979J(P1)1192> proposed that when adopting the three acyclic reagents method, the nitrile will first be converted into an amidine which then undergoes a further reaction with SCl_2 as already described (Section 6.11.8.1.1). In other words, perhaps only the cyclic reagents operate as effective NSCl donors en route to the dithiadiazole core.

Expanding the dithiadiazole ring to give the dithiatriazine derivative has already been documented (Section 6.11.5, Scheme 1). In the UV section (Section 6.11.3.3) we also introduced briefly the opposite transformation, in which a six-membered ring is converted into a five-membered analogue. Thermolysis of 1,3,2,4,6-dithiatriazine **27** in toluene gave chloride salt **20** in a yield of 91% <1989CC96>. Compounds **18**, **19**, and **21** were also obtained, in good yields, by contraction of the relevant dithiatriazine, when heated.

6.11.10 Synthesis of Particular Classes of Compounds

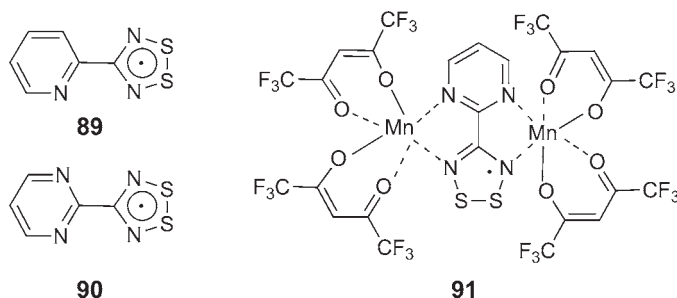
6.11.10.1 Formation of Dithiatetrazocines

Though the dithiatetrazocine rings are not formed from the dithiadiazoles, it was deemed relevant to mention the close synthetic parallels between the two structural families. In 1981, Woodward and co-workers reported <1981JA1540> the synthesis of four novel dithiatetrazocines (see Sections 6.11.3.3 and 6.11.3.4) using the amidine, SCl_2 , and DBU procedure described earlier for dithiadiazole production (Section 6.11.8.1.1). These thermally stable, crystalline, and often planar eight-membered ring systems were shown to form in yields ranging from 3.8% to 54%, though typical conversion was less than 10%.

The major product of this reaction was the 1,2,3,5-dithiadiazole, with the dithiatetrazocine evident as a competing by-product, as alluded to in Section 6.11.3.4 <1989J(P1)2495>. With this in mind, Rees and Amin <1989CC1137> reported distinct routes for both the five- and eight-membered ring systems. For the dithiadiazole product, *N,N,N'*-tris(trimethylsilyl)benzamidine (see Scheme 2, Section 6.11.8.1.1) was the preferred reagent, whereas the dithiatetrazocine was found to form more effectively in the presence of a sulfur transfer agent.

6.11.10.2 Formation of Metal Complexes

Combining the 4-phenyl-1,2,3,5-dithiadiazole dimer **36** with $[\text{Fe}_2(\text{CO})_9]$ or $[\text{Fe}_3(\text{CO})_{12}]$ produces the $[\text{Fe}_2(\text{CO})_6(\text{PhCN}_2\text{S}_2)]$ complex. X-ray crystal data confirm this formation with a reported butterfly structure that shows Fe–S bond distances of 2.225 Å [<1989JCD2229>](#). In addition to S-coordination, examples of dithiadiazoles acting as N-coordinating ligands also exist. The 4-(2'-pyridyl)-1,2,3,5-dithiadiazolyl radical **89** forms a bidentate chelation to bis(hexafluoro-acetyl-acetonato)-cobalt [<2004JA9942>](#). Chelation involving both the pyridine and dithiadiazole nitrogens is confirmed by the X-ray crystallography. The same N-coordinating behavior is also observed when combining bis(hexafluoro-acetyl-acetonato)-manganese with the pyrimidine radical **90** [<2006CC341>](#). However, X-ray crystal data illustrate that radical **90** is actually capable of acting as a bis-bidentate ligand, to give dimanganese complex **91**.



In a previous study, involving two dithiadiazole ligands structurally related to **89** and **90**, no evidence for coordination between the dithiadiazole nitrogen and metal center was observed [<2000EJI1045>](#).

6.11.11 Important Compounds and Applications

Much of the interest in the dithiadiazole series centers around their potential as conductors [<1989JA9276, 1989IC1326, 1991JA582, 1992IC1802, 1992CBR148, 1993JA7232, 1994AM798, 1995JA4755, 1995JA6880>](#) and magnetic materials [<1995CC679, 1996AGE2533, 1999CC1393, 2001MI93>](#). Based on such properties, this family of stable molecular radicals show future promise in many areas including thin film devices [<1996IC7626, 1999CC2269>](#). Other potential applications relate to their ability as dehalogenating agents [<1989CC351>](#) and as radical traps [<1989JCD1705>](#).

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Biographical Sketch



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6.12

Three or Four Heteroatoms including at least One Selenium or Tellurium

S. Yamazaki

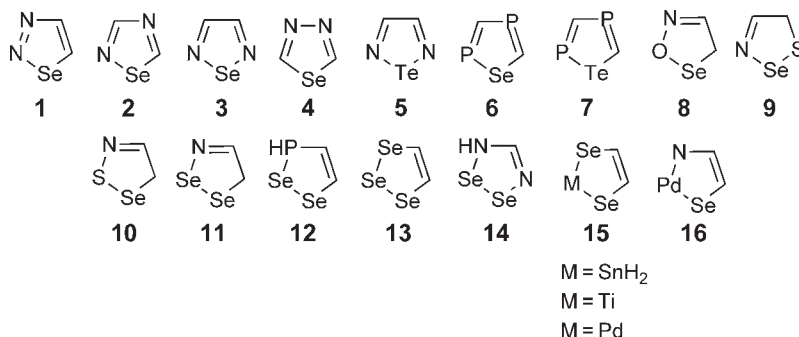
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6.12.1	Introduction	518
6.12.2	Theoretical Methods	518
6.12.3	Experimental Structural Methods	524
6.12.3.1	X-Ray diffraction	524
6.12.3.2	NMR Spectroscopy	532
6.12.3.3	Mass Spectrometry	536
6.12.3.4	IR Spectroscopy	537
6.12.3.5	Photoelectron, UV, and ESR Spectroscopy	537
6.12.4	Thermodynamic Aspects	539
6.12.4.1	Melting Points and Solubilities	539
6.12.4.2	Aromaticity and Stability	540
6.12.5	Reactivity of Fully Conjugated Rings	540
6.12.5.1	Thermal and Photochemical Reactions	540
6.12.5.2	Electrophilic Attack at Nitrogen	543
6.12.5.3	Electrophilic Attack at Carbon	543
6.12.5.4	Nucleophilic Attack at Carbon	544
6.12.5.5	Electrophilic Attack at Selenium and Tellurium	544
6.12.5.6	Nucleophilic Attack at Selenium and Tellurium	545
6.12.5.7	Nucleophilic Attack at Hydrogen	547
6.12.5.8	Reaction with Radicals, Transition Metal Complexes, and Reduction	549
6.12.5.9	Intermolecular Cycloaddition Reactions	555
6.12.6	Reactivity of Nonconjugated Rings	557
6.12.7	Reactivity of Substituents Attached to Ring Carbon Atoms	557
6.12.8	Reactivity of Substituents Attached to Ring Heteroatoms	561
6.12.9	Syntheses	562
6.12.9.1	1,2,3-Selenadiazoles	562
6.12.9.2	1,2,4-Selenadiazoles	566
6.12.9.3	1,2,5-Selenadiazoles	567
6.12.9.4	1,3,4-Selenadiazoles	570
6.12.9.5	1,2,4-Selenadiphospholes, Telluradiphospholes	571
6.12.9.6	Oxaselenazoles, Thiaselenazoles, Diselenazoles	572
6.12.9.7	Diselenaphospholes	575
6.12.9.8	Triselenoles	575
6.12.9.9	Diselenadiazoles	576

6.12.10 Important Compounds and Applications**577****6.12.11 Further Developments****578****References****578****6.12.1 Introduction**

In this chapter, the following ring systems are described, although a number of ring systems are possible for the title. They are 1,2,3-, 1,2,4-, 1,2,5-, and 1,3,4-selenadiazoles **1–4**, 1,2,5-telluradiazole **5**, 1,2,4-selenadiphosphole **6**, 1,2,4-telluradiphosphole **7**, 1,2,5-oxaselenazole **8**, 1,2,3- and 1,2,5-thiaselenazoles **9** and **10**, 1,2,3-diselenazole **11**, 1,2,3-diselenaphosphole **12**, 1,2,3-triselenole **13**, 1,2,3,5-diselenadiazole **14**, 1,3,2-diselenastannole, 1,3,2-diselenatitanole, 1,3,2-diselenapalladole **15**, and 1,2,3-selenapalladazole **16**. The structural types also include their dihydro derivatives and fused compounds.



CHEC(1984) <1984CHEC(6)333> described compounds containing five-membered selenium–nitrogen heterocycles and early reviews. CHEC-II(1996) <1996CHEC-II(4)743> covered the literature for compounds with three or four heteroatoms including at least one selenium or tellurium from 1982 to 1995. Houben-Weyl's *Science of Synthesis* has provided a comprehensive account of this type of heterocycle <2004HOU777, 2004HOU659>. Recent work on selenadiazoles has been also reviewed <2002CHE1437, B-1990M11, 2003PHC230, 2002PHC200, 2001PHC188, 1998PHC172, 1997PHC170>. This chapter covers literature published since 1995.

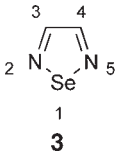
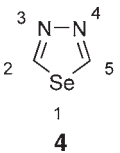
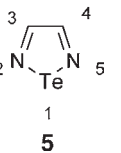
It is difficult to generalize the ring systems treated in this chapter. Some common features arise from the presence of selenium and tellurium atoms. One of the main types of compounds among the reported ring systems are the 1,2,3-selenadiazoles. The interest in 1,2,3-selenadiazoles arises from the fact that they undergo a wide variety of reactions with the loss of nitrogen and/or selenium. They are converted to different organoselenium compounds, or acetylenes, and also act as a source of elemental selenium. 1,2,5-Selenadiazoles, 1,2,3- and 1,2,5-thiaselenazoles, and 1,2,3,5-diselenadiazoles are of interest because of their potential use in conducting materials, by incorporation into various ring systems and addition of substituents, related to their electronic properties and crystal structures <1984CHEC(6)513>. 1,2,5-Selenadiazoles are also considered as a protecting group for 1,2-diamines. The various relatively rare ring systems indicated above are studied because they represent a so far unexplored area.

6.12.2 Theoretical Methods

Theoretical calculations for 1,2,5- and 1,3,4-selenadiazoles and 1,2,5-telluradiazole were reported <1995ACS11, 1997JST451, 2001JST81>.

Geometric parameters (bond lengths and bond angles, rotational constants, dipole moments) and vibrational infrared (IR) spectra of 1,2,5- and 1,3,4-selenadiazoles have been calculated by density functional theory (DFT) with the combined Becke3-LYP gradient exchange-corrected functional (DFT(B3LYP)) and the conventional *ab initio* MP2(full) approach and are shown in **Table 1** <1997JST451>. The standard 6-31G(d,p) basis set was used for all atoms except selenium, for which a partially uncontracted Huzinaga basis set supplemented with a set of d-polarization functions was employed. The molecular parameters computed by means of the DFT method are in a good agreement with those predicted by the MP2 approach and with the experimental data. The IR spectra of 1,2,5- and 1,3,4-selenadiazoles and their deuterated species were calculated. The calculated IR wave numbers by the DFT method and the experimental data for 1,2,5-selenadiazole are shown in **Table 2**. The DFT–vibrational IR spectra of 1,2,5-selenadiazole and related compounds agree well when using a single scaling factor of 0.98 for the predicted DFT-harmonic wave numbers.

Table 1 Geometries, rotational constants, and dipole moments of 1,2,5- and 1,3,4-selenodiazoles **3** and **4**^a

			
	3	4	5
	<i>DFT</i>	<i>MP2</i>	<i>Experimental</i> ^b
1,2,5-Selenodiazole			
Se–N(2)	1.824 2	1.8073	1.80
N(2)–C(3)	1.315 0	1.3451	
C(3)–C(4)	1.449 6	1.4257	
C(3)–H	1.089 2	1.0856	
∠SeN(2)C(3)	106.41	105.44	
∠N(2)C(3)C(4)	117.08	117.24	
∠N(5)SeN(2)	93.02	94.64	94.31
∠N(2)C(3)H	119.19	118.28	
<i>A</i>	7748.51	7753.51	7855.36
<i>B</i>	3800.48	3841.56	3875.07
<i>C</i>	2549.84	2568.81	2593.58
μ	1.145	0.979	1.11(3)
1,3,4-Selenodiazole			
Se–C(2)	1.888 5	1.865 6	1.868
C(2)–N(3)	1.301 5	1.322 9	
N(3)–N(4)	1.372 6	1.370 6	
C(2)–H	1.085 0	1.082 6	
∠SeC(2)N(3)	114.89	115.06	114.8
∠C(2)N(3)N(4)	114.58	113.98	114.4
∠C(5)N(3)N(4)	81.07	81.92	81.8
∠SeC(2)H	122.76	123.24	122.6
<i>A</i>	8419.20	8469.67	8479.55(2.06)
<i>B</i>	3284.12	3304.20	3342.64(5)
<i>C</i>	2362.55	2376.91	2396.37(4)
μ	3.317	3.599	3.40(5)

^aBond distances in Å, bond angles ∠ in degrees, rotational constants *A*, *B*, and *C* in MHz, dipole moments μ in debye.^bReferences are cited in <1997JST451>.**Table 2** Calculated and experimental IR spectra of 1,2,5-selenadiazole **3**

<i>Symmetry</i>	<i>Mode</i> ^a	<i>Calculations</i> ^b <i>DFT, ν^c</i>	<i>Experiment</i> ^c <i>ν^c</i>
A₁ species			
1	$\nu(\text{C}(3)\text{H} + \text{C}(4)\text{H})$	3202 (3138)	3067 m
2	$\nu(\text{N}(2)\text{C}(3) + \text{N}(5)\text{C}(4))$ $\beta(\text{C}(3)\text{H} + \text{C}(4)\text{H})$ $\nu(\text{C}(3)\text{C}(4))$	1414 (1386)	1360 s
3	$\beta(\text{C}(3)\text{H} + \text{C}(4)\text{H})$ $\nu(\text{N}(2)\text{C}(3) + \text{N}(5)\text{C}(4))$	1316 (1290)	1290 w
4	$\nu(\text{C}(3)\text{C}(4))$ $\beta(\text{C}(3)\text{H} + \text{C}(4)\text{H})$	1022 (1002)	
5	$\nu(\text{SeN}(2) + \text{SeN}(5))$ $\beta(\text{RI})$	728 (713)	726 s
6	$\beta(\text{RI})$ $\nu(\text{SeN}(2) + \text{SeN}(5))$	493 (483)	

(Continued)

Table 2 (Continued)

Symmetry	Mode ^a	Calculations ^b DFT, ν^c	Experiment ^c ν^c
A ₂ species			
7	$\gamma(\text{C}(3)\text{H} + \text{C}(4)\text{H})$	920 (902)	868
8	$r(\text{R1})$	597 (585)	672
B ₁ species			
9	$\nu(\text{C}(3)\text{H} - \text{C}(4)\text{H})$	3185 (3121)	3028 sh
10	$\nu(\text{N}(2)\text{C}(3) - \text{N}(5)\text{C}(4))$	1551 (1520)	
11	$\beta(\text{C}(3)\text{H} - \text{C}(4)\text{H})$	1251 (1226)	1234 s
12	$\beta(\text{R2})$	884 (866)	880 s
13	$\nu(\text{SeN}(2) - \text{SeN}(5))$	573 (565)	589 s
B ₂ species			
14	$\nu(\text{C}(3)\text{H} - \text{C}(4)\text{H})$	843 (826)	833 s
15	$r(\text{R2})$	455 (436)	428 vs

^aNotation for in-plane modes: ν , stretching; β , bending or ring deformation. Notation for out-of-plane modes: γ , bending; r , ring deformation.

^bWave numbers in cm^{-1} . The calculated harmonic wave numbers scaled by a factor of 0.98 are given in parentheses under the unscaled wave numbers.

^c<1968SAA57>.

Geometric parameters and vibrational IR spectra of 1,2,5-selenadiazole **3** and 1,2,5-telluradiazole **5** have been calculated by the B3LYP, MP2, and Hartree–Fock (HF) theory with CEP-121G, CEP-31G, LanL2DZ, SDDALL, and SDD basis sets in addition to the 6-31G(p) and 6-311G(d,p) basis sets for 1,2,5-selenadiazole **3** <2001JST81>. Good agreement between the calculated and experimental geometries was obtained. Geometric parameters of 1,2,5-telluradiazole **5** calculated by B3LYP with SDD basis set and experimental data are shown in Table 3. The force field scale factors were calculated. Table 4 shows the experimental frequencies and the corresponding scaled vibrational frequencies by B3LYP method and the CEP-121G basis set for 1,2,5-telluradiazole.

Table 3 Geometric parameters of 1,2,5-telluradiazole **5** calculated by B3LYP with SDD basis set and experimental data

Coordinate ^a	Calculated	Experimental ^b
Te–N(2)	2.058	2.023
N(2)–C(3)	1.326	1.274
C(3)–C(4)	1.472	1.421
C(3)–H	1.088	1.079
$\angle\text{TeN}(2)\text{C}(3)$	107.8	109.4
$\angle\text{N}(2)\text{C}(3)\text{C}(4)$	119.6	119.3
$\angle\text{N}(5)\text{TeN}(2)$	85.1	82.5
$\angle\text{N}(2)\text{C}(3)\text{H}$	118.2	123.6
μ	0.329	

^aBond distances in Å, bond angles $\angle$ in degrees, dipole moments μ in debye.

^bX-Ray data <1984SAA847, 1984AXC653>.

Geometrical optimization of 1,2,4-selenadiphosphole **6** was carried out at the MP2 level of theory using the standard 6-31G* basis set (Table 5) <1995J(P2)315>. The results show that 1,2,4-selenadiphosphole **6** is planar

and exhibits significant bond length equalization, thus indicating that the system is aromatic (Section 6.12.4.2). Since the bond angles at the ring carbon atoms are close to 120° , the ring strain should be small. The calculated ionization energies are discussed in Section 6.12.3.5.

Table 4 Calculated and experimental IR spectra of 1,2,5-telluradiazole **5** calculated by the B3LYP/CEP-121G method (bands in parentheses were not included in the fit)

Symmetry	Calculations ^a	Experiment ^{a,b}
A ₁	3038	2998
	1313	1358
	1258	1290
	929	974
	593	660
	365	388
A ₂	884	860
	531	511
	3019	2975
B ₂	1450	(1377)
	1217	1252
	804	870
	409	492
	824	828
B ₁	362	359

^aWave numbers in cm^{-1} .

^b<1984SAA847>.

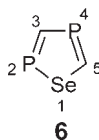
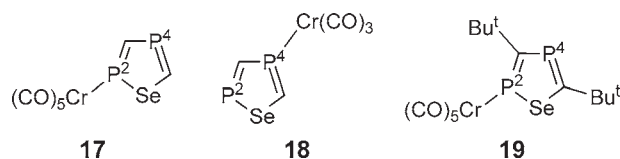


Table 5 MP2/6-31G* bond length (Å) and bond angles ($^\circ$) of 1,2,4-selenadiphosphole **6**

Coordinate	Calculated
Se–C(5)	1.841
C(5)–P(4)	1.717
P(4)–C(3)	1.751
C(3)–P(2)	1.722
P(2)–Se	2.200
$\angle \text{PSeC}(5)$	97.2
$\angle \text{SeCP}(4)$	121.8
$\angle \text{C}(5)\text{P}(4)\text{C}(3)$	98.1
$\angle \text{P}(4)\text{C}(3)\text{P}(2)$	126.8
$\angle \text{C}(3)\text{P}(2)\text{Se}$	96.2

The relative stabilities of the two possible η^1 -P-bonded chromium pentacarbonyl complexes of 1,2,4-selenadiazole **17** and **18** were calculated at the HF/3-21G(*) and at the B3LYP/3-21G(*) level of theory <1999JOM156>. At both levels, the preferred site is the P-4 position rather than that found in complex **19**. However, the energy difference is quite small between the isomeric structures (1.5, 1.6, and 3.1 kcal mol^{-1} , respectively, at the HF/3-21G(*), B3LYP/3-21G(*), and B3LYP/6-311-G**//B3LYP/3-21G(*) levels). Attachment of Bu^t groups to both ring C-atoms changes the relative stabilities of the two complexes at the B3LYP/3-21G* level and complex **19** is more stable by 6.5 kcal mol^{-1} in accord with the experimental data. The different relative stabilities of the H- and the Bu^t -substituted complexes presumably can be attributed to steric congestion.



A computational study of dimers of 1,2,5-selenadiazole and 1,2,5-telluradiazole using DFT was performed as part of understanding the factors that control the association of these molecules, the influence of the nature of the chalcogen, and the viability of the 1,2,5-chalcogenadiazoles as building blocks for supramolecular structures <2005JA3184>. The dimers of the 1,2,5-chalcogenadiazoles, **20** and **21** were fully optimized (Table 6). Both dimers converged to centrosymmetric coplanar structures with the two expected secondary bonding interactions. These pairs are in principle stable because their energies are lower than those of the two isolated molecules and all their vibrational frequencies are real. The Se(Te)---N secondary bonding interaction distances are in agreement with the average of the distances experimentally observed. Further detail on the origin of the association energies was discussed.

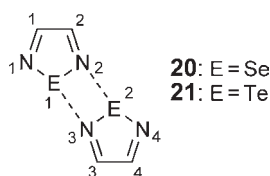
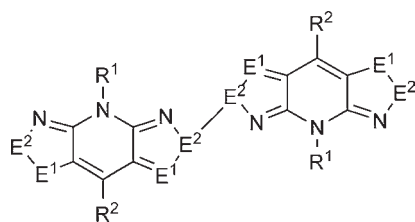


Table 6 Optimized bond lengths (Å) and angles (°) for the structures of dimers of 1,2,5-selenadiazole and telluradiazole

	<i>E</i>	
	<i>Se</i> (20)	<i>Te</i> (21)
E(1)–N(1)	1.835	2.071
E(1)–N(2)	1.845	2.064
N(1)=C(1)	1.317	1.303
N(2)=C(2)	1.317	1.304
C(1)–C(2)	1.437	1.456
C(1)–H(1)	1.093	1.098
C(2)–H(2)	1.092	1.095
E(1)---N(3)	2.924	2.604
N(1)–E(1)–N(2)	92.2	83.3
C(1)=N(1)–E(1)	106.7	108.2
C(2)=N(2)–E(1)	106.3	108.9
N(1)=C(1)–C(2)	117.3	120.2
N(2)=C(2)–C(1)	117.5	119.2
C(1)–C(2)–H(2)	123.5	120.1
C(2)–C(1)–H(1)	123.5	121.5

In the chalcogenadiazoles there is a progression of secondary binding interaction strength as the mass of the chalcogen increases. The heaviest atom leads to association energies that are as strong as hydrogen bonds. The potential of tellurium–nitrogen heterocycles as building blocks in supramolecular architecture is suggested.

In order to investigate the electronic and energetic changes associated with σ -dimerization of N-alkylated pyridine-bridged 1,2,3-thiaselenazolo-1,2,3-thiaselenazolyl derivative **22** in crystals, DFT calculations at the B3LYP/6-31G** level on model radicals **22–24** ($R^1 = R^2 = H$) and their respective σ -bonded dimers were carried out <2005JA18159>. The resulting dimer dissociation energies are shown in Table 7. The enthalpy changes for the reaction shown in Equation (1) indicate that dimers for derivatives **22** and **24** are stable with respect to the radicals. The preferred combination for maximum dimer stability appears to be that which combines a bridging Se–Se bond with a terminal thione group, as found for the derivative **22**.



[22]₂: E¹ = S; E² = Se

[23]₂: E¹ = Se; E² = S

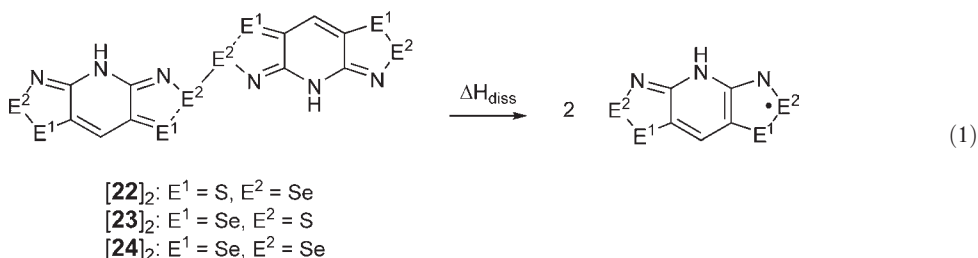
[24]₂: E¹ = Se; E² = Se

Table 7 B3LYP/6-31G** dimer dissociation enthalpies (kcal mol⁻¹) and bond distances (Å)^a of model radicals **22–24** (R¹ = R² = H)

	22 : E ¹ = S; E ² = Se	23 : E ¹ = Se; E ² = S	24 : E ¹ = E ² = Se
ΔH_{diss}^b	18.19	-1.123	8.87
E(2)–E(2)	2.475	2.263	2.496
E(2)–E(1)	2.892	2.930	2.910
E(2)–N	1.811	1.660	1.811
C=E(1)	1.678	1.807	1.812
C=N	1.293	1.297	1.296

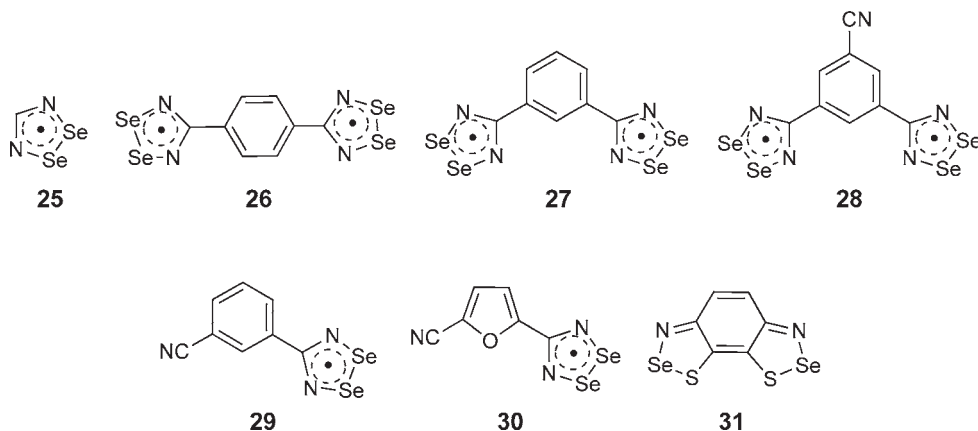
^aBond distances for the fused rings.

^bFor the reaction presented in Equation (1).



To probe the electronic structures of the materials in the solid state, band structure calculations on the crystal structure of compound **22** were carried out. The results obtained by using the linear muffin-tin orbital (LMTO) self-consistent field (SCF) method support the interpretation that compounds **22** (R¹ = Me, Et; R² = H) are small-band-gap semiconductors.

Band structure calculation using extended Hückel methods have been performed on compounds **25–31** <1991JA582, 1992JA1729, 1994CM508, 1993CM820, 1996CM762, 2001IC6820, 2001IC4705>.



6.12.3 Experimental Structural Methods

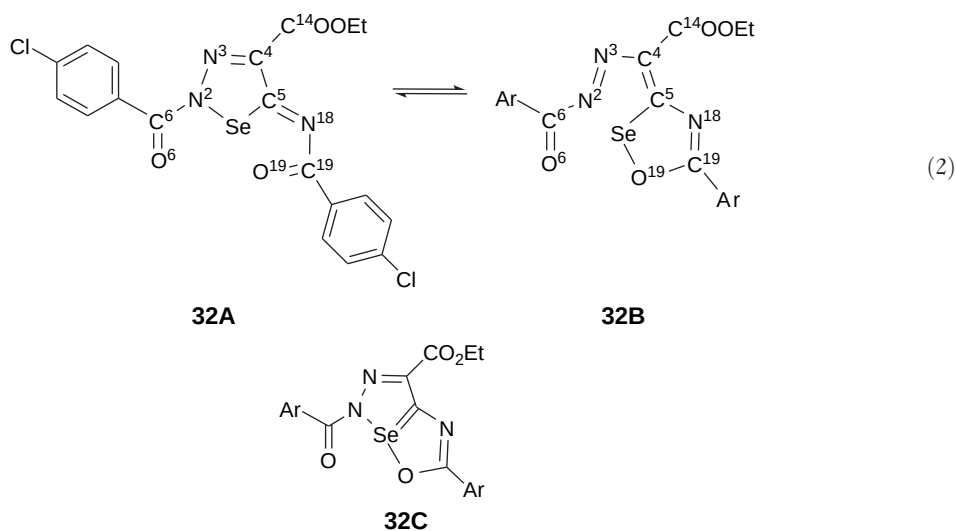
6.12.3.1 X-Ray diffraction

A number of X-ray diffraction studies were performed in order to determine the heterocyclic ring structures including their metal complexes and to determine the intermolecular interactions.

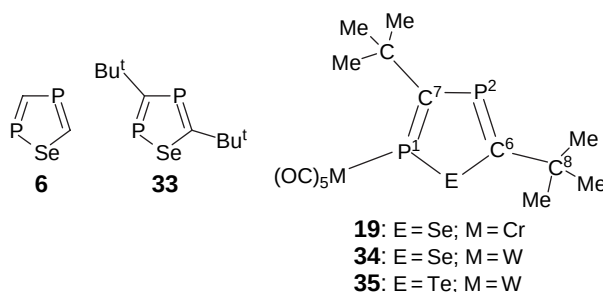
The structure of 2,5-dihydro-1,2,3-selenadiazole **32** was determined by X-ray crystallography <2000HCA539>. The crystal structure of compound **32** shows a nearly planar molecule. The heterocyclic core and the (4-methylbenzoyl)imino group at C-5 form a planar system with the maximum deviation from the plane being 0.044(4) Å for C-14). The plane of the other 4-methylbenzoyl ring at N-2 makes an angle of 16.48° with this plane. The Se-atom appears to be nearly tricoordinated. The Se–O(19) distance is ca. 0.35 Å longer than the Se–C(5) and Se–N(2) bonds, but O-19 is still close enough to be considered to have a strong interaction with the Se-atom. The C(19)–O(19) carbonyl bond is correspondingly slightly longer than normal (Table 8). The O–Se interaction could be described as a dative bond. This arrangement could also favor a resonance structure **32B** or structure **32C** with a hypervalent Se-atom, although the N–C bond lengths give preference to a more localized depiction (structure **32A**) (Equation 2).

Table 8 Selected bond lengths (Å) of compound **32**

Se(1)–O(19)	2.242(2)	N(2)–C(6)	1.421(4)
Se(1)–N(2)	1.915(3)	N(3)–C(4)	1.324(4)
Se(1)–C(5)	1.878(3)	N(18)–C(5)	1.312(4)
O(6)–C(6)	1.211(4)	N(18)–C(19)	1.373(4)
O(14)–C(14)	1.200(4)	C(4)–C(5)	1.440(4)
O(19)–C(19)	1.259(4)	C(4)–C(14)	1.494(4)
N(2)–N(3)	1.313(3)		



The molecular geometries of the 1,2,4-selenadiphosphole and 1,2,4-telluradiphosphole complexes **19**, **34**, and **35** were established by single crystal X-ray diffraction studies <1999JOM156>. The ring angles at carbon are close to 120° while those at P or Se are closer to 100° and the ring geometry is essentially independent of the nature of the [M(CO)₅] fragment to which it is attached (see Table 9). The Se–P(1) and Se–C(6) bond lengths for complexes **19** and **34** are significantly shorter than Se–P and Se–C single bonds (2.273 and 1.972 Å, respectively), and are in good agreement with values obtained from theoretical calculations on ring system **6** (Section 6.12.2), suggesting that the ring geometry of 1,2,4-selenadiphosphole **33** may be very similar to that in complexes **19** and **34**. The P–W bond distances in complexes **34** and **35** are almost identical and the overall geometry of the planar 1,2,4-telluradiphosphole ring in complex **35** is very similar to that of the 1,2,4-selenadiphosphole ring in complexes **19** and **34**, with the expected lengthening of the Te–C (2.067(4) Å) and Te–P distances (2.378(2) Å) compared with their Se analogues and a narrowing of the CTeP angle (90.9°) in complex **35** compared with the corresponding CSeP angle (96.2° in complex **19** and 95.9° in complex **34**). In all three complexes, **19**, **34**, and **35**, the sum of the angles at the P-atom coordinated to the metal center is very close to 360°.

**Table 9** Selected bond lengths (Å) and bond angles (°) in complexes **19**, **34**, and **35**

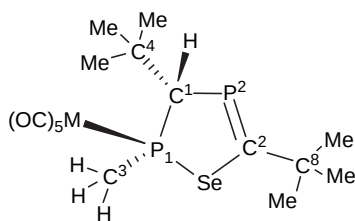
	19	34	35
E–C(6)	1.873(6)	1.868(6)	2.067(7)
E–P(1)	2.182(2)	2.180(2)	2.378(2)
M–P(1)	2.359(2)	2.489(2)	2.506(2)
P(1)–C(7)	1.695(6)	1.687(6)	1.702(7)
P(2)–C(6)	1.681(6)	1.690(6)	1.695(7)
P(2)–C(7)	1.774(6)	1.772(6)	1.785(7)
C(6)–E–P(1)	96.2(2)	95.9(2)	90.9(2)
C(7)–P(1)–E	101.1(2)	101.3(2)	101.7(3)
E–P(1)–M	111.83(7)	111.91(7)	111.69(7)
C(6)–P(2)–C(7)	103.7(3)	103.1(3)	106.3(3)
P(1)–C(7)–P(2)	120.0(3)	120.4(4)	122.3(4)
P(2)–C(6)–E	118.9(3)	119.3(3)	118.8(4)

2,3-Dihydro-1,2,4-selenaphosphole η^1 -metal pentacarbonyl complexes, $[\text{M}(\text{CO})_5\{\eta^1\text{-P}_2\text{SeC}_2\text{Bu}_2^t(\text{H})\text{Me}\}]$ (M = Cr, M = Mo, M = W), have been structurally characterized by single crystal X-ray diffraction studies (**Table 10** <2002JOM84>. In complexes **36–38**, the bond distances between ring positions P-2 and C-2 are typical of a $\text{P}=\text{C}$ bond distance in the range 1.669–1.697 Å, whereas the corresponding distances between positions P-1 and C-1 are more typical of $\text{P}-\text{C}$ single bonds (1.878–1.883 Å). Similarly, the sum of the bond angles around the carbon atom adjacent to selenium is in all cases 360° , clearly indicating a sp^2 -hybridized carbon atom. The metal pentacarbonyl coordination of

Table 10 Selected bond lengths (Å) and angles (°) in complexes **36–38**

	36	37	38
Se–C(2)	1.914(4)	1.931(6)	1.906(11)
C(2)–P(2)	1.669(5)	1.671(7)	1.697(12)
P(2)–C(1)	1.883(4)	1.878(7)	1.882(12)
C(1)–P(1)	1.853(5)	1.850(7)	1.859(11)
P(1)–Se	2.244 9(13)	2.242(2)	2.242(3)
C(2)–C(8)	1.535(6)	1.513(9)	1.478(17)
C(1)–C(4)	1.557(6)	1.569(9)	1.567(15)
P(1)–C(3)	1.828(5)	1.830(7)	1.812(13)
P(1)–M	2.389 6(13)	2.540 5(18)	2.525(3)
P(1)–Se–C(2)	94.04(14)	94.3(2)	94.9(4)
Se–C(2)–P(2)	120.4(2)	119.9(4)	119.7(7)
Se–C(2)–C(8)	115.1(3)	114.1(5)	116.7(8)
C(8)–C(2)–P(2)	124.5(3)	126.0(5)	123.6(9)
C(2)–P(2)–C(1)	102.3(2)	101.8(3)	101.7(5)
P(2)–C(1)–P(1)	111.4(2)	112.1(4)	111.3(5)
C(1)–P(1)–C(3)	104.2(2)	105.2(3)	105.8(6)
C(1)–P(1)–Se	95.57(15)	94.8(2)	94.9(4)
C(3)–P(1)–Se	102.94(18)	103.3(2)	102.7(4)
M–P(1)–C(1)	131.77(15)	132.6(2)	131.7(4)
M–P(1)–C(3)	112.01(16)	112.2(2)	112.5(5)
M–P(1)–Se	105.77(5)	103.58(7)	103.99(12)

2,3-dihydro-1,2,4-selenaphosphole also occurs via the phosphorus atom which is adjacent to the chalcogen as well as the above-described η^1 -M(CO)₅ complexes of the 1,2,4-chalcogeno-diphospholes **19**, **34**, and **35**.



36: M = Cr

37: M = Mo

38: M = W

The X-ray crystal structure determination of telluradiazole **39** showed that it exists as a weakly associated dimer in the solid state; half of the dimer represents the asymmetric unit [<1996IC9>](#). Selected bond distances and bond angles are summarized in [Table 11](#). The intramolecular Te–N distances of 2.002(3) and 2.006(4) Å are slightly shorter than the reported average distances of 2.02 Å for the parent 1,2,5-telluradiazole and phenanthro[9,10-*c*]-1,2,5-telluradiazole [<1984AXC653>](#). The bond angle of 85.8(1)° at tellurium is comparable to the values of 82.5(5)° and 84.3(3)° found for the other telluradiazoles. These data indicate that the tellurium(II) resonance form **40A** is a more important contributor than the tellurium(IV) form **40B** to the overall structure **39**.

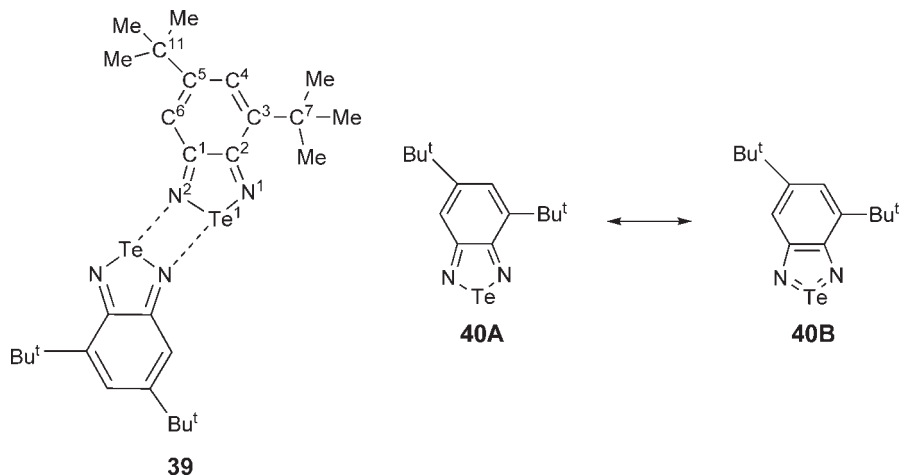


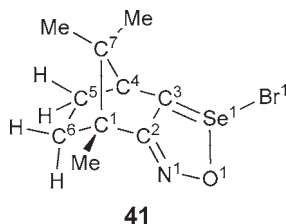
Table 11 Selected bond distances (Å) and bond angles (°) for structure **39**

Te(1)–N(1)	2.006(4)	Te(1)–N(2)	2.002(3)
N(1)–C(2)	1.332(5)	N(2)–C(1)	1.321(5)
C(1)–C(2)	1.477(6)	C(1)–C(6)	1.443(5)
C(2)–C(3)	1.462(6)	C(3)–C(4)	1.366(5)
C(4)–C(5)	1.457(6)	C(5)–C(6)	1.350(6)
N(1)–Te(1)–N(2)	85.8(1)	Te(1)–N(1)–C(2)	108.9(3)
Te(1)–N(2)–C(1)	108.9(3)	N(2)–C(1)–C(2)	118.6(4)
N(2)–C(1)–C(6)	121.3(4)	C(2)–C(1)–C(6)	120.0(4)
N(1)–C(2)–C(1)	117.7(4)	N(1)–C(2)–C(3)	123.5(4)
C(1)–C(2)–C(3)	118.8(4)	C(2)–C(3)–C(4)	116.8(4)
C(2)–C(3)–C(7)	120.9(4)	C(4)–C(3)–C(7)	122.3(4)
C(3)–C(4)–C(5)	124.6(4)	C(4)–C(5)–C(6)	119.8(4)
C(4)–C(5)–C(11)	116.7(4)	C(6)–C(5)–C(11)	123.5(4)
C(1)–C(6)–C(5)	119.8(4)		

Reproduced from T. Chivers, X. Gao, and M. Parvez, *Inorg. Chem.*, 1996, **35**, 9, American Chemical Society [<1996IC9>](#).

There are strong intermolecular attractions in compound **39** with Te–N distances of 2.628(4) Å; cf. 3.70 Å for the sum of the van der Waals radii of these atoms. Significantly, there are no interactions between dimeric units in compound **39** whereas the other 1,2,5-telluradiazoles exist as either planar or ladder-type polymers <1984AXC653, 1987ZNB84>. Inspection of the packing diagram for compound **39** suggests that the bulky *tert*-butyl groups prevent further association of the dimeric units in this case.

The structure of oxaselenazole **41** was determined by X-ray crystallography. The relatively short bond lengths of 1.790 and 1.313 Å confirm the double-bond character of the C(3)–Se(1) and C(2)–N(1) bonds, respectively <2002JOC499>. The O-1 and Se-1 atoms are clearly joined by a covalent bond with a bond length of 1.981 Å. The molecules occur as pairs in the unit cell, where the respective O–Se–Br moieties are associated and aligned head to tail. The O(1)–Se(1)–Br(1) bond angle of 175.94° indicates a nearly linear geometry.



The structure of 4,7-dimethoxybenzotrisesenole **42** was determined by X-ray crystallography (Table 12) <1996H(43)1843>. The planar diselenobenzene moiety has a selenium at the 2-position displaced from plane (Se–Se–Se–C torsion angles are 39.0° and 37.2°). A unique distorted geometry of the five-membered trisesenole ring indicates the presence of lone pair–lone pair repulsion of the divalent selenium atoms neighboring each other. X-Ray crystallographic analysis of benzotrisesenole **43** was also reported <2004JOC4716>.

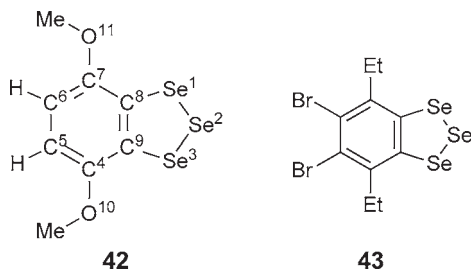


Table 12 Selected bond distances (Å), bond angles (°), and torsion angles (°) for 4,7-dimethoxybenzotrisesenole **42**

Se(1)–Se(2)	2.340(3)	Se(1)–Se(2)–Se(3)–C(9)	39.0(4)
Se(1)–Se(3)	2.339(3)	Se(3)–Se(2)–Se(1)–C(8)	–37.2(5)
Se(1)–C(8)	1.91(1)	Se(1)–C(8)–C(9)–Se(3)	5(1)
Se(3)–C(9)	1.89(1)	Se(1)–C(8)–C(7)–C(6)	–179(1)
C(8)–C(9)	1.44(2)	Se(1)–C(8)–C(9)–C(4)	–179(1)
Se(1)–Se(2)–Se(3)	91.88(9)	Se(3)–C(9)–C(8)–C(7)	–177(1)
Se(2)–Se(1)–C(8)	93.6(5)	Se(3)–C(9)–C(4)–C(5)	–179(1)
Se(2)–Se(3)–C(9)	92.9(5)		
Se(1)–C(8)–C(9)	119(1)		
Se(3)–C(9)–C(8)	120.7(9)		

Molecular structures of unusual heterocycles selenadiphosphole **44**, 1,2,3-diselenaphosphole **45**, 1,2,3,4-selenadiphosphazole **46**, and 1,2,3-diselenaphosphole **47** were determined crystallographically <2002CEJ2705>. X-Ray crystallographic analysis reveals a diversity of structural motifs within these heterocyclic systems (Tables 13–16). Within the C₂P₂Se ring of compound **44**, the P(1)–C(7)–C(10)–P(2) chain has a mean deviation from planarity of 0.03 Å, with Se-3 displaced by 0.37 Å from this plane. The two exocyclic P–Se bonds adopt a *trans*-orientation, a common feature of ring systems containing a P(Se)–Se–P(Se) linkage. For compound **45** there are two independent molecules within the unit cell. The Se(3)–C(7)–C(10)–P(1) chain of atoms has a mean deviation of 0.02 Å from planarity, with Se-2 lying 0.74 Å out of this plane and the phenyl group on the same side of the C₂PSe₂ ring as this

atom. The C=C distances within the two independent molecules of compound **45** are dissimilar (1.300(12) and 1.368(14) Å) relative to that found in structure **44** (1.336(4) Å).

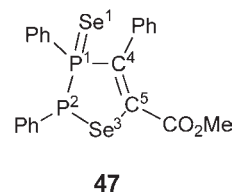
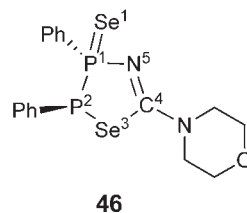
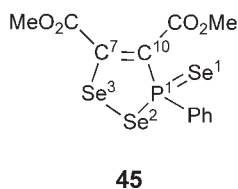
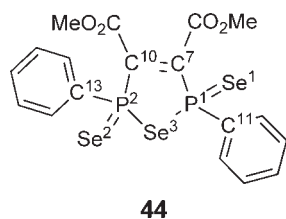


Table 13 Molecular structure of compound **44**: selected bond lengths (Å) and angles (°)

Se(1)–P(1)	2.091 6(9)	C(1)–P(1)–Se(1)	115.15(11)
P(1)–C(1)	1.798(3)	C(7)–P(1)–Se(1)	112.12(10)
P(1)–C(7)	1.831(3)	C(1)–P(1)–Se(3)	107.69(10)
P(1)–Se(3)	2.243 5(9)	C(7)–P(1)–Se(3)	100.06(11)
Se(3)–P(2)	2.280 2(9)	Se(1)–P(1)–Se(3)	114.77(4)
P(2)–C(13)	1.803(3)	P(1)–Se(3)–P(2)	93.74(3)
P(2)–C(10)	1.831(3)	C(13)–P(2)–Se(2)	115.64(12)
P(2)–Se(2)	2.082 2(10)	C(10)–P(2)–Se(2)	111.44(11)
C(7)–C(10)	1.336(4)	C(13)–P(2)–Se(3)	103.29(11)
		C(10)–P(2)–Se(3)	99.22(11)
		Se(2)–P(2)–Se(3)	117.43(4)

Table 14 Molecular structure of compound **45**: selected bond lengths (Å) and angles (°) (dimensions for second independent molecule in square parentheses)

Se(1)–P(1)	2.113(3) [2.116(3)]
P(1)–C(10)	1.828(9) [1.791(10)]
P(1)–C(1)	1.841(12) [1.807(11)]
P(1)–Se(2)	2.251(3) [2.261(3)]
Se(2)–Se(3)	2.359(2) [2.356(2)]
Se(3)–C(7)	1.916(9) [1.864(11)]
C(7)–C(10)	1.300(12) [1.368(14)]
C(10)–P(1)–Se(1)	110.5(3) [115.8(3)]
C(1)–P(1)–Se(1)	114.2(4) [114.4(3)]
C(10)–P(1)–Se(2)	100.5(3) [101.8(4)]
C(1)–P(1)–Se(2)	107.2(4) [104.9(3)]
Se(1)–P(1)–Se(2)	116.48(11) [115.32(11)]
P(1)–Se(2)–Se(3)	91.52(8) [94.20(8)]
C(7)–Se(3)–Se(2)	95.5(3) [96.8(3)]
C(10)–C(7)–Se(3)	123.3(7) [124.6(7)]

Table 15 Molecular structure of compound **46**: selected bond lengths (Å) and angles (°)

P(1)–P(2)	2.237 2(14)	Se(3)–P(2)–P(1)	89.65(4)
P(1)–Se(1)	2.107 3(10)	P(2)–P(1)–N(5)	104.58(11)
P(2)–Se(3)	2.241 2(10)	P(1)–N(5)–C(4)	118.5(3)
P(1)–N(5)	1.653(3)	N(5)–C(4)–Se(3)	122.4(3)
Se(3)–C(4)	1.968(4)	C(4)–Se(3)–P(2)	95.26(10)
N(5)–C(4)	1.290(4)	P(2)–P(1)–Se(1)	108.78(5)
		N(5)–P(1)–Se(1)	116.62(12)

Table 16 Molecular structure of compound **47**: selected bond lengths (Å) and angles (°)

Se(1)–P(1)	2.095(2)	C(5)–P(1)–Se(1)	115.9(3)
P(1)–C(5)	1.822(7)	C(5)–P(1)–P(2)	102.3(3)
P(1)–P(2)	2.215(3)	Se(1)–P(1)–P(2)	112.79(11)
P(2)–Se(3)	2.266(3)	P(1)–P(2)–Se(3)	91.98(10)
Se(3)–C(4)	1.930(8)	C(4)–Se(3)–P(2)	97.4(2)
C(4)–C(5)	1.317(11)	C(5)–C(4)–Se(3)	121.7(6)
		C(4)–C(5)–P(1)	119.2(6)

In molecule **46**, P-1 and P-2 possess opposite chiralities, with the phenyl groups being oriented above and the morpholine ring below the P_2SeCN plane. Atom P-2 lies 0.17 Å out of the plane defined by P(1)–N(5)–Se(3)–C(4) (mean deviation from planarity of 0.04 Å), with P-1 being 0.25 Å above this plane, the P(1)–Se(1) and P(2)–Se(3) distances being 2.107 3(10) and 2.241 2(10) Å, respectively. X-Ray crystallographic analysis of compound **47** reveals that the internal dimensions vary little from those of the P_2SeCN ring in molecule **46** with the exception of P(1)–C(5), which is 0.17 Å longer than the P(1)–N(5) distance in **46**. The P(2)–Se(3) distance, 2.266(3) Å, is only marginally elongated from the corresponding parameter in compound **46** (2.241 2(10) Å). The P(2) atom lies 0.69 Å out of the mean plane defined by the P(1)–C(4)–C(5)–Se(3) atoms (mean deviation from planarity of 0.01 Å).

The structures of a series of 1,2,3-thiaselenazoles and 1,2,3-thiaselenazolyl and 1,2,3,5-diselenadiazolyl radicals have been studied extensively by X-ray diffraction.

Crystals of $[22][OTf]$ ($R^1 = Me$; $R^2 = H$) consist of 1,2,3-thiaselenazolo-1,2,3-thiaselenazolylum $[22]^+$ cations bridged by triflate anions (Se(1)–O(1') = 2.855(3) Å, S(1)–O(1') = 3.123(3) Å, Se(2)–O(3') = 2.826(3) Å, S(2)–O(3') = 3.141(3) Å <2005JA18159>. At an intramolecular level, the internal bond lengths in the cation are similar to those observed in the corresponding cation $[22]^+$ ($R^1 = R^2 = H$) <2005CC1543>. In addition to ion-pairing contacts, neighboring cations are laced together into ribbon-like arrays by close centrosymmetric four-center Se···N' interactions. These latter interactions, which are ubiquitous in both closed-shell and open-shell selenazoles, are stronger than the corresponding S···N contacts and play a major role as structure-making supramolecular synthons.

Crystals of dimers $[22]_2$ ($R^1 = Me$, Et; $R^2 = H$) are isostructural. The molecules adopt a normal slipped σ -stacked motif, in which the molecules appear to be linked laterally into ribbons, much as the cations are in the triflate salt above. However, closer inspection of the lateral intermolecular contacts reveals that, while the radicals are coupled at both ends by short four-center Se(1)···N(1') contacts, they are actually fused at one end by a covalent Se(2)–Se(2') σ -bond (2.460(2) Å for $R^1 = Me$, 2.4628(8) Å for $R^1 = Et$). At the same time, the associated Se(2)–S(2) bond opens to a value (2.785(3) Å for $R^1 = Me$, 2.7847(9) Å for $R^1 = Et$) intermediate between the sum of the covalent radii and the expected van der Waals contact. Within this dimer or supermolecule there is a series of bond length changes relative to those seen in the cation $[22]^+$, for example, a shortening of the C(3)–N(3) and C(4)–S(2) distances (Table 17), all of which are consistent with the closed-shell valence bond formulation $[22]_2$.

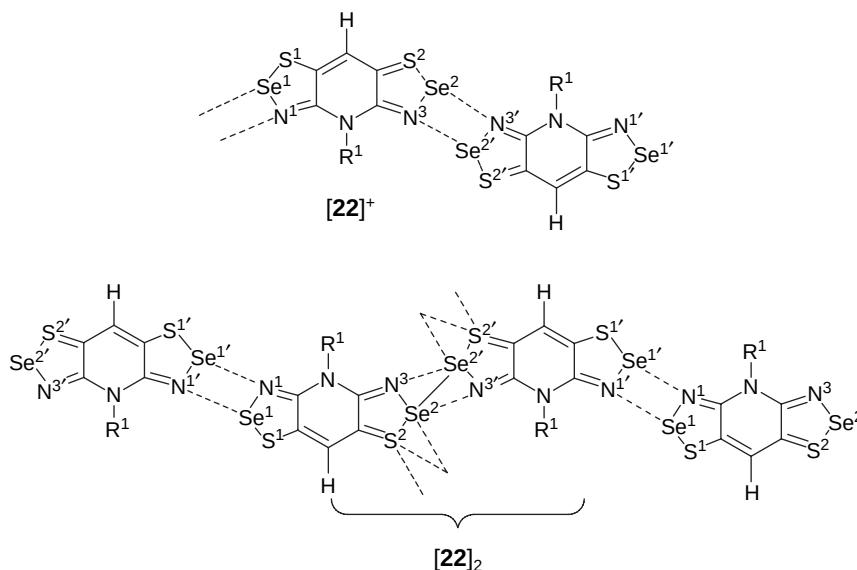


Table 17 Intra- and intermolecular distances (Å) and angles (°) in compounds [22][OTf] and [22]₂

	Compound		
	[22][OTf] ($R^1 = Me$; $R^2 = H$)	[22] ₂ ($R^1 = Me$; $R^2 = H$)	[22] ₂ ($R^1 = Et$; $R^2 = H$)
C(2)–N(1)	1.299(4)	1.309(8)	1.303(4)
C(3)–N(3)	1.301(4)	1.298(7)	1.288(3)
N(1)–Se(1)	1.792(2)	1.823(5)	1.818(2)
N(3)–Se(2)	1.789(2)	1.816(5)	1.811(2)
C(4)–S(2)	1.707(3)	1.694(6)	1.679(3)
C(1)–S(1)	1.704(3)	1.726(6)	1.719(3)
Se(1)–S(1)	2.198 4(10)	2.232(2)	2.214 5(9)
Se(2)–S(2)	2.194 9(10)	2.785(3)	2.784 7(9)
Se(2)–Se(2')		2.460(2)	2.462 8(8)
τ^a		45.89(5)	47.53(2)
δ^b		3.535(2)	3.5811(6)
θ^c		174.4(5)	168.1(2)
Se(1)---N(1')	3.092(3)	2.892(5)	3.238(3)
Se(2)---N(3')	2.959(3)	2.984(5)	3.004(3)
S(2)---S(1')		3.268(3)	3.245(1)
S(2)---Se(1')		3.177(2)	3.335(1)
Se(2)---S(1')		3.663(3)	3.966(1)

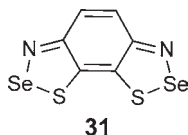
^a τ is the tilt angle between the mean molecular plane and the x-axis.

^b δ is the interplanar separation of molecules.

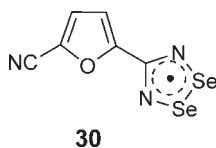
^c θ is the C(3)–N(3)–Se(2)–Se(2') torsion angle.

Reproduced from L. Beer, J. L. Brusso, R. C. Haddon, M. E. Itkis, H. Kleinke, A. A. Leitch, R. T. Oakley, R. W. Reed, J. F. Richardson, R. A. Secco, *et al.*, *J. Am. Chem. Soc.*, 2005, **127**, 18159, American Chemical Society <2005JA18159>.

The crystal structure of S–Se–N–based heterocycle benzo[2,1-*c*:3,4-*c'*]bis(1,2,3-thiaselenazole) **31** allows for more extensive intermolecular Se···Se contacts <2001IC4705>. The crystal structure of the charge-transfer (CT) salt [31]₃[ClO₄]₂ consists of slipped π -stacks based on the triple-decker closed-shell [31]₃²⁺ building block.



A crystal structure of 5-cyanofuran-2-[1,2,3,5-diselenadiazolyl] **30** consists of diselenadiazolyl π -dimer stacks running parallel to the *x*-direction <2001IC6820>; the asymmetric unit consists of four π -dimer units. The dimers are aligned into snake-like ribbons along the *y*-direction, with consecutive dimers linked by head-to-tail CN–Se contacts. Each π -dimer stack is bordered by two out-of-register stacks, but most interstack Se–Se contacts lie outside the van der Waals separation. Along the π -dimer stacks, the intradimer Se–Se distances range from 3.183(10) to 3.294(1) Å, and the interdimer Se–Se distances range from 3.826(1) to 3.945(1) Å.



The crystal structure of the gallate salt **48** of the selenium-based cation [49]⁺ has been determined by single crystal X-ray diffraction <2005IC1837>. Summaries of pertinent intramolecular and intermolecular distances are provided in Table 18. The crystal structure of the salt **48** consists of cations [49]⁺ and anions [GaCl₄][–] oriented so as to allow a pair of close intermolecular Cl···Se contacts. In addition, there is a third contact (Cl(3)···Se(1')) to the anion located above the molecular plane. The cations, which are planar to within 0.021(4) Å, adopt a head-to-tail π -stacked arrangement running parallel to the *x*-direction. The interplanar separation within the head-to-tail pairs is

3.513(5) Å, while that between the pairs is 3.383(6) Å. The π -stacked arrays of cations are linked by centrosymmetric pairs of Se(2)–N(1') contacts, thereby generating ribbons running along the y -direction. These four-center Se–N supramolecular synthons, which are common in diselenadiazolylium salts and diselenadiazolyl radicals, are likely to dominate the solid-state structures of reduced diselenazolyli materials.

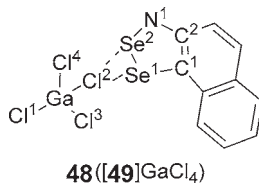
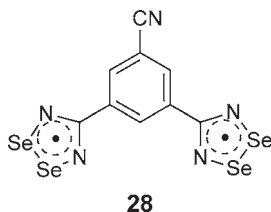


Table 18 Intra- and intermolecular distances (Å) of compound **48**

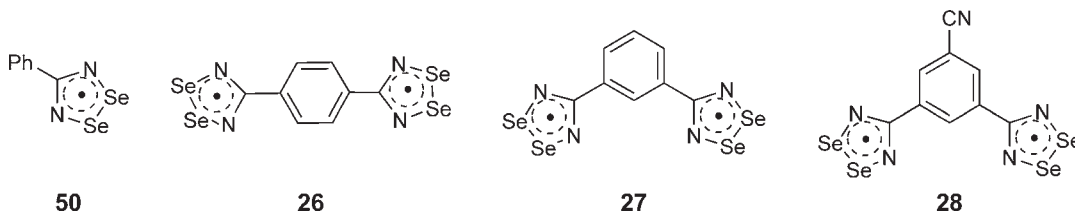
<i>Intramolecular</i>		<i>Intermolecular</i>	
Se(1)–Se(2)	2.290 0(12)	Se(1)–Cl(2')	3.534(2)
Se(2)–N(1)	1.766 7(4)	Se(2)–Cl(2')	3.389(2)
Se(1)–C(1)	1.844(5)	Se(1)–Cl(3')	3.578(4)
C(1)–C(2)	1.428(7)	Se(2)–N(1')	2.874(4)

The solid-state characterization of the bifunctional radical [4,4'-(5-cyanobenzene)-1,3-bis(1,2,3,5-diselenadiazolyl)] **28** has been studied <1993CM820>. The crystal structure consists of stacks of diradicals running parallel to x ; radical dimerization up and down the stack generates a zigzag arrangement, as seen in the related 1,3-phenylene structures. Along the stacking axis the mean intradimer Se–Se contact is 3.23 Å, while the mean interdimer Se–Se distance is 3.91 Å.

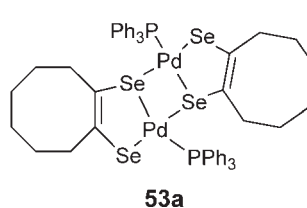
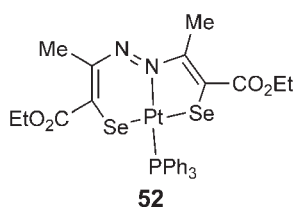
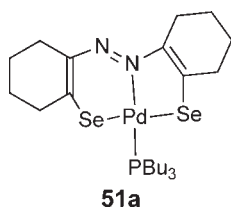


The solid-state structures of the mixed valence salts containing 1,2,3,5-diselenadiazole [**50**]₃[I₃] have been determined by X-ray crystallography <1994CM508>. The molecular (asymmetric) unit consists of a trimeric cation [**50**]₃⁺ and an associated triiodide anion. Within the cation the mean interannular Se–Se contact is 3.377 Å. The trimer units form dovetailed stacks in which consecutive layers are oriented in a transantipodal fashion. This arrangement introduces close interannular contacts between the blocks along the stack, as well as close lateral contacts.

The structures of 1:1 CT salts [**26**][I] and [**27**][I] consist of perfectly superimposed stacks of molecular units interspersed by columns of disordered iodines <1996CM762>. Interstack contacts in both structures are limited, indicative of one-dimensional electronic structures.



Several structures of selenium and transition metal-containing five-membered heterocycles derived from 1,2,3-selenadiazoles such as complexes **51a**, **52**, and **53a** were determined by X-ray crystallographic analysis <2004POL2967, 2005TL1001, 1999JCD791>.



6.12.3.2 NMR Spectroscopy

Nuclear magnetic resonance (NMR) spectra of 1,2,3-selenadiazoles have been described previously [\(<1996CHEC-II\(4\)743, 1981ZNB1017>\)](#). The characteristic ^1H chemical shifts of H-4 and H-5 lie in the range δ 8.2–8.4 and δ 8.8–9.4 ppm, respectively. The newly reported data also show similar chemical shifts ([Table 19](#)). ^1J H–Se for 4-substituted-1,2,3-selenadiazoles and ^1J and ^2J C–Se coupling constants for 4,5-disubstituted-1,2,3-selenadiazoles were also reported ([Tables 19 and 20](#)).

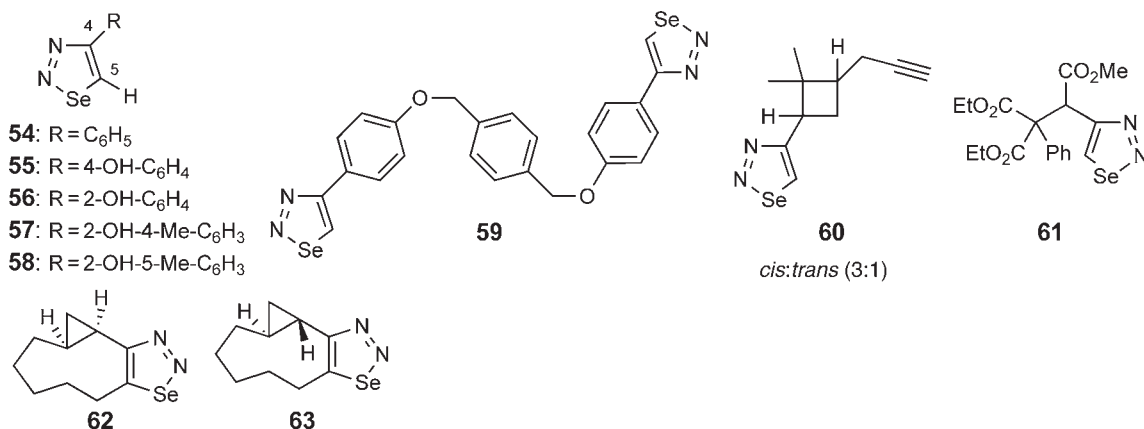


Table 19 ^1H NMR spectra of ring hydrogens (H-5) in 4-substituted-1,2,3-selenadiazoles

Compound	δ (ppm)	$^2J_{\text{HSe}}$ (Hz)	Solvent	Reference
54	8.93 s		CDCl ₃	2004MOL957
55	9.20 s		CDCl ₃	2004MOL957
56	10.09 s	42	(CD ₃) ₂ SO	1999TL3903, 2000RJO605
57	9.4 s	40	(CD ₃) ₂ SO	2001RJO1643, 2002RJC1282
58	9.52 s	40	(CD ₃) ₂ SO	2001RJO1643
59	9.72 s		(CD ₃) ₂ SO	2004JHC887
60	8.21 s		CDCl ₃	2001HCO173
61	8.94 s		CDCl ₃	2003JOC1947

Table 20 Selected ^{13}C NMR spectra of 4-substituted- and 4,5-disubstituted-1,2,3-selenadiazoles

Coordinate	62 ^{a,b}	63 ^{a,b}	56 ^{c,d}	57 ^{c,d}	58 ^{c,d}
δ C5 (ppm)	163.2	162.8	142.1	136.7	131.77
$^1J_{\text{CSe}}$ (Hz)	137	137	133	135	135
δ C4 (ppm)	159.8	160.5	155.2	162.33	162.26
$^2J_{\text{CSe}}$ (Hz)	30	31			

^a<1997LA1557>.

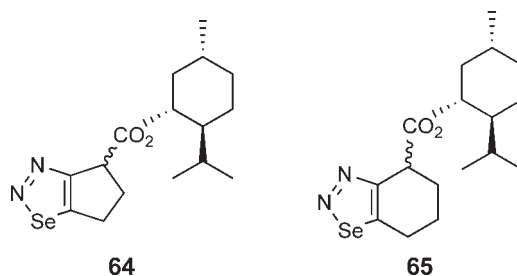
^bIn CDCl₃.

^c<1999TL3903, 2000RJO605>.

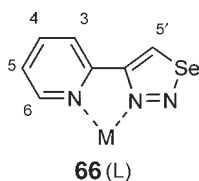
^dIn (CD₃)₂SO.

^e<2001RJO1643, 2002RJC1282>.

^{77}Se and ^{13}C NMR spectra of some bicyclic 1,2,3-selenadiazoles were studied and it was shown that the ^{77}Se chemical shifts are a suitable tool for chiral discrimination in diastereomeric compounds <1995MRC490>. The diastereomeric mixtures of menthyl ester-substituted 1,2,3-selenadiazoles **64** and **65** show different splitting in their ^{77}Se signals.



^1H NMR spectra of metal complexes of 2-(1,2,3-selenadiazol-4-yl)pyridine **66** showed coordination-induced shift (CIS) values similar to those observed for related chelating ligands <2002AJC783>. The downfield shifts, compared with free ligand, suggest that the ligand **66** would chelate to a metal center (**Table 21**).

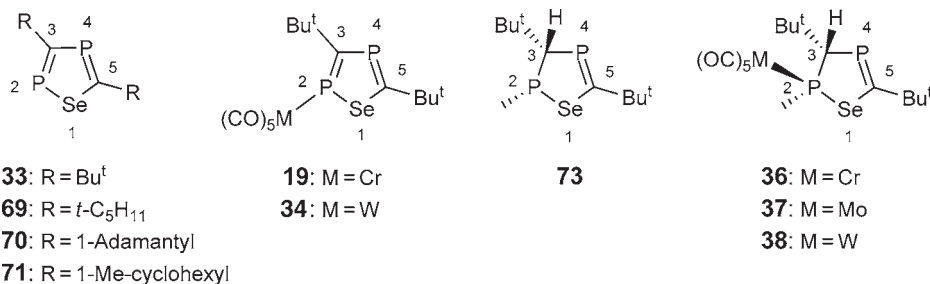


67: PdCl_2
68: $[\text{Ru}(\text{bpy})_2\text{L}](\text{PF}_6)_2$

Table 21 ^1H NMR chemical shifts and CISs of compound **66** and its palladium and ruthenium complexes (CIS = $(\delta_{\text{complex}} - \delta_{\text{ligand}})$)

Complex	Solvent	H-5'	H-3	H-4	H-5	H-6
66	$(\text{CD}_3)_2\text{SO}$	10.30	8.37	8.00	7.45	8.71
67	$(\text{CD}_3)_2\text{SO}$	10.71	8.47	8.30	7.73	9.06
CIS	$(\text{CD}_3)_2\text{SO}$	+0.41	+0.10	+0.30	+0.28	+0.35
66	CD_3CN	10.19	8.46	7.99	7.44	8.74
68	CD_3CN	9.91	8.46	8.15	7.48	7.77
CIS	CD_3CN	-0.28	0.00	+0.16	+0.04	-0.97

^{13}C , ^{31}P , and ^{77}Se NMR spectra of 1,2,4-selenadiphospholes **33**, **69–71**, and the related complexes **19**, **34** and **73**, and **36–38** are shown in **Table 22**. ^{31}P NMR chemical shifts and coupling constants $^2J_{\text{PP}}$ and $^1J_{\text{PSe}}$ of compounds **33** and **69–71** are all similar.



The mode of attachment of the $[\text{M}(\text{CO})_5]$ fragment to the 1,2,4-selenadiphosphole ring was established as being via the phosphorus P-2 atom bonded directly to selenium. The ^{31}P NMR spectrum of both compounds **19** and **34** shows a pattern of lines typical for an [AB] spin system with satellites due to further coupling to the ^{77}Se nucleus. Additional

Table 22 Selected ^{13}C , ^{31}P , and ^{77}Se NMR spectra of 1,2,4-selenadiphospholes and related compounds

<i>Coordinate</i>	33^{a,b}	19ⁱ	34ⁱ	69^{f,c}	70^d	71^b	73^{e,b}	36^{e,b}	37^{e,b}	38^{e,b}
δ C-3 (ppm)	222.5 dd			220.4 d	223.5 dd ^c	223.3 dd	73.1 dd			
$^1\text{JC}(3)\text{P}$ (Hz)	82.2,71.8			80.5, 72.7	85.4, 73.2 ^c	83.5, 68.1	55.0			
$^2\text{JC}(3)\text{P}$ (Hz)							33.6			
δ C-5 (ppm)	216.0 dd			214.1	216.2 ^c	215.7 dd	207.4 dd	160.48 dd	153.3 dd	
$^1\text{JC}(5)\text{P}$ (Hz)	67.2			73.4	66.8 ^c	64.7	56.4	96.0	100.2	
$^2\text{JC}(5)\text{P}$ (Hz)	6.13			5.9	5.5 ^c	5.2	5.9	1.6		
$^1\text{JC}(5)\text{Se}$ (Hz)								150.5	147.7	
δ P-2 (ppm)	291.6 d	282 d	221.8 d	295.6 dd	287.2 ^b	292.9	230.0 d	105.2 d	75.4	47.5
$^2\text{JP}(2)\text{P}(4)$ (Hz)	49.2	62.3	64.0	48.1	49.3 ^b	48.4	12.5	23.8	23.9	25.0
$^1\text{JP}(2)\text{Se}$ (Hz)	440.2	480.2	473.2	439.5	449 ^b	379	42.4	101.1	101.3	102.0
$^1\text{JP}(2)\text{W}$ (Hz)			241.1							126.4
δ P-4 (ppm)	261.9 d	271.9 d	266.4 d	261.0 d	255.8 d ^b	263.9	269.1 d	249.8 d	249.8 d	245.3 d
$^2\text{JP}(4)\text{Se}$ (Hz)	62.9	54.6	54.9	62.3	79 ^b	63	244.2			
δ Se (ppm)	949.4 dd ^{a,b,g} 773.0 dd ^{f,h,c}		935.1 dd ^{g,h}	723.0 dd ^h			1050.9 dd ^g			

^a<1996BSB675>.^bIn C_6D_6 .^cIn CDCl_3 .^d<1999S1642>.^e<2002JOM84>.^f<1996PS99>.^gStandard for Se was not described.^hRelative to Me_2Se .ⁱ<1999JOM156>.

evidence for the structure of compound **34** comes from its ^{77}Se NMR spectrum which shows a doublet of doublets pattern and the observation of tungsten (^{183}W) satellites around the resonance of P-2. The magnitude of the $^1J_{\text{P}(2)\text{W}}$ coupling constant lies in the expected range for complexes containing an η^1 -ligated $[\text{W}(\text{CO})_5]$ fragment (234–276 Hz).

The ^{31}P NMR chemical shifts of compounds **36–38** are also in line with the expected trends previously reported for δ P within group 6 metal carbonyl–phosphine complexes. The ^{31}P NMR spectra of compound **38** also exhibit the tungsten (^{183}W) satellites around the resonance of P-2 and the typical $^1J_{\text{P–W}}$ coupling constants for η^1 -ligated $[\text{W}(\text{CO})_5]$ –phosphine complexes.

The ^{13}C , ^{31}P , and ^{125}Te NMR spectra of 1,2,4-telluraadiphosphole **74**, and its W-complex **35** are shown in Table 23. The ^{31}P NMR spectrum of 1,2,4-telluradiphosphole **74** is similar to that of 1,2,4-selenadiazole **33**. ^{125}Te satellites are visible on both resonances. The spectrum is in accord with the generalization that spin–spin couplings involving tellurium, $^1J_{\text{PTe}}$ (1028 Hz) and $^2J_{\text{PTe}}$ (151 Hz), are approximately 2–3 times greater than the same coupling involving selenium <B-1986MI189>. The single-bond phosphorus–tellurium coupling, 1028 Hz, is higher than the known value (e.g., $^1J_{\text{PTe}} = 451$ Hz in $(\text{Bu}^t)_2\text{P}_2\text{Te}$), and is closer to the value for double-bond phosphorus–tellurium coupling of 1600 Hz in $\text{Bu}^t_3\text{P}=\text{Te}$. This suggests that the tellurium–phosphorus bond in compound **74** has appreciable double-bond character and the 1,2,4-telluradiphosphole ring may have 6π -electron aromatic character.

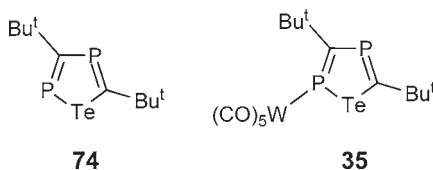


Table 23 Selected ^{13}C , ^{31}P , and ^{125}Te NMR spectra of 1,2,4-telluradiphosphole **74** and its W-complex **35**

Coordinate	74 ^{b,c}	35 ^d
δ C-3 (ppm)	223 dd	
$^1J_{\text{C}(3)\text{P}}$ (Hz)	87.0, 77.8	
δ C-5 (ppm)	204 dd	
$^1J_{\text{C}(5)\text{P}}$ (Hz)	65.6	
$^2J_{\text{C}(5)\text{P}}$ (Hz)	8	
δ P-2 (ppm)	302 d	216.0 d
$^2J_{\text{P}(2)\text{P}(4)}$ (Hz)	50.8	66.1
$^1J_{\text{P}(2)\text{Te}}$ (Hz)	1028	132
δ P-4 (ppm)	299 d	58.0 d
$^2J_{\text{P}(4)\text{Te}}$ (Hz)	151.3	53
δ Te (ppm) ^a	1383 dd	1373 dd

^aRelative to Me_2Te .

^b<1999TL3815>.

^cIn C_6D_6 .

^d<1999JOM156>.

NMR spectra of oxaselenazole **41**, thiaselenazoles **[75]** GaCl_4 and **[76]** GaCl_4 , diselenazole **[49]** GaCl_4 , and triselenoles **43** and **77** were reported and are shown in Table 24.

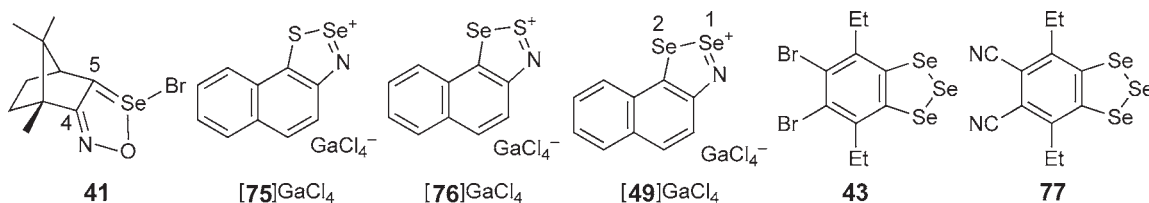
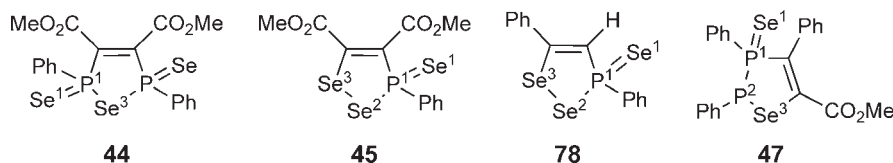


Table 24 Selected ^{13}C and ^{77}Se NMR spectra of compounds **41**, **75**, **76**, **49**, **43**, and **77**

Coordinate	41 ^{b,c}	[75] <i>GaCl</i> ₄ ^{d,e}	[76] <i>GaCl</i> ₄ ^{d,e}	[49] <i>GaCl</i> ₄ ^{d,e}	43 ^{f,e}	77 ^{f,e}
δ C-4 (ppm)	205.3					
δ C-5 (ppm)	176.3					
δ Se (ppm)	1422.5 ^a	1536 ^a	1399.9 ^a	1561 (Se-1), 1324 (Se-2) ^a	457.5, 576.8	463.5, 563.5
$^2J_{\text{SeSe}}$ (Hz)					260	271

^aRelative to Me_2Se .^b<2002JOC499>.^cIn CDCl_3 .^d<2005IC1837>.^eIn CD_3CN .^f<2004JOC4716>.

^{77}Se NMR spectra of selenadiphospholes and diselenaphospholes **44**, **45**, **78**, and **47** were reported (Table 25) <2002CEJ2705>. In compounds **44**, **45**, **78**, and **47**, the exocyclic selenium atom is at lower frequency relative to those within the heterocycle. A $^1J(\text{Se},\text{Se})$ coupling of 271 Hz is characteristic of compound **45**. In molecule **47**, the ring atom Se-3 has a $^2J(\text{P},\text{Se})$ coupling to the phosphorus(v) center P-1 of 20 Hz. On the other hand, there is no resolved coupling between the exocyclic Se-1 and the internal phosphorus(III) center P-2.

**Table 25** Chemical shift δ (ppm) and coupling constants J (Hz) for ^{77}Se NMR spectra of compounds **44**, **45**, **78**, and **47**^{a,b}

44		45		78		47	
δ Se-3	434.6 t	δ Se-3	542.6 d	δ Se-3	558.1 d	δ Se-3	417.1 dd
$^1J/P(1)Se(3)$	381	$^2J/P(1)Se(3)$	7	$^2J/P(1)Se(3)$	7	$^1J/P(2)Se(3)$	239
δ Se-1	−82.3 d	$^1JSe(3)Se(2)$	271	δ Se-2	410.8 d	$^1J/P(1)Se(3)$	20
$^1J/P(1)Se(1)$	808	δ Se-2	420.0	$^1J/P(1)Se(2)$	350	δ Se-1	−240.0 d
δ Se-3		$^1J/P(1)Se(2)$	360	δ Se-1	−23.4 d	$^1J/P(1)Se(1)$	772
$^1JPSe(3)$		δ Se-1	−7.8 d	$^1J/P(1)Se(1)$	775		
		$^1J/P(1)Se(1)$	806				

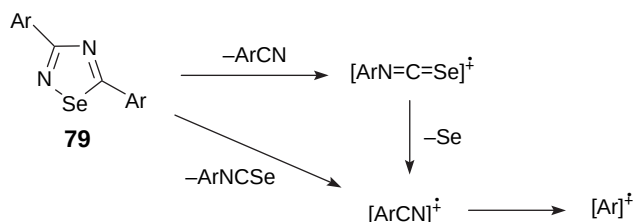
^aIn CDCl_3 .^bRelative to Me_2Se .

6.12.3.3 Mass Spectrometry

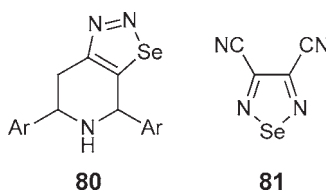
As described in CHEC-II(1996) and CHEC(1984) <1996CHEC-II(4)743, 1984CHEC(6)333>, fragmentation of 1,2,3-selenadiazoles shows the loss of N_2 followed by extrusion of selenium and formation of the corresponding alkynes. The newly characterized 1,2,3-selenadiazoles also show such fragmentation patterns, for example, <1997IJB923, 2002RJC1282, 2001RJO1643, 2001HCO173, 1997LA1557>.

The mass spectra of 3,5-diaryl-1,2,4-selenadiazoles **79** show a molecular ion and the base peak arising from ArCN^+ . In general, the first fragmentation step is the loss of arenenitrile. The proposed fragmentation pattern of the studied compounds is shown in Scheme 1.

The cleavage process to give 2,6-diaryl pyridinium cation of 5,7-diaryl piperidino[3,4-*d*]-1,2,3-selenadiazoles **80** was discussed <1998IJB1194>. Dissociative ionization of 3,4-dicyano-1,2,5-selenadiazole **81** leads to cyanogen *N*-selenide radical cation, $\text{N}\equiv\text{C}-\text{C}\equiv\text{N}-\text{Se}^{\bullet+}$. Further reactions of the generated ion in the gas phase were studied <1998TL533, 1998PCA9021, 1999IJM39>.



Scheme 1

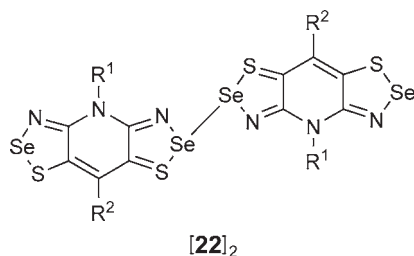


6.12.3.4 IR Spectroscopy

IR spectra of 1,2,5- and 1,3,4-selenadiazoles and 1,2,5-telluradiazole have been compared with the results obtained by theoretical calculations <1995ACS11, 1997JST451, 2001JST81>. Good agreement between the experimental data and calculated results was found and precise assignments were made (Section 6.12.2).

IR spectra of 1,2,3-selenadiazole and the pyrolysis products including selenoketene were recorded <1995CPL211>.

The near-IR spectra of crystalline samples of the two radical dimers [**22**]₂ (R¹ = Me, Et; R² = H) were measured <2005JA18159>. The absorptions in the mid-IR region between 650 and 3100 cm⁻¹ are due to molecular vibrations of the dimer. A well-developed, low-lying absorption cutoff was interpreted as corresponding to a valence band to conduction band excitation. The optical energy gap values are qualitatively in agreement with the values predicted by the LMTO band structure calculations.



6.12.3.5 Photoelectron, UV, and ESR Spectroscopy

The HeI photoelectron spectra of 3,5-di-*tert*-butyl-1,2,4-selenadiazole **33** were recorded and interpreted by theoretical calculations and correlation with the related compounds (Table 26) <1995JCS315>. The peaks at 8.2 and 8.49 eV were assigned to π -orbital energies. The peaks at 8.86 and 9.43 eV may be attributed to the two combinations of the phosphorus lone pairs.

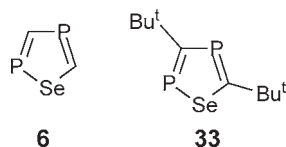


Table 26 Measured and calculated^a ionization energies (eV) of compound **33**

<i>Exp.</i>	<i>Calc.</i>
8.2 (sh)	8.05 π
8.49	8.79 π
8.86	9.64 n_p^-
9.43	11.20 n_p^+
10.02	11.66

^aThe effect of the substituent groups (with standard geometrical features) to the MP2/6-31G* optimized unsubstituted ring system **6** (Section 6.12.2).

Ultraviolet–Visible (UV–Vis) spectra were reported for the following compounds (Table 27). [1,2,5]Selenadiazolo[3,4-*f*]-benzo[*c*][1,2,5]thiadiazoles **82** and **83** show the absorption maxima at longer wavelengths than the corresponding benzo-bis(thiadiazole)s, which is regarded as a polar effect caused by the selenium atom <1997T10169>. Also, 1,2,5-selenadiazole derivatives **86** and **87** have the longest wavelengths among the corresponding thiadiazoles and oxadiazoles <2001JOC8954>. UV–Vis spectra for [1,2,5]selenadiazole-fused porphyrazines and phthalocyanines **89–92** were also studied.

Table 27 UV–Vis spectra of some 1,2,5- and 1,2,3-selenadiazole derivatives

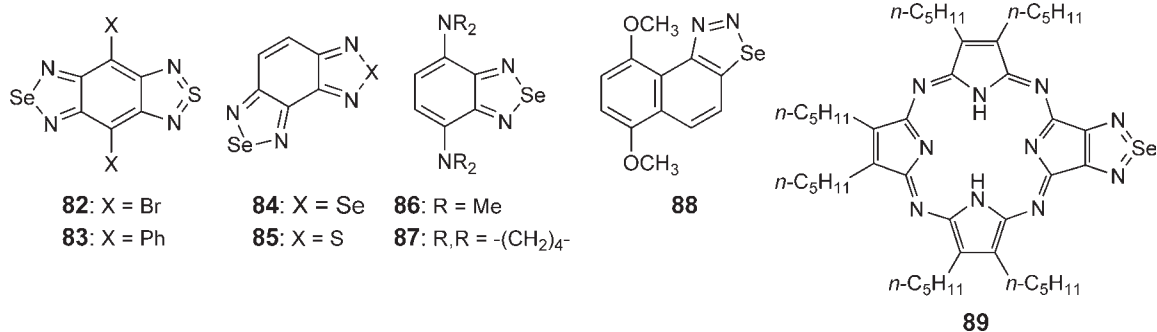
<i>Compound</i>	$\lambda_{\max}$ (log ϵ) (nm)	<i>Reference</i>
82 ^a	609	1997T10169
83 ^a	625 (4.01)	1997T10169
84 ^b	205 (4.00), 312 (4.13), 393 (sh, 3.15)	2004JHC955
85 ^b	204 (4.17), 294 (4.41), 326 (sh, 3.19)	2004JHC955
86 ^c	258 (4.18), 324 (3.86), 330 (3.86), 512 (3.38)	2001JOC8954
87 ^c	270 (4.30), 322 (3.82), 580 (3.40)	2001JOC8954
88 ^b	255 (3.53), 308 (2.6)	2000JHC1325
89 ^a	785, 334	2001MC45
90 ^a	599, 659	2003JOC1665
91 ^a	552, 653	2003JOC1665
92 ^d	345 (4.96), 462 (3.89), 530 (2.85), 626 (3.72), 882 (4.66)	1995ACS658

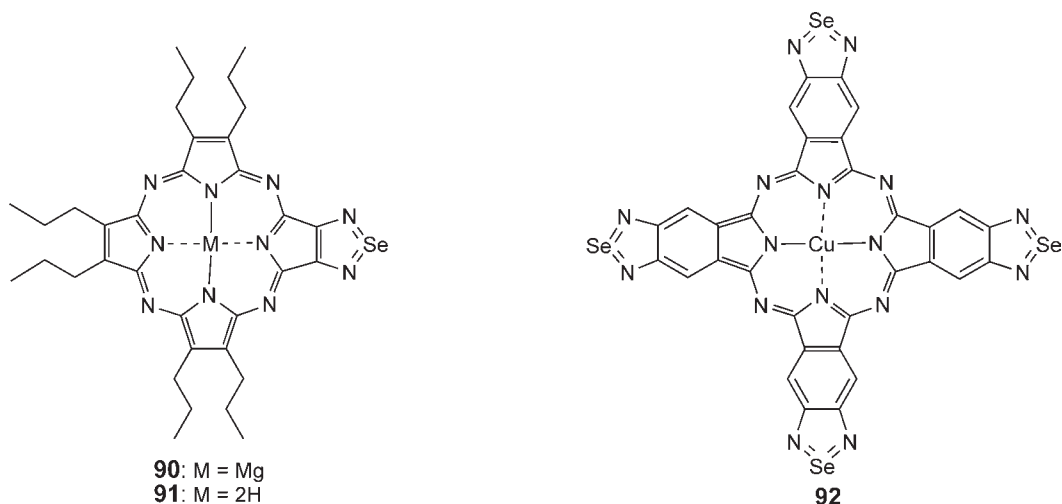
^aIn CH₂Cl₂.

^bIn MeOH.

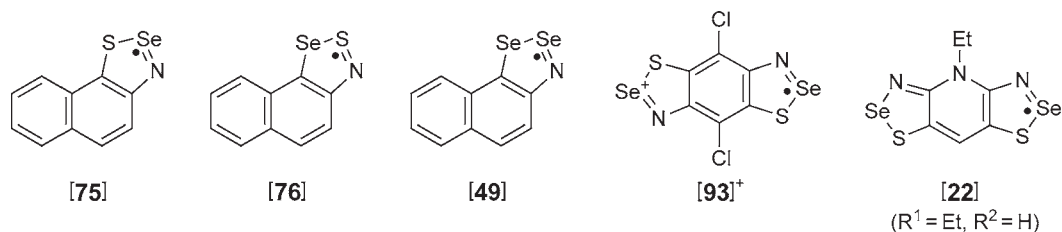
^cIn MeCN.

^dIn H₂SO₄.





Electron spin resonance (ESR) spectra have been reported for several stable radical species having the 1,2,3-thiaselenazoyl, selenathiazoyl, and diselenazoyl structures shown below [\[2005IC1837, 1997JA12136, 2005JA18159, 2005CC1543\]](#). The experimental values were in good agreement with those predicted by calculation.

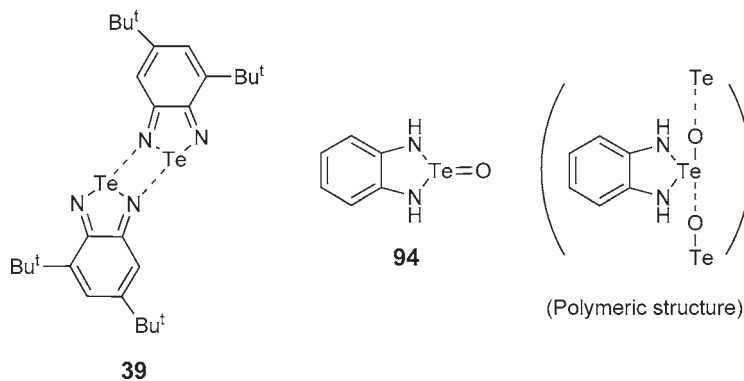


6.12.4 Thermodynamic Aspects

6.12.4.1 Melting Points and Solubilities

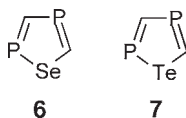
The properties of 1,2,5-telluradiazole dimer **39** are in distinct contrast to those of the parent 1,2,5-telluradiazole, which is a high-melting solid with poor solubility in organic solvents [\[1982S681\]](#). Compound **39** melts sharply at 207–208 °C and can be recrystallized from pentane.

The high melting points and lack of solubility in all common solvents of compound **94** suggest that it may exist in a polymeric form in the solid state [\[1998PS221\]](#).



6.12.4.2 Aromaticity and Stability

Aromaticity of new members of the fully conjugated heterocycles has been discussed. A theoretical study of 1,2,4-selenadiphosphole **6** indicates that the system is aromatic <1995J(P2)315>. NMR study of 1,2,4-telluradiphosphole also suggests that 1,2,4-telluradiphosphole **7** may have 6π -electron aromatic character <1999TL3815> (Section 6.12.3.2).

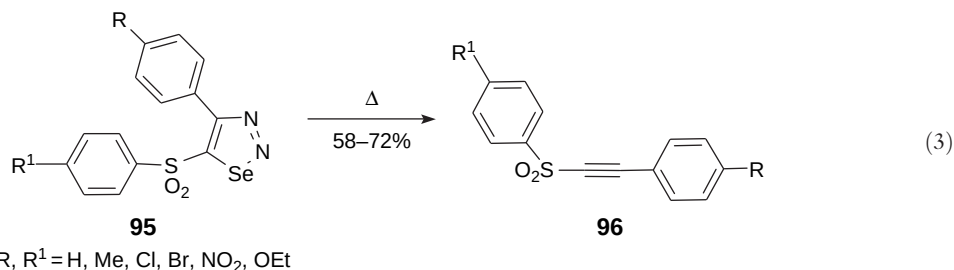


6.12.5 Reactivity of Fully Conjugated Rings

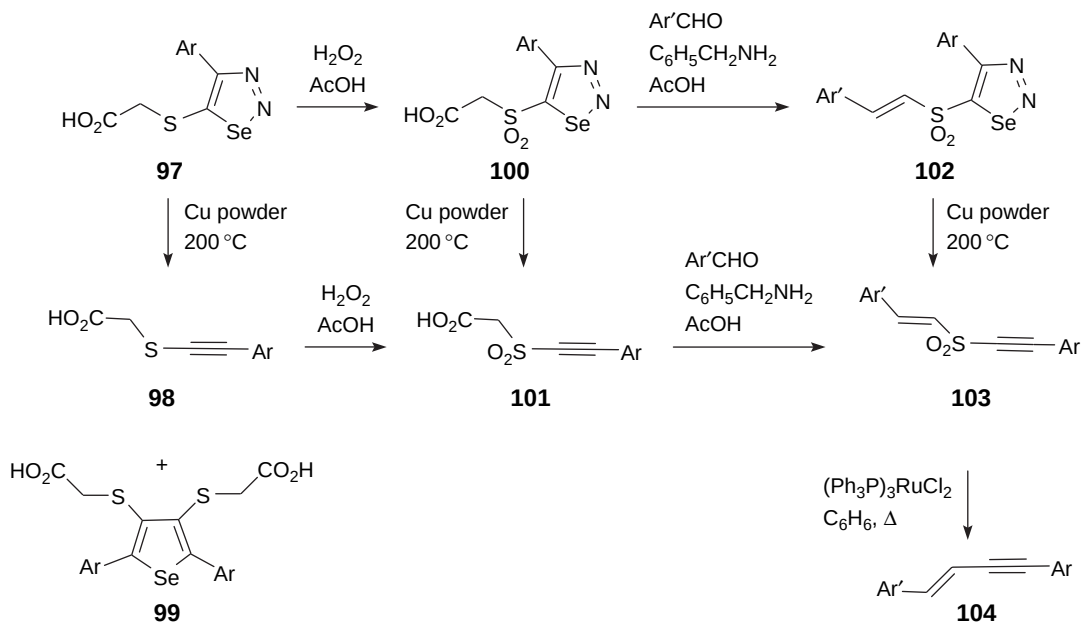
6.12.5.1 Thermal and Photochemical Reactions

The aspects of thermal and photochemical decomposition reactions of 1,2,3-selenadiazoles with nitrogen and selenium atoms have been described in CHEC(1984) and CHEC-II(1996) <1984CHEC(6)333, 1996CHEC-II(4)743>. The ready thermal decomposition reactions of 1,2,3-selenadiazoles have been continuously utilized.

Thermal reaction of 1,2,3-selenadiazoles **95** above their melting points (in the range of 136–160 °C) for 10–15 min leads to the formation of 1-arylsulfonyl-2-arylacetylenes **96** in 58–72% yields (Equation 3) <1997IJB1062>.



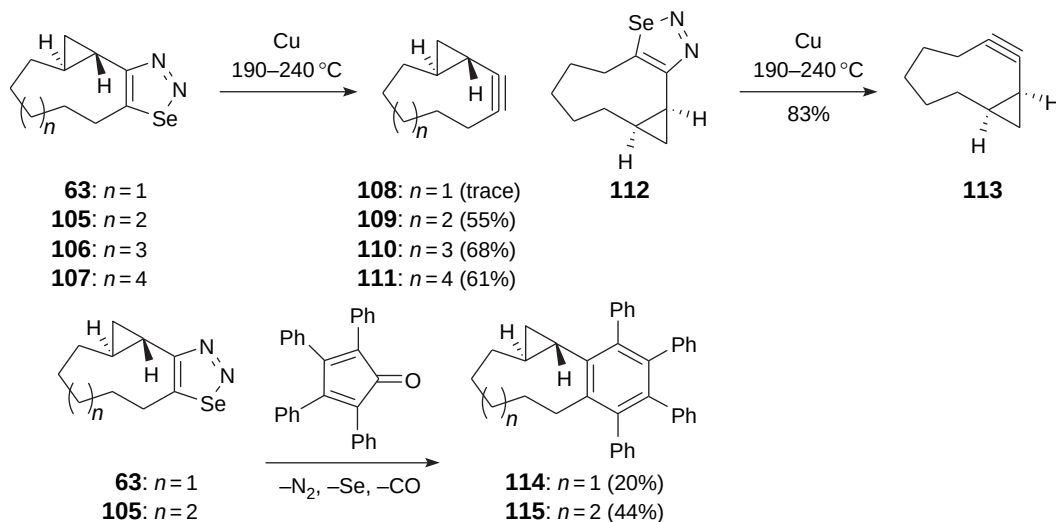
The thermolysis of selenadiazole **97** with copper powder at 200 °C gave product **98** as a major product (Ar = Ph, 58%) and product **99** as a minor one (Scheme 2) <1997T17351>. The thermolysis of sulfones **100** and **102** gave



Scheme 2

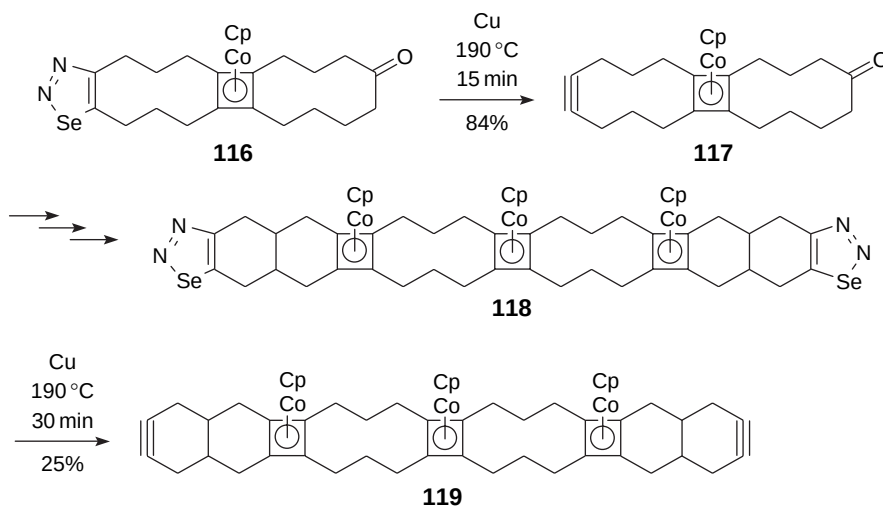
acetylene derivatives **101** and **103** exclusively. The method is considered to be a new facile route to potentially useful enyne sulfones **103** and the subsequently transformed enynes **104**.

As an extension of work on synthesis of strained cycloalkynes, *trans*- and *cis*-cyclopropane-fused medium ring (9–11-membered) cycloalkynes **108–111** and **113** were synthesized by thermolysis of 1,2,3-selenadiazoles **63**, **105–107**, and **112** with copper powder at 190–240 °C (Scheme 3) <1997LA1557>. *trans*-Bicyclo[7.1.0]dec-2-yne **108** is highly strained and has a low kinetic stability toward polymerization. Only traces of compound **108** were detected in the thermolysis of selenodiazole **63**. The trapping with tetraphenylcyclopentadienone yielded an adduct **114** in 20% yield, whereas precursor **105** gave product **115** in 44% yield.



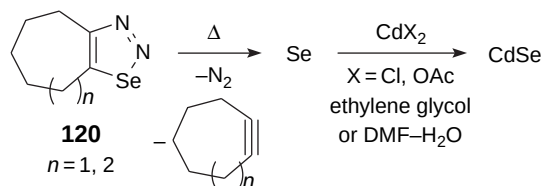
Scheme 3

The thermolysis of cobalt complex **116** in the presence of copper powder at 190 °C gave 10-membered cyclic acetylene **117** (Scheme 4) <2002AGE1181>. The reaction was iterated to lead to belt-like macrocycles. The same procedure was also utilized to synthesize twofold CpCo-capped bis(cyclopentadieno)superphane <2000OM1578>.



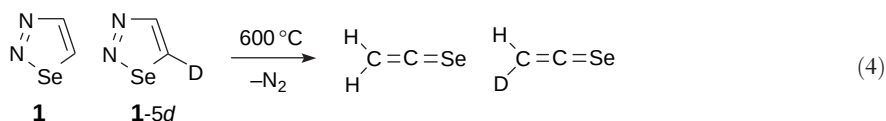
Scheme 4

Heating cyclohepteno- or cycloocteno-1,2,3-selenadiazoles **120** with cadmium chloride or acetate in aqueous ethylene glycol or aqueous dimethylformamide (DMF) afforded cadmium selenide (**Scheme 5**) <2003MAL1464, 2004MAL966, 2004MCH323>. Heating cyclohepteno-1,2,3-selenadiazole with silver nitrate in ethylene glycol gave silver selenide nanopowder <2004MAL1030>. The method using 1,2,3-selenadiazoles is considered as a greener source of selenium.

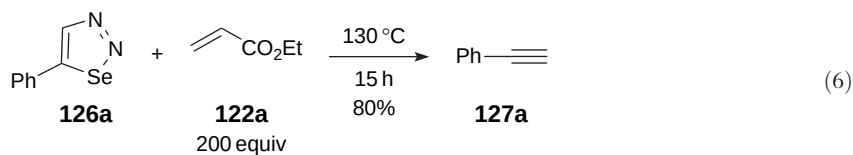
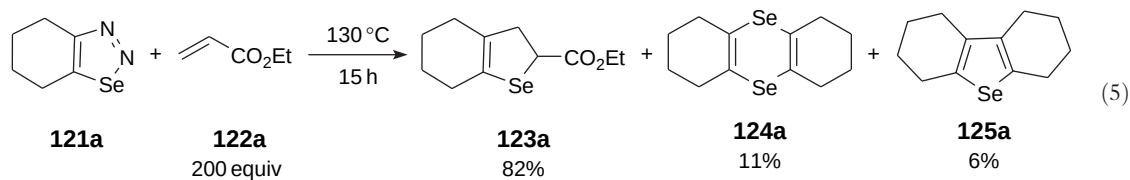


Scheme 5

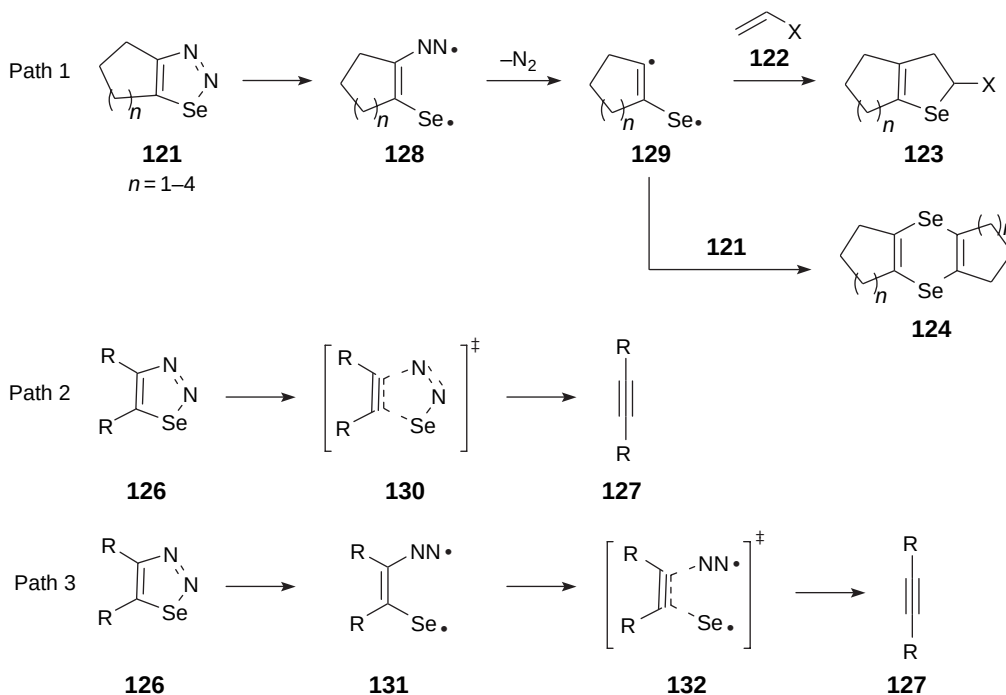
The IR spectra of selenoketene and selenoketene-*d*₁, which were prepared by flow thermolysis of the 1,2,3-selenadiazoles **1** and **1-5d** at 600 °C, were investigated (**Equation 4**) <1995CPL211>. With the aid of *ab initio* predictions of vibrational frequencies and intensities, the spectra were assigned in detail.



Thermal reactions of 1,2,3-selenadiazoles synthesized from cyclic ketones **121** with an excess amount (200 equiv) of alkene, such as ethyl acrylate **122a**, at 130 °C gave dihydroselenophenes **123** in moderate to good yields along with the formation of the corresponding 1,4-diselenines **124** and selenophenes **125** as by-products (**Equation 5**) <2000JOM488>. When compound **121a** was treated in the absence of an alkene at 150 °C, 1,4-diselenine **124a** was formed in 82% yield. On the other hand, in the thermal reaction of the 1,2,3-selenadiazoles derived from linear and aromatic ketones such as compound **126a** in the presence of alkene, compounds **123–125** were not formed and the corresponding alkynes **127** were obtained as the sole product (**Equation 6**).

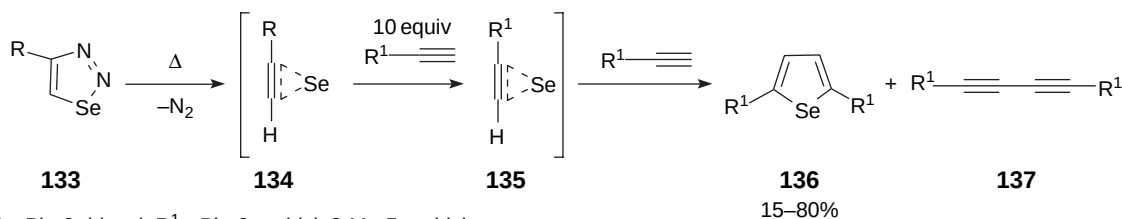


Possible reaction pathways to give compounds **123** and **124** involving the generation of vinyl radicals **129** (path 1) were suggested as shown in **Scheme 6**. The formation of acetylenes **127** for the monocyclic 1,2,3-selenadiazoles **126** was explained by involving the retro [2+3] addition reaction (path 2) or the concerted elimination of molecular nitrogen and selenium atom from the radical intermediate **131** (path 3). The paths 2 or 3 were suppressed for the reaction of bicyclic 1,2,3-selenadiazoles **121** due to the difficulty in the formation of the transition states **130** and **132**.



Scheme 6

Thermolysis of 1,2,3-selenadiazoles **133** in the presence of 10 equiv of arylacetylenes leads to the formation of 2,5-diarylselenophenes **136** in moderate to good yields and 1,4-diarylbuta-1,3-dynes **137** as by-products (Scheme 7) <2002TL4817>. The mechanism of this reaction includes the thermal elimination of nitrogen and the formation of intermediates **134**. During the second step, the intermediates **134** are converted into species **135** by the reaction of arylacetylene ($R^1-C\equiv CH$). Subsequently, intermediates **135** react with a second molecule of the arylacetylene to yield the corresponding 2,5-diarylselenophenes **136** and 1,4-diarylbuta-1,3-dynes **137**.



$R = \text{Ph, 2-thienyl}; R^1 = \text{Ph, 2-pyridyl, 2-Me-5-pyridyl}$

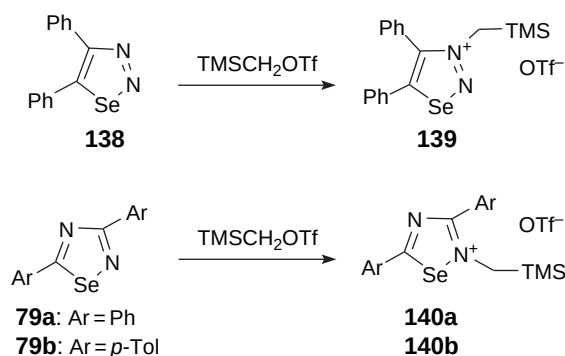
Scheme 7

6.12.5.2 Electrophilic Attack at Nitrogen

4,5-Diphenyl-1,2,3-selenadiazole **138** and 3,5-diphenyl-1,2,4-selenadiazole **79** were alkylated with trimethylsilylmethyl trifluoromethanesulfonate to give the salts **139** and **140** (Scheme 8) <2001J(P1)394>. Quaternizations occurred at N-3 and N-2, respectively. The structures and quaternization sites were confirmed by ^1H , ^{13}C , and ^{15}N NMR spectra and the subsequent reactions. The salts **139** and **140** were desilylated to generate transient selenadiazoliumylmethanide (ylide) intermediates. The transformation is described in Section 6.12.8.

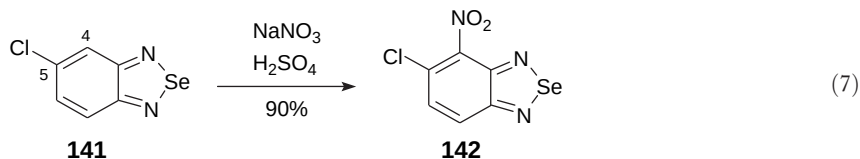
6.12.5.3 Electrophilic Attack at Carbon

As described in CHEC-II(1996) <1996CHEC-II(4)743>, examples of electrophilic attack in substituted 2,1,3-benzoselenadiazoles at position 4 have been reported. Nitration of 5-chlorobenzo[2,1,3]selenadiazole **141** with



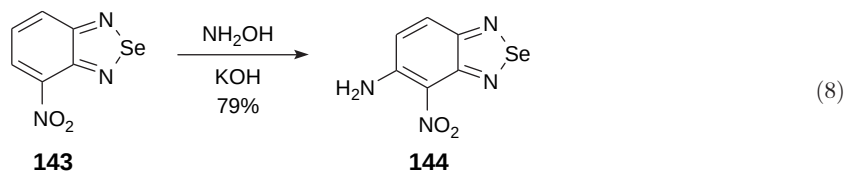
Scheme 8

NaNO_3 and conc. H_2SO_4 gave 5-chloro-4-nitrobenzo[2,1,3]selenadiazole **142** in 90% yield (Equation 7) <2004RJC428>. An improved method for nitration of fluorine-substituted benzo[2,1,3]selenadiazoles was also reported. Treatment of a variety of benzo[2,1,3]selenadiazoles with commercially available 90% nitric acid dissolved in a mixture of methanesulfonic acid and phosphorus pentoxide at room temperature gave 4-nitrobenzo[2,1,3]selenadiazoles in 81–94% yield <2004JHC1023>. The obtained 2,1,3-benzoselenadiazoles were used as precursors to *o*-phenylenediamines (see Section 6.12.5.8).



6.12.5.4 Nucleophilic Attack at Carbon

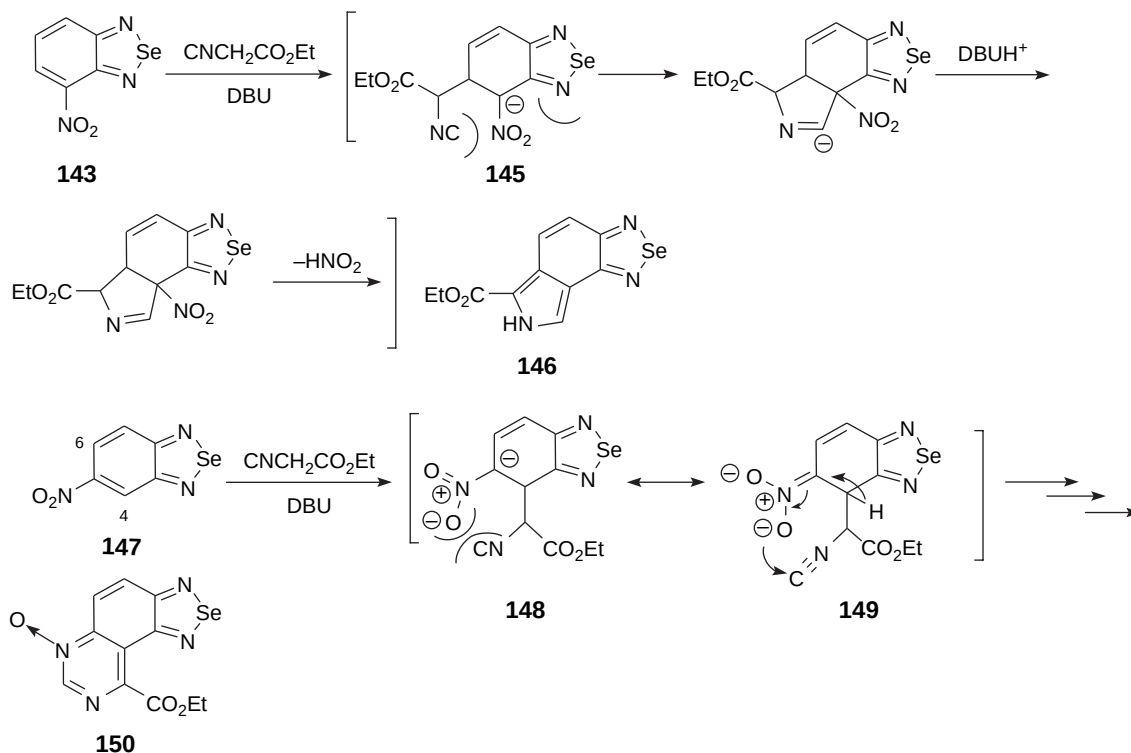
As described previously <1996CHEC-II(4)743>, nucleophilic substitution in the benzene ring of 2,1,3-benzoselenadiazole is known. Amination of 4-nitrobenzo-2,1,3-selenadiazole **143** with hydroxylamine and potassium hydroxide gave nitroamine **144** in 79% yield (Equation 8) <2004JHC955>.



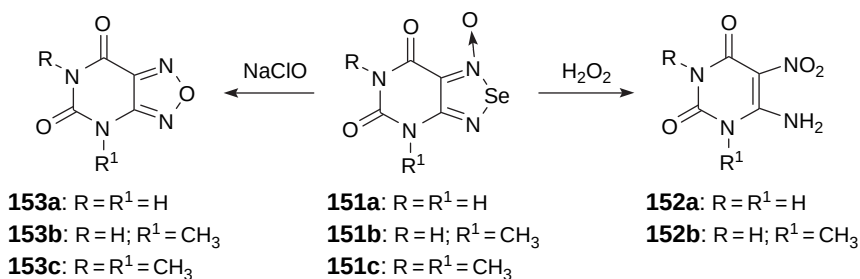
Reaction of 4-nitro-2,1,3-benzoselenadiazole **143** with ethyl isocyanoacetate in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in tetrahydrofuran (THF) at room temperature gave the pyrrole-fused product **146** in 56% yield as the sole product (Scheme 9) <1996J(P1)1403>. Reaction of 5-nitro-2,1,3-benzoselenadiazole **147** with ethyl isocyanoacetate under similar reaction conditions gave the pyrimidine *N*-oxide-fused product **150** in 28% yield as the sole product. Proposed mechanism for the formation of pyrrole and pyrimidine rings involves initial attack of the ethyl isocyanoacetate anion at the β -position to the nitro groups forming the anionic intermediates **145** and **148** and the resonance structure intermediate **149**. The reactivity and chemoselectivity were explained by the steric effect in the intermediates.

6.12.5.5 Electrophilic Attack at Selenium and Tellurium

In general, benzoselenadiazole is stable to oxidizing agents such as 30% hydrogen peroxide in acetic acid <1957JOC503>. However, 1,2,5-selenadiazoles annelated with pyrimidine rings **151a–c** are less stable (Scheme 10)



Scheme 9

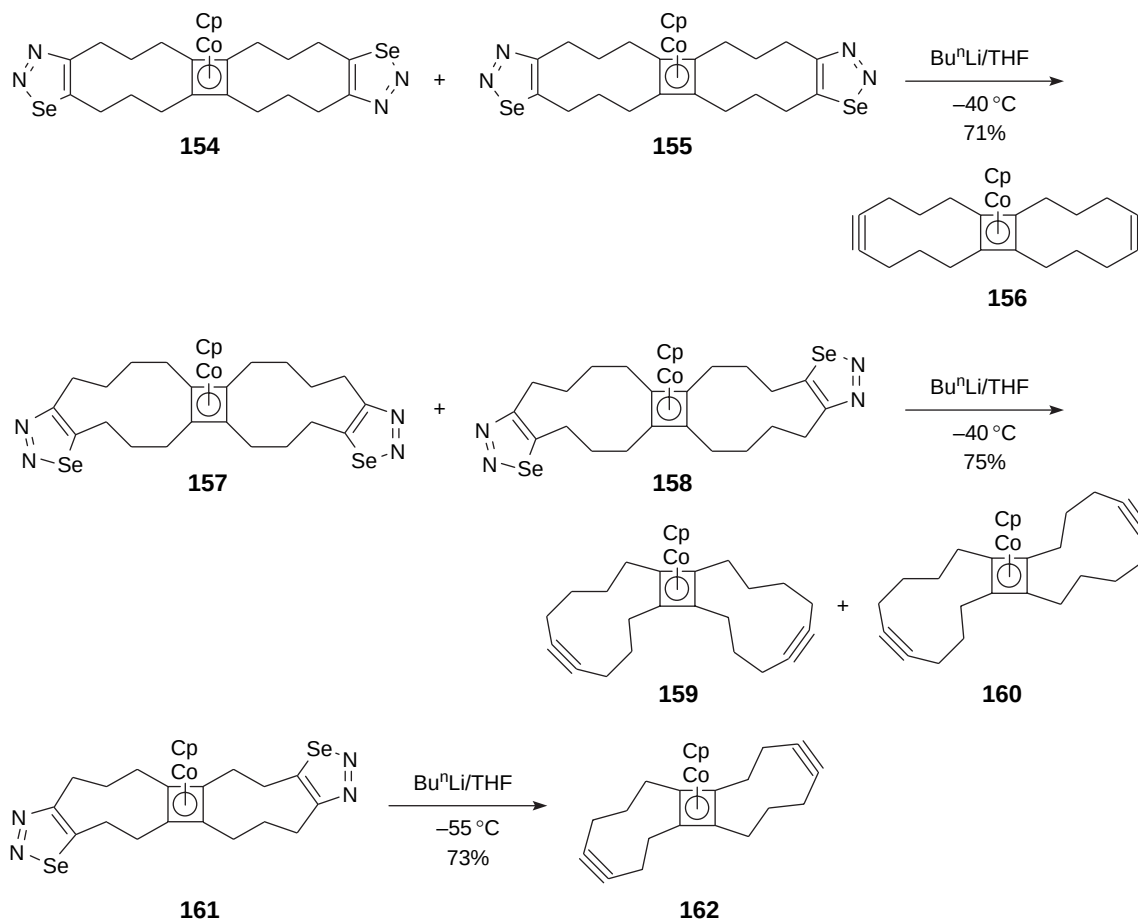


Scheme 10

<2000CHE1359>. Treatment of compounds **151a** and **151b** with 10–30% hydrogen peroxide gave 6-amino-5-nitro-uracils **152a** and **152b**. Reaction of compounds **151a-c** with sodium hypochlorite gave 1,2,5-oxadiazoles **153a-c**.

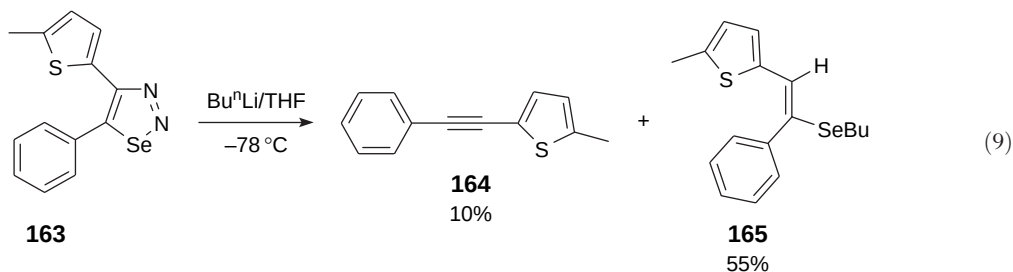
6.12.5.6 Nucleophilic Attack at Selenium and Tellurium

Reaction of 4,5-cycloalkeno-1,2,3-benzoselenadiazoles with organolithium reagents to form intermediate anions and subsequent loss of RSeLi leading to cycloalkynes is considered as an alternative method to the thermolysis <1986T1711, 1996CHEC-II(4)743>. Treatment of bis(1,2,3-benzoselenadiazole)s **154** and **155**, **157** and **158**, and **161** with Bu^nLi in THF at -40 to -55°C yielded the cyclic diynes **156**, **159**, **160**, and **162** in 71–75% yields as shown in Scheme 11 <1995OM975>. The diynes **156**, **159**, and **160** were transformed to CpCo-capped fourfold-bridged cyclobutadienophanes.

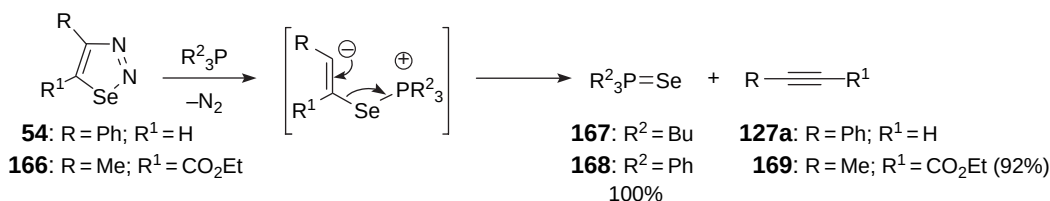


Scheme 11

Nucleophilic attack of Bu^nLi on 1,2,3-selenadiazole **163** at -78°C gave alkyne **164** in low yield along with vinylselenide **165** as a major product (Equation 9) <1998HCO81>.

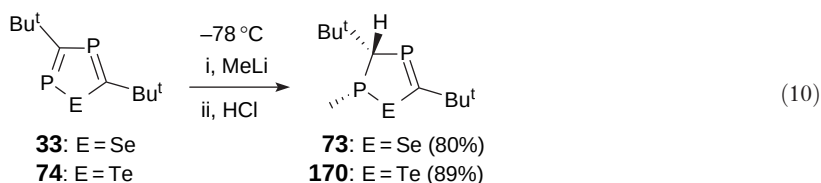


Nucleophilic attack of phosphines on 1,2,3-selenadiazoles leads to formation of selenophosphoranes and substituted acetylenes <2004CHE503>. Thus, 4-phenyl-1,2,3-selenadiazole **54** reacted with tributylphosphine in benzene at room temperature (Scheme 12). In the first stage, the Se–N bond is broken as a result of nucleophilic attack by tributylphosphine. Elimination of a molecule of nitrogen follows. A molecule of phenylacetylene is released from the intermediate and tributylselenophosphorane **167** is produced. When triphenylphosphine is used, triphenylselenophosphorane **168** is formed in quantitative yield after boiling for 1 h. In the reaction of 5-ethoxycarbonyl-4-methyl-1,2,3-selenadiazole **166** with phosphines, selenophosphoranes **167** and **168** are formed in 100% yield. Ethyl but-2-ynecarboxylate **169** was isolated from the reaction mixtures in 92% yield.



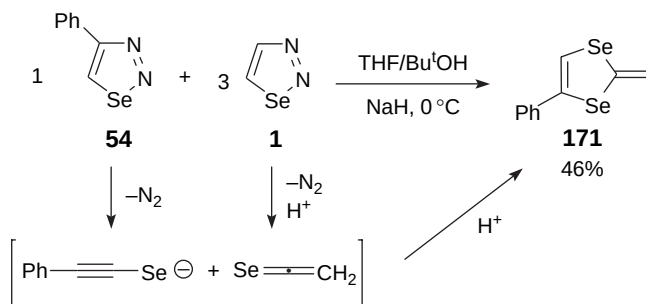
Scheme 12

Methylation of the 1,2,4-selena- and telluradiphospholes $\text{P}_2\text{EC}_2\text{Bu}^t_2$ (E = Se, Te) with MeLi occurs at the phosphorus atom adjacent to selenium or tellurium [<2002JOM84>](#). Thus, compounds **33** or **74** in THF were each treated with 1 equiv of MeLi at -78°C , followed by 1 equiv of HCl, resulting in the compounds $\text{P}_2\text{EC}_2\text{Bu}^t_2(\text{H})\text{Me}$ (E = Se, **73** (80%); E = Te, **170** (89%)) (Equation 10). The subsequent protonation of the initially generated methylated chalcogenadiphosphaaallyl anion occurred on the carbon atom which lies between the two phosphorus atoms, leading to compounds **73** and **170**. One isomer resulting from protonation in a *trans*-position relative to the methyl group formed exclusively. The structure of compound **73** was confirmed by single crystal X-ray diffraction studies of their η^1 -metal pentacarbonyl complexes (Sections 6.12.3.1 and 6.12.6).



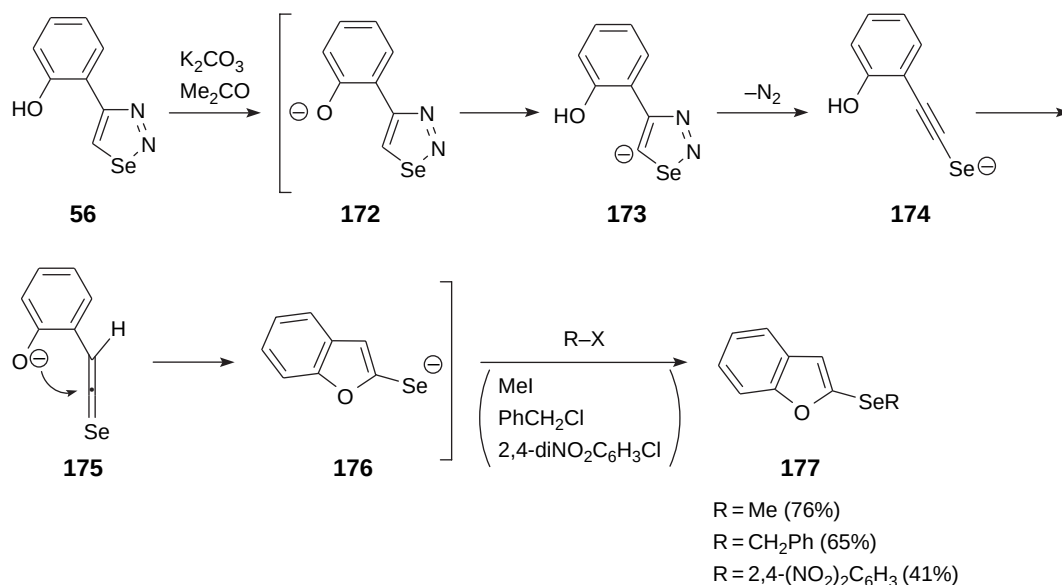
6.12.5.7 Nucleophilic Attack at Hydrogen

Deprotonation of 1,2,3-selenadiazoles at position 5 by strong bases to form carbanions which collapse with loss of N_2 to give alkyneselenolate salts was described in CHEC-II(1996) [<1996CHEC-II\(4\)743>](#). Further reactions of selenolates were also discussed. For example, in the presence of proton sources, the alkyne selenolates generate the alkyneselenols which equilibrate with the selenoketenes. [2+3] Cycloaddition of alkyneselenols to selenoketenes affords 1,3-diselenafulvenes. Mixed [2+3] cycloaddition by the protonation of a mixture of alkyne selenolates was investigated [<2002SUL129>](#). The use of 3 equiv of 1,2,3-selenadiazole **1** to 1 equiv of 4-phenyl-1,2,3-selenadiazole **54** in THF/ Bu^tOH at 0°C in the presence of NaH led to the isolation of 1:1 adduct **171** most efficiently in 46% yield (Scheme 13).



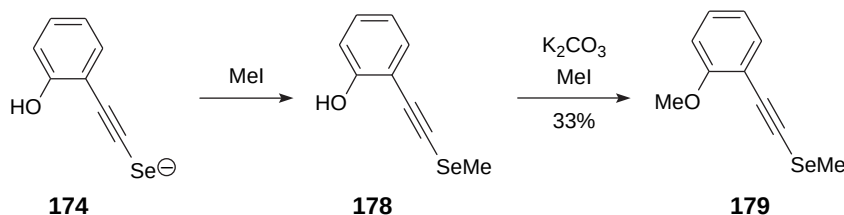
Scheme 13

The 4-(2-hydroxyaryl)-1,2,3-selenadiazole **56** undergoes ready decomposition by the action of potassium carbonate to form benzofuran-2-selenolate **177**. The intermediate **176** can be alkylated with methyl iodide and benzyl chloride and arylated with 2,4-dinitrochlorobenzene (Scheme 14) [<2001RJO1643, 2000RJO605, 1999TL3903>](#). Intermediate formation of 2-(*o*-hydroxyphenyl)ethyneselenolate **174** during decomposition of 1,2,3-selenadiazoles was proven by

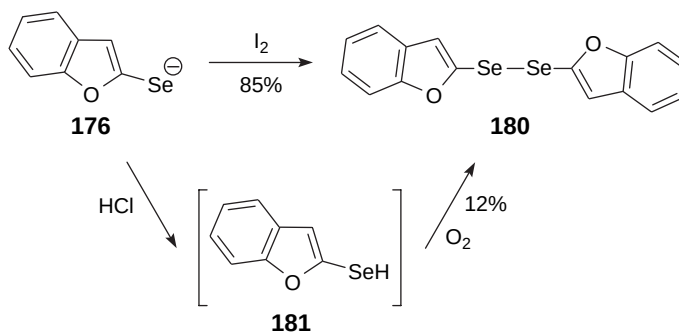


Scheme 14

the isolation of methyl *o*-methoxyphenylethynyl selenide **179** and a small amount of 2-methylselenobenzofuran **177** when the substrate **56** was treated with potassium carbonate in the presence of methyl iodide (Scheme 15). When methyl iodide was added after preliminary decomposition of selenadiazole **56** with potassium carbonate for at least 30 min, the product was 2-methylselenobenzofuran **177** (76%, Scheme 14). Oxidation of potassium benzofuran-2-selenolate **176** with iodine gives bis(2-benzofuranyl) diselenide **180** in good yield <2002RJC1282, 2000RJC1652>. Alternatively, neutralization of potassium selenolate **176** with hydrochloric acid, followed by oxidation of the benzofuran-2-selenol **181** with atmospheric oxygen provides diselenide **180** in lower yield (12%) (Scheme 16).



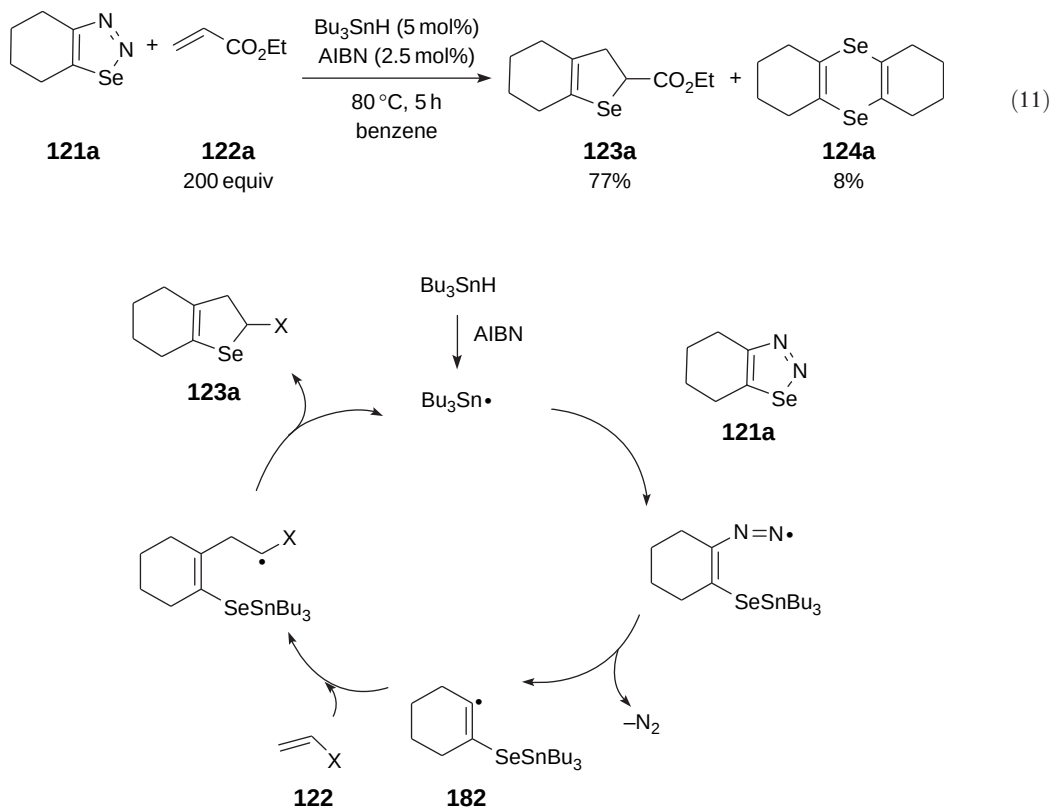
Scheme 15



Scheme 16

6.12.5.8 Reaction with Radicals, Transition Metal Complexes, and Reduction

The reaction of 1,2,3-selenadiazoles derived from cyclic ketones with alkenes or dienes is markedly promoted by a catalytic amount of tributylstannyl radical to give the corresponding dihydroselenophenes in moderate to good yields <2002JOC1520, 1999TL6293>. Thus, the reaction of compound **121a** with ethyl acrylate **122a** (200 equiv) in the presence of Bu₃SnH (5 mol%) and AIBN (2.5 mol%) in benzene at 80 °C for 5 h gave compound **123a** in 77% yield along with compound **124a** (8%) (Equation 11). Without Bu₃SnH and AIBN in the same reaction, the yield of compound **123a** was decreased (17%) (see also the thermal condition (130 °C, 15 h) in Section 6.12.5.1). When azobisvaleronitrile or Et₃B/O₃ was used instead of AIBN as the radical initiator, the reaction occurred at a lower reaction temperature (60 and 20 °C, respectively). As well as the thermal reaction without Bu₃SnH and AIBN, when 1,2,3-selenadiazoles derived from linear and aromatic ketones were used as substrates, alkynes were formed as the sole product. The plausible mechanism for the formation of compound **123a** is considered to be as shown in Scheme 17.

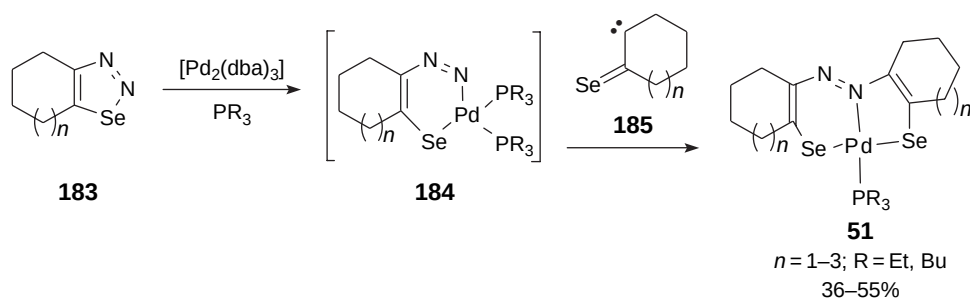


Scheme 17

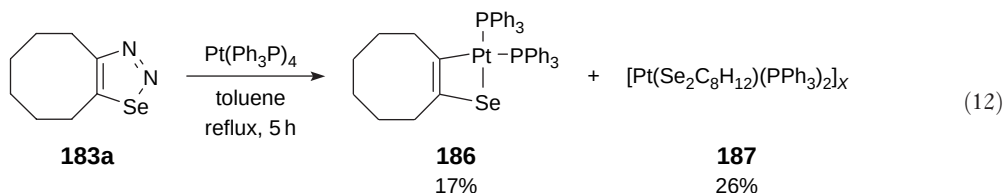
The reactions of 1,2,3-selenadiazoles with transition metal complexes have been of interest to prepare a variety of selenium-containing complexes. A recent review describes reactions of 1,2,3-selenadiazoles with transition metal complexes from the literature from 1987 to 2002 <2002CHE1437>.

The reaction of cycloalkeno-1,2,3-selenadiazole **183** with a mixture of [Pd₂(dba)₃] and trialkylphosphine in toluene under reflux for 1 h gave the novel complexes **51** in 36–55% yields (dba = dibenz[*a,h*] anthracene) <2004POL2967, 1998CC1305>. The molecular structure of complex **51** (*n* = 1, R = Bu) was determined by X-ray crystallography. The proposed mechanism is shown in Scheme 18. Insertion of palladium(0) into the selenium–nitrogen bond of 1,2,3-selenadiazole occurs, followed by 1,3-dipolar addition of a selenaketocarbene **185** formed *in situ* by thermal elimination of dinitrogen with the elimination of a trialkylphosphine.

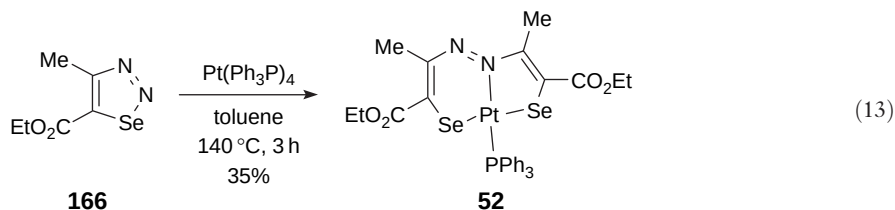
The reaction of 1,2,3-selenadiazole **183a** with 1 equiv of Pt(PPh₃)₄ in toluene at reflux for 5 h gave a selenaketocarbene complex **186** and polymeric compound [Pt(Se₂C₈H₁₂)(PPh₃)₂]_x **187** in 17% and 26% yields, respectively (Equation 12) <1995JCM64>.



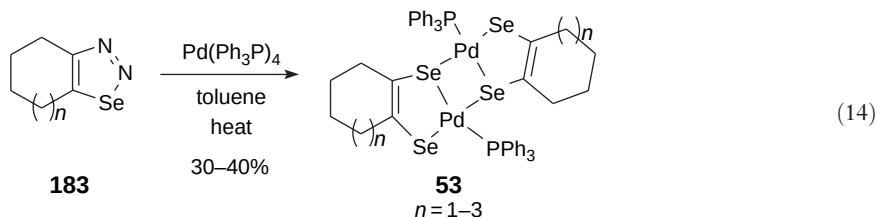
Scheme 18



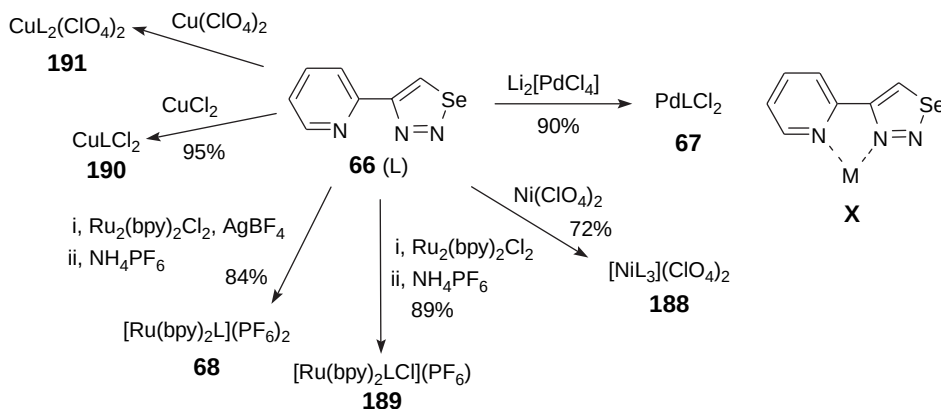
On the other hand, the reaction of 1,2,3-selenadiazole **166** with 1 equiv of $\text{Pt}(\text{PPh}_3)_4$ in toluene at 140°C (3 h) led to the formation of new selenoplatinum complex **52** in 35% yield (Equation 13) <2005TL1001>. This reaction may involve the insertion of di(triphenylphosphino)platinum into the selenadiazole ring, followed by 1,3-dipolar addition of an intermediate formed *in situ* by thermal elimination of dinitrogen with the elimination of triphenylphosphine, similar to the reaction with $[\text{Pd}_2(\text{dba})_3]$ and trialkylphosphine described above. The structure of complex **52** was established by X-ray analysis. Complex **52** is a selective catalyst for the hydrosilylation of terminal alkynes.



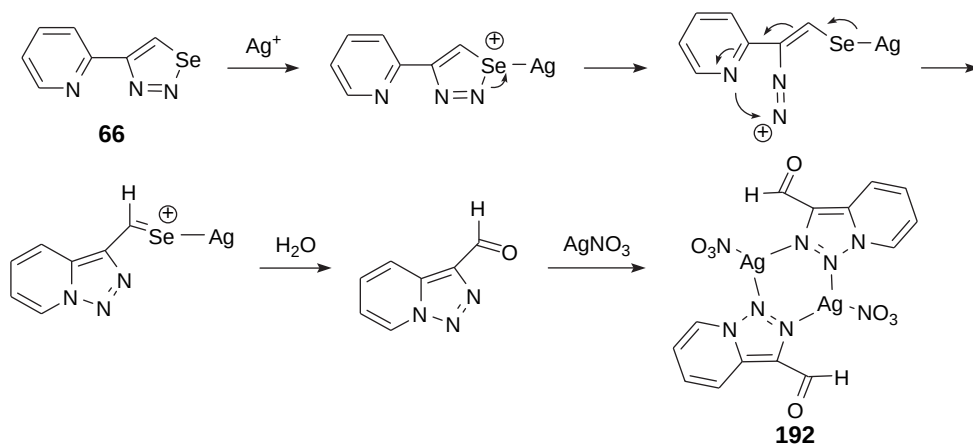
A different type of product, the dimer of 1,3-selena-2-palladiumcyclopentene **53**, was obtained by the reaction of selenadiazole with $\text{Pd}(\text{PPh}_3)_4$ (Equation 14) <1999JCD791>. The reaction of compound **183** with $\text{Pd}(\text{PPh}_3)_3$ in toluene under reflux led to complexes **53** in 30–40% yields. The molecular structure of complex **53a** ($n = 3$) has been determined by X-ray analysis.



2-(1,2,3-Selenadiazol-4-yl)pyridine **66** is expected to act as chelating ligand such as **X**, with coordination via N-3 of the 1,2,3-selenadiazole <2002AJC783>. Reactions of compound **66** with transition metals such as palladium(II), nickel(II), and ruthenium(II) gave 1:1, 1:2, or 1:3 metal:ligand complexes in high yields (Scheme 19). Their metal:ligand stoichiometries were determined by elemental analyses. The CIS values by ^1H NMR suggest that the ligand **66** chelates to a metal center (Section 6.12.3.2). However, the metal complexes show positional disorder in X-ray crystal structures. Treatment of compound **66** with a fourfold excess silver nitrate leads to a silver complex of 3-formyl-1,2,3-triazolo[1,5-*a*]pyridine **192** in 68% yield. The structure of the product **192** was determined by X-ray crystallography. The selenadiazole ligand **66** may undergo a rearrangement to produce a silver complex **192** as shown in Scheme 20.

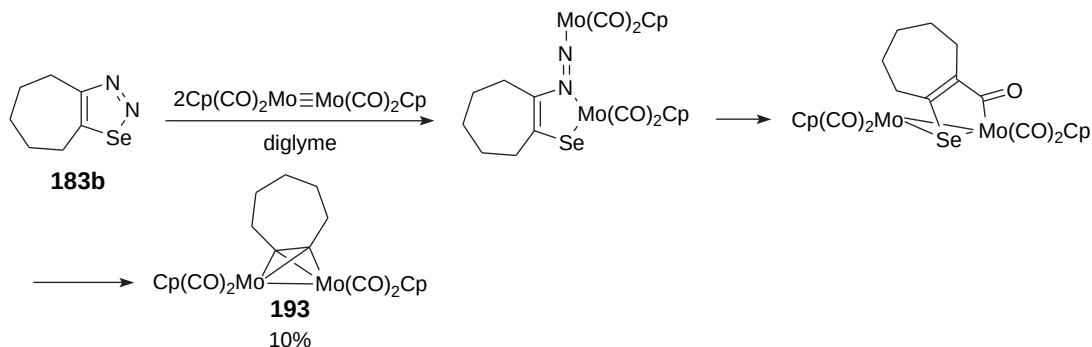


Scheme 19



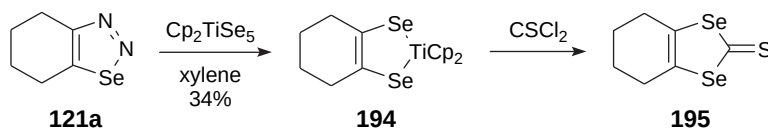
Scheme 20

The reaction of cyclohepteno-1,2,3-selenadiazole **183b** with 2 equiv of $(\eta^5\text{-C}_5\text{H}_5)_2\text{Mo}_2(\text{CO})_4$ in diglyme gave a dimolybdenum complex **193** in 10% yield (Scheme 21) <1998JOM29>. The structure of complex **193** was established by X-ray analysis.



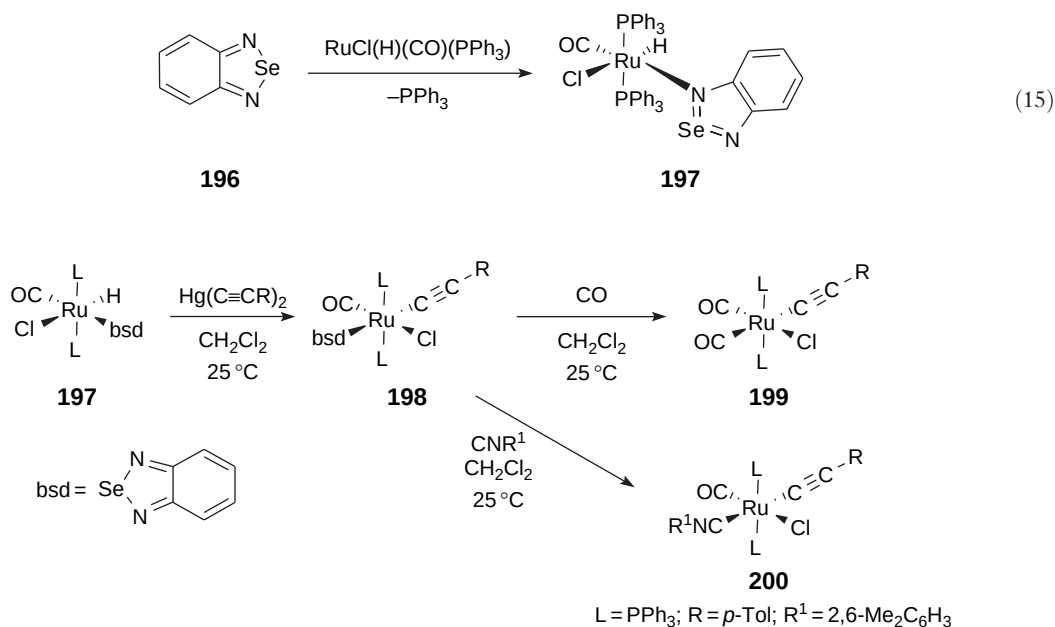
Scheme 21

The reaction of selenadiazole **121a** with titanocene pentaselenide in xylene at 140°C (15 min) affords titanocene complex **194** in 34% yield (Scheme 22) <1999SM1703>. The titanocene complex **194** was treated with CSCl_2 to afford the 1,3-diselenole-2-thione **195**.



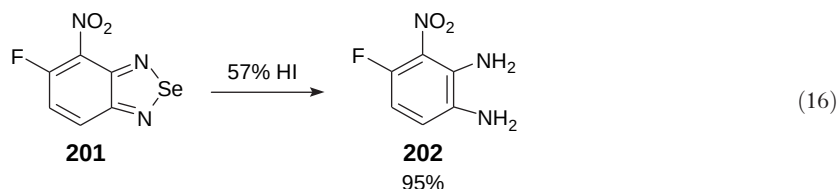
Scheme 22

Reaction of 2,1,3-benzoselenadiazole **196** with $[\text{RuCl}(\text{H})(\text{CO})(\text{PPh}_3)_3]$ gave a complex **197** in 98% yield <1990JCD1737>. The X-ray diffraction study of the sulfur analogue may suggest the coordination mode of complex **197**, as shown in Equation (15). As part of the study on the mechanism of *trans*-alkynylation and catalytic demercuration of bis(alkynyl)mercurials, the reaction of 2,1,3-benzoselenadiazole (bsd) ruthenium complex was investigated (Scheme 23) <1996CC1059>. The reaction of $[\text{RuCl}(\text{H})(\text{CO})(\text{bsd})(\text{PPh}_3)_2]$ **197** with $\text{Hg}(\text{C}\equiv\text{CR})_2$ ($\text{R} = \text{Bu}^n$, *p*-Tol, Ph) in CH_2Cl_2 at 25°C for 30 min gave $[\text{Ru}(\text{C}\equiv\text{CR})\text{Cl}(\text{CO})(\text{bsd})(\text{PPh}_3)_2]$ **198** and 1 equiv of free alkyne and elemental mercury. The bsd ligand binds sufficiently strong to prevent reaction with the liberated $\text{RC}\equiv\text{CH}$, but it is labile enough to be replaced by sterically modest π -acidic ligands 'L' (CO, CNR) to give stable octahedral acetylide complexes $[\text{Ru}(\text{C}\equiv\text{CR})\text{Cl}(\text{CO})(\text{PPh}_3)_2\text{L}]$ ($\text{L} = \text{CO}$, **199**; $\text{CNC}_6\text{H}_3\text{-2,6-Me}_2$, **200**).

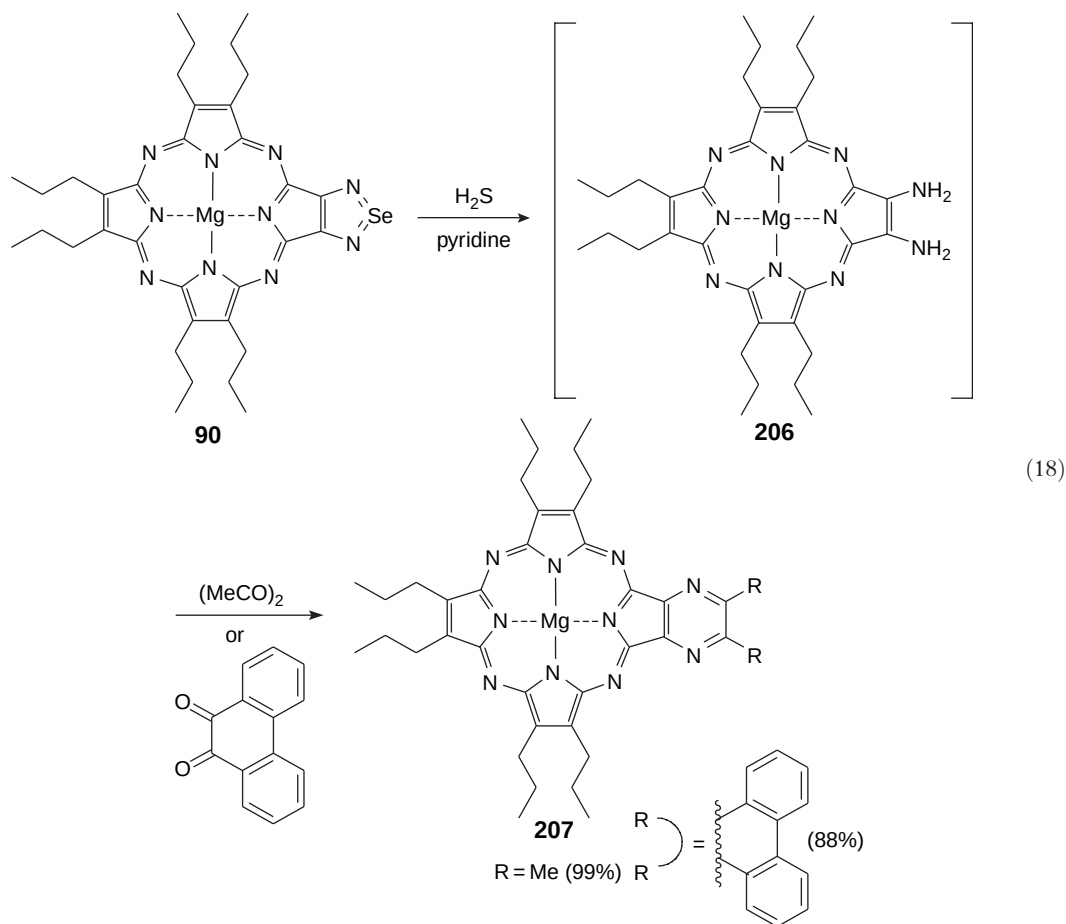
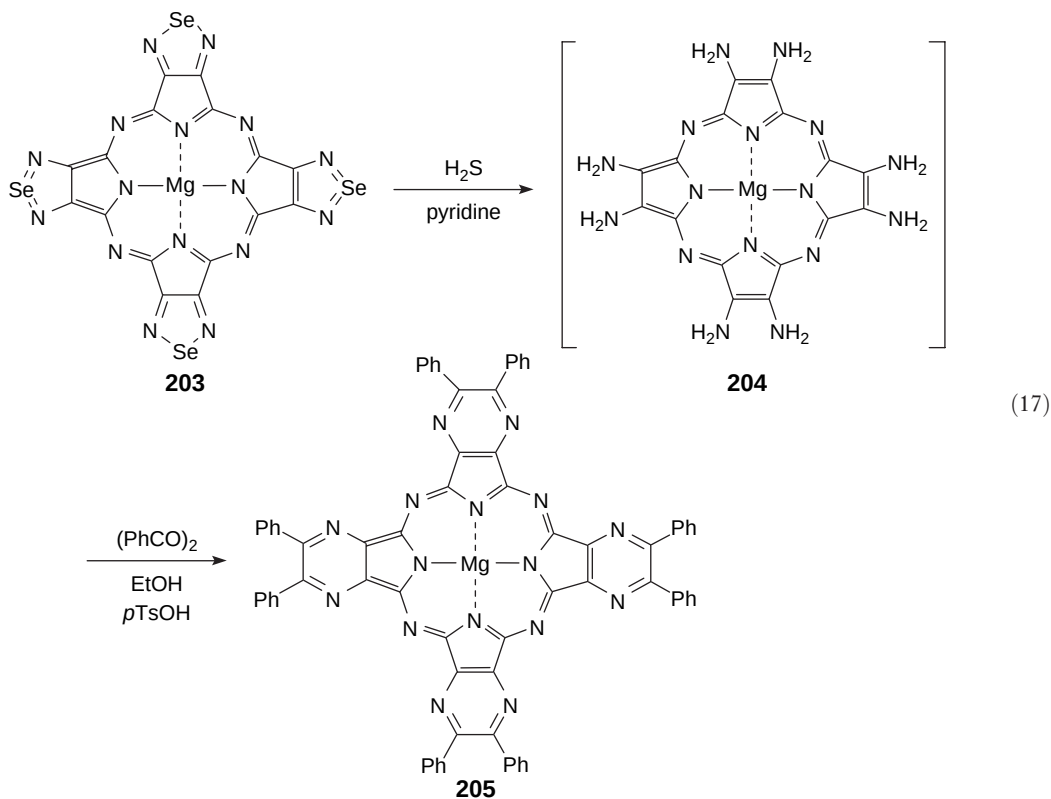


Scheme 23

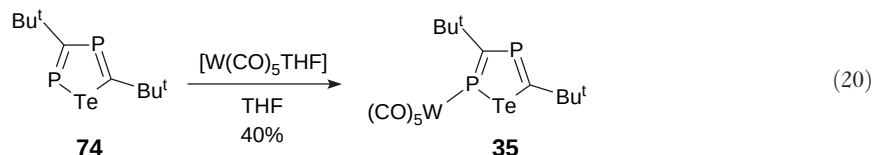
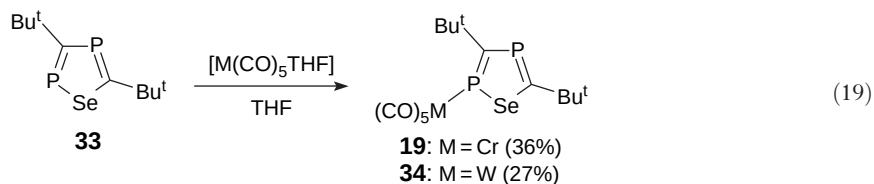
As described in CHEC-II(1996) <1996CHEC-II(4)743>, reduction of 2,1,3-benzoselenadiazoles was widely used to obtain *o*-phenylenediamines. Reduction of 5-chloro-4-nitrobenzo[2,1,3]selenadiazole with a mixture of 50% HI and 35% HCl to give 4-chloro-3-nitro-1,2-phenylenediamine in 52% yield was reported <2004RJC428>. 4-Fluoro-3-nitrobenzene-1,2-diamine **202** was prepared by the reaction of 5-fluoro-4-nitrobenzo-2,1,3-selenadiazole **201** with 57% HI in high yield on multigram scale (Equation 16) <2004JHC1023>.



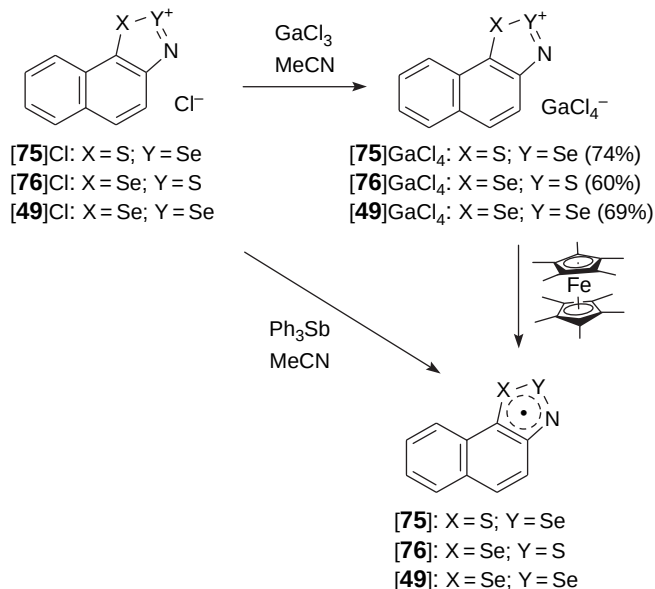
Reduction of selenodiazole rings of porphyrazine **203** with H_2S in pyridine gave octaamino compound **204**, which was converted into other porphyrazine macrocycles, such as compound **205** (Equation 17) <1999MI371>. This method was also applied to porphyrazine containing monoselenodiazole **90** (Equation 18) <2003AGE462, 2003JOC1665>.



Treatment of a THF solution of 1,2,4-selenadiphosphole **33** with $[M(CO)_5THF]$ ($M = Cr, W$) gave the complexes $[M(CO)_5-P_2SeC_2Bu^t_2]$ **19** ($M = Cr$) and **34** ($M = W$) in 36% and 27% yield, respectively (Equation 19) <1999JOM156>. The 1,2,4-telluradiphosphole **74** was converted into its $[W(CO)_5]$ adduct **35** in 40% yield (Equation 20). The molecular geometries of the 1,2,4-selenadiphosphole and 1,2,4-telluradiphosphole complexes were determined by single crystal X-ray diffraction studies (Section 6.12.3.1).



The chloride salts of [1,2,3]thiaselenazolylum cation and its variants **[75][Cl]**, **[76][Cl]**, **[49][Cl]** were readily converted, by treatment with $GaCl_3$ in MeCN, into the corresponding tetrachlorogallate salts in 60–74% yields (Scheme 24) <2005IC1837>. The crystal structure of the gallate salt of the diselenadiazolium **[49][GaCl₄]** was determined by single crystal X-ray diffraction (Section 6.12.3.1). Conversion to the radicals **[75]**, **[76]**, and **[49]** was effected by chemical reduction of either the chloride salts with triphenylantimony or the tetrachlorogallate salts with decamethylferrocene. The selenium-containing radicals **[75]**, **[76]**, and **[49]** were thermally unstable. All of the radicals were fully characterized by electron paramagnetic resonance (EPR) spectroscopy and cyclic voltammetry.

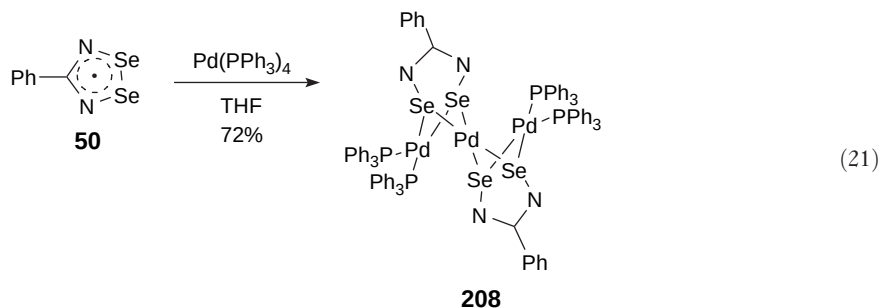


Scheme 24

Conversion of the chloride salts of [1,2,3]thiaselenazolylum cation to the corresponding tetrachlorogallate, hexafluoroantimonate, and triflate salts was reported <2005JA18159, 2005IC1837, 1997JA12136>. Various [1,2,3]thiaselenazolylum cations were also converted to the corresponding radicals by chemical reduction such as use of triphenylantimony, decamethylferrocene, octamethylferrocene, or by electrochemical reduction. Chemical reduction

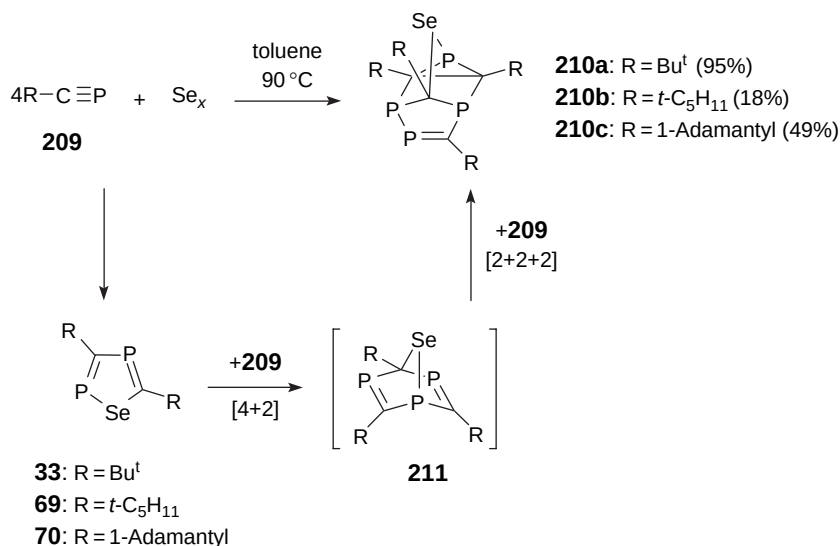
and electrochemical reduction of 1,2,3,5-diselenadiazolium dications to form stable 1,2,3,5-diselenadiazolyl radicals were also reported <1991JA582, 1993CM820, 2001IC6820>.

Reaction of 1,2,3,5-diselenadiazolyl radical **50** with $\text{Pd}(\text{PPh}_3)_4$ in THF gave the metal complex **208** in 72% yield (Equation 21) <1998NJC763>. The structure of complex **208** was determined by X-ray diffraction. The structure **208** reveals three Pd atoms bridged by two diselenadiazolyl ligands in which the Se–Se bond is formally cleaved.



6.12.5.9 Intermolecular Cycloaddition Reactions

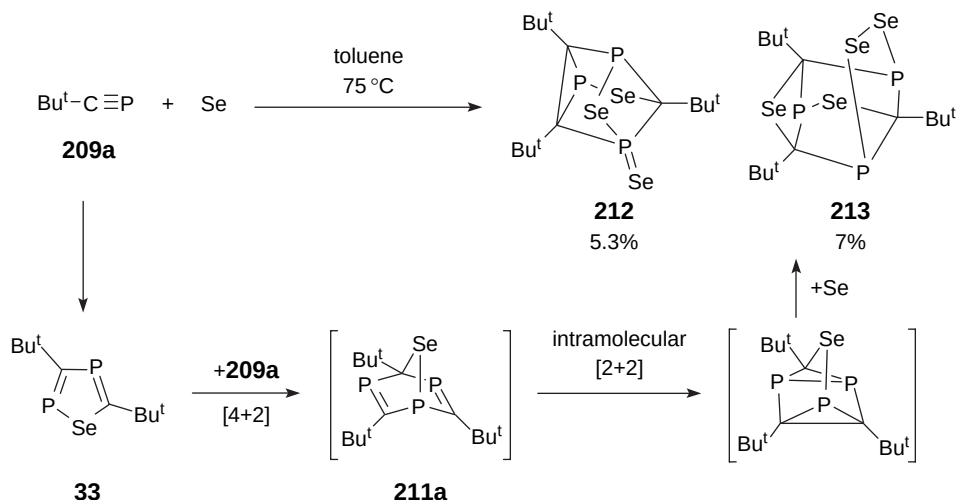
In the reaction of phosphalkynes **209** with elemental selenium (see Section 6.12.9.5), use of a deficit of selenium (0.2 equiv to **209**) resulted in the formation of tetracyclic products **210a–c** in 18–95% yield (Scheme 25) <1999S1642>. The formation of compounds **210a–c** is explained as follows. 1,2,4-Selenadiphospholes **33**, **69**, and **70** are produced at first and then they undergo a [4+2] cycloaddition with 1 equiv of the phosphalkyne **209** to furnish the 7-selena-1,3,5-triphosphabicyclo[2.2.1]hepta-2,5-diene **211**, which reacts in a homo-Diels–Alder process with another equivalent of the phosphalkyne **209** to afford the products **210a–c**. Furthermore, it was shown in an independent experiment that compound **33** reacts with 2 equiv of **209** ($\text{R} = \text{Bu}^t$) to give **210a** <2001HAC406>.



Scheme 25

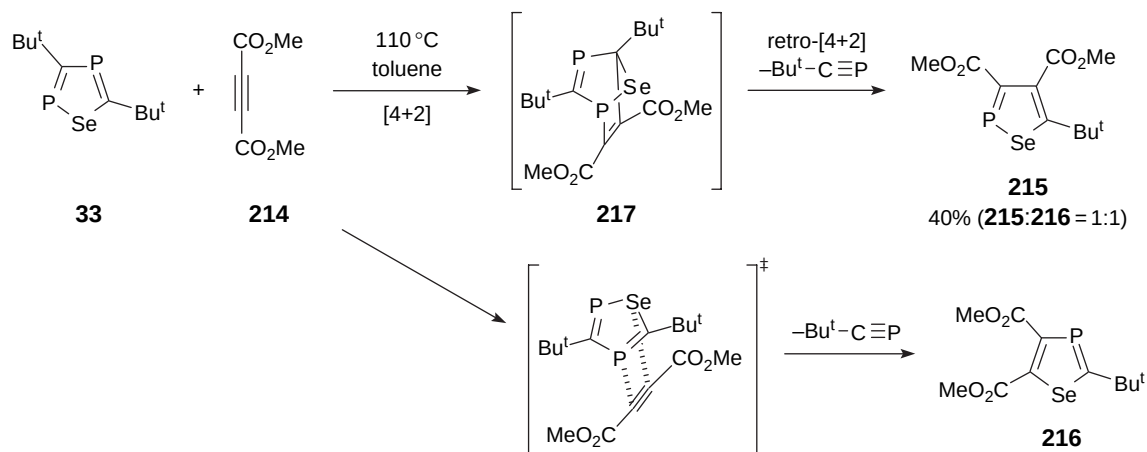
A related reaction of reagent **209a** with selenium to give new cage compounds was also reported (Scheme 26) <2000CC1745>. Treatment of a slight excess of selenium in toluene with reagent **209a** for 4 days at 75 °C afforded compound **33** as the main product together with the cage compounds **212** (5.3%) and **213** (7%). Both cages are most likely derived from a common intermediate **211a**, which would be formed via the initial [4+2] cycloaddition reaction of compound **33** with reagent **209a**. Thus compound **212** probably arises from (1) insertion of Se into the weak P–P

bond resulting from the intramolecular [2+2] cycloaddition cage-formation step of the intermediate **211a** and (2) a second exocyclic Se addition to one of these phosphorus atoms. Similarly, in an analogous way, the more symmetrical cage compound **213** would result from insertion of Se₂ into the P–P bond, as well as a separate single Se atom insertion into the C–C bond of the initially formed strained three-membered CPC ring. The structures of compounds **212** and **213** were determined by single crystal X-ray diffraction studies.



Scheme 26

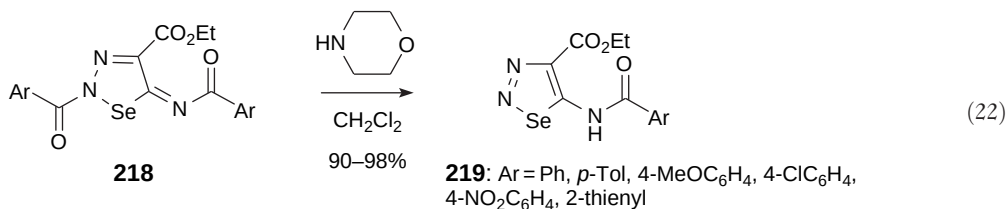
The reaction of 1,2,4-selenadiphosphole **33** with dimethyl acetylenedicarboxylate (DMAD) **214** resulted in a mixture of 1,2-selenaphosphole **215** and 1,3-selenaphosphole **216** at 110 °C in boiling toluene (Scheme 27) <2001J(P2)1968>. The mechanism has been interpreted using quantum-chemical calculations. A [4+2] cycloaddition of the acetylene to the selenadiphosphole results in the 1,2-selenaphosphole via an intermediate **217**. A [3+2] cycloaddition via a single transition structure results in the 1,3-selenaphosphole. While the energies of the products differ considerably, transition structures on the two cycloaddition routes are predicted to have similar energies, explaining the observed 1:1 product ratio.



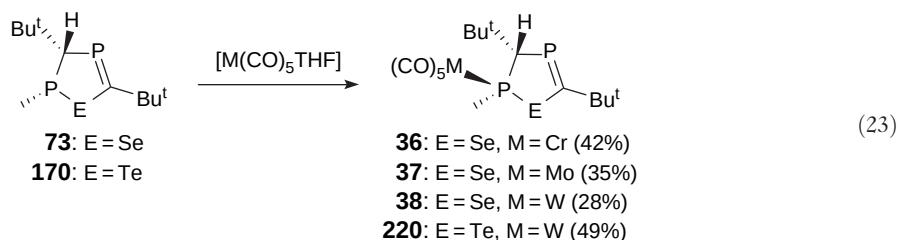
Scheme 27

6.12.6 Reactivity of Nonconjugated Rings

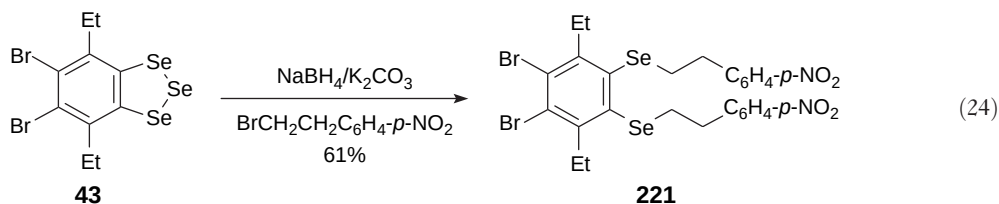
Treatment of CH_2Cl_2 solutions of 2,5-dihydro-1,2,3-selenadiazoles **218** with 1 equiv of morpholine at room temperature led to ethyl 1,2,3-selenadiazole-4-carboxylates **219** in 90–98% yield (Equation 22) <2000HCA539>.



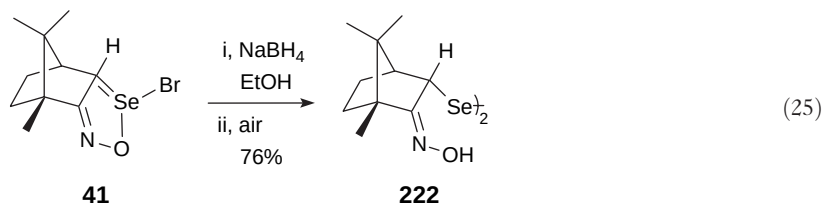
Treatment of THF solutions of 2,3-dihydro-1,2,4-selena- and telluradiphospholes **73** and **170** with $[\text{M}(\text{CO})_5(\text{THF})]$ complexes (M = Cr, Mo, or W) gave complexes **36–38** and **220** in moderate yields (Equation 23) <2002JOM84>. The structures of compounds **36–38** were confirmed by single crystal X-ray diffraction studies (Section 6.12.3.1).



Treatment of benzo[1,2,3]triselenole **43** with sodium borohydride, potassium carbonate, and 4-nitrophenethylbromide gave 1,2-bis(4-nitrophenethylseleno)-3,6-diethyl-4,5-dibromobenzene **221** in 61% yield (Equation 24) <2004JOC4716>.

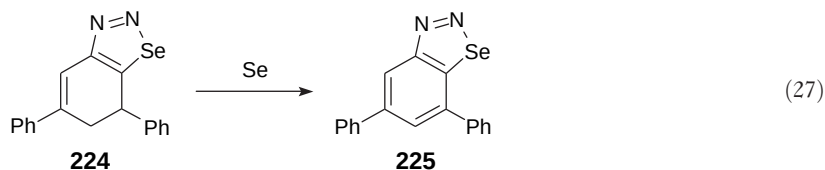
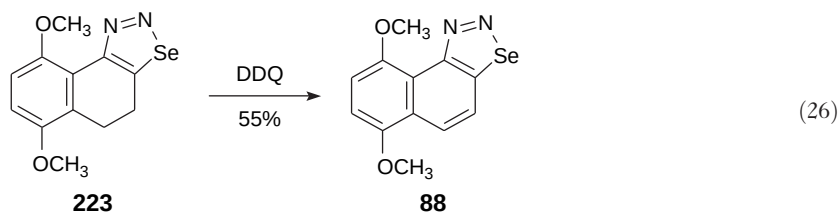


Reduction of oxaselenazole **41** by sodium borohydride, followed by aerial oxidation, gave diselenide **222** in 76% yield as a major product (Equation 25) <2002JOC499>.

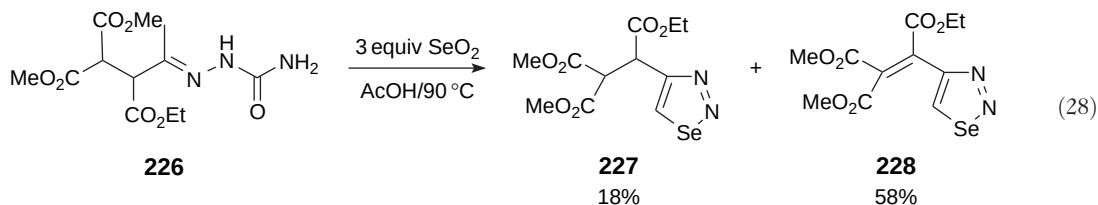


6.12.7 Reactivity of Substituents Attached to Ring Carbon Atoms

Oxidation of fused 1,2,3-selenadiazole **223** with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) at room temperature gave naphtho[1,2-*d*][1,2,3]selenadiazole **88** in 55% yield (Equation 26) <2000JHC1325>. Reaction of compound **224** with selenium powder in an equimolar ratio in an inert atmosphere gave aromatized product **225** (Equation 27) <1998JCM784>.

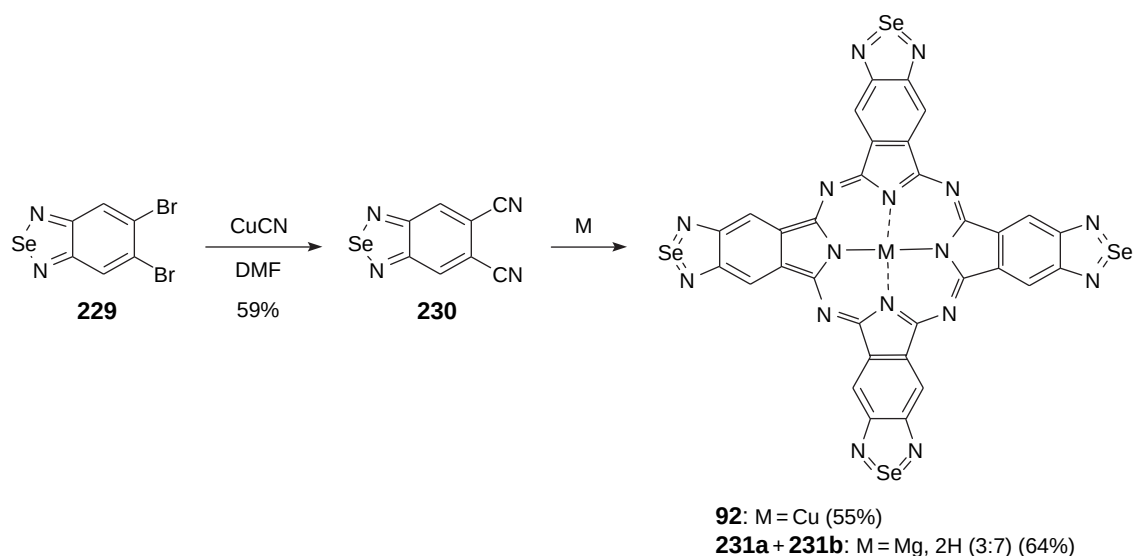


Reaction conditions similar to those for the preparation of 1,2,3-diselenadiazoles (3 equiv SeO_2/AcOH) (see Section 6.12.9.1) gave 1,2,3-diselenadiazole **228** (58%) as a major product along with the expected 1,2,3-diselenadiazole **227** (18%) (Equation 28). The compound **228** was probably produced from compound **227** by mean of the carbon–carbon single bond oxidation <2003JOC1947>.



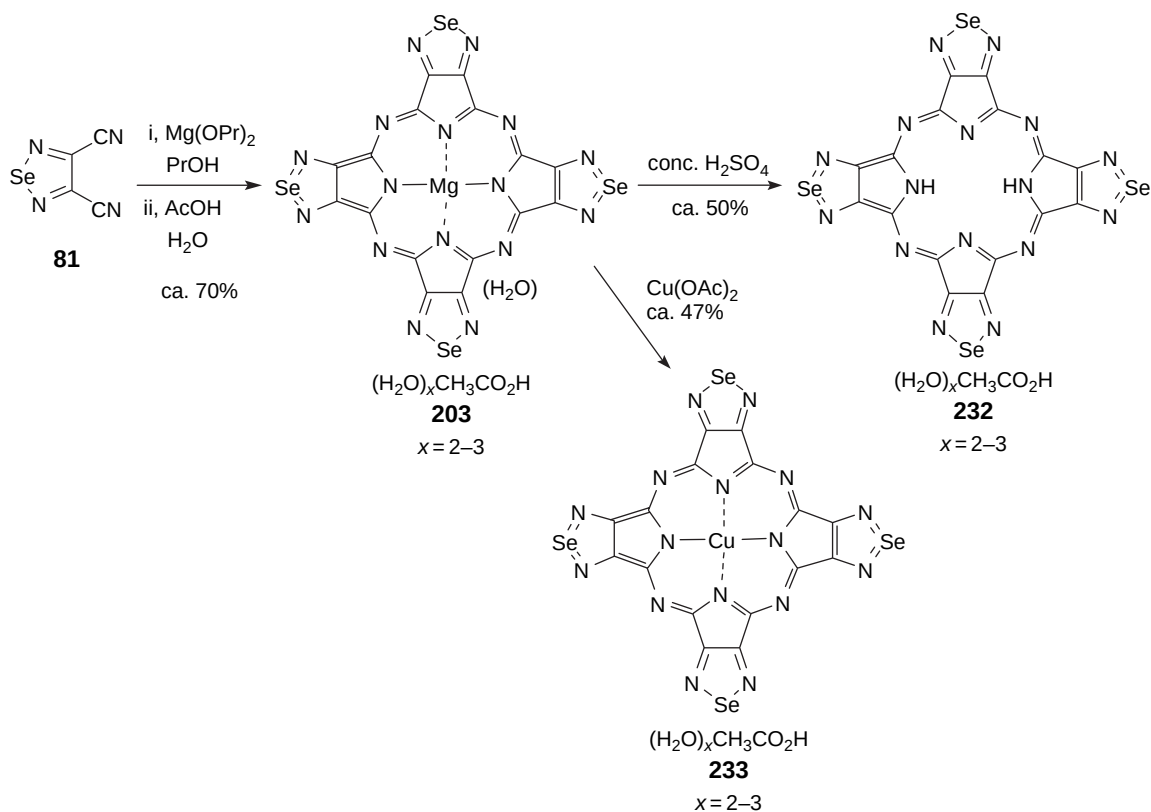
Some reactions of substituents attached to ring carbons of 1,2,3-selenadiazoles are shown in Scheme 2 in Section 6.12.5.1.

The reaction of dibromide **229** with copper(I) cyanide in DMF gave dicarbonitrile **230** in 59% yield (Scheme 28) <1995ACS658>. Template-assisted cyclization of the dicarbonitrile **230** with copper or magnesium powder gave metal phthalocyanines **92** (M = Cu) and **231a** (M = Mg) containing metal-free phthalocyanine **231b** (M = 2H) (3:7 mixture) in 55% and 64% yields, respectively.



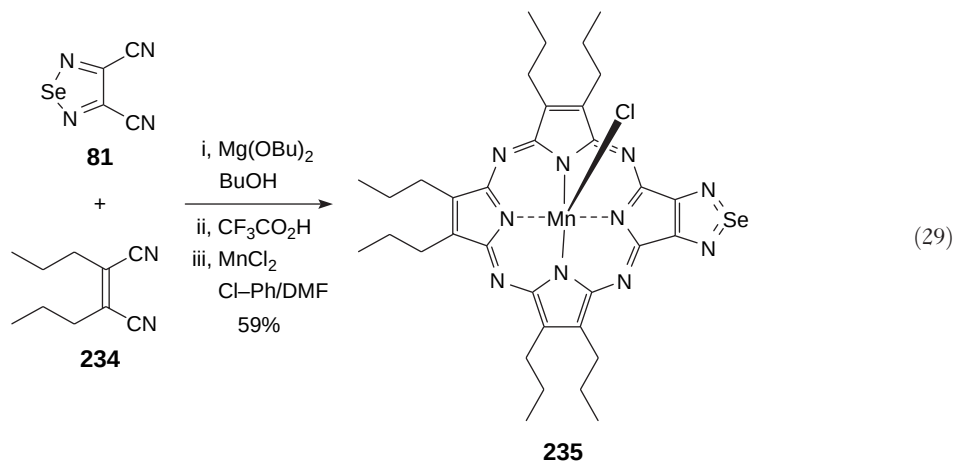
Scheme 28

The macrocycle tetrakis(selenadiazole)porphyrazine and its Mg(II) and Cu(II) complexes were prepared <1999MI371>. Reaction of the 3,4-dicyano-1,2,5-selenodiazole **81** with magnesium propylate in propanol gave Mg(II) complex with water and acetic acid **203** (Scheme 29). The Mg(II) complex **203** was transformed to compounds **232** and **233** as shown.

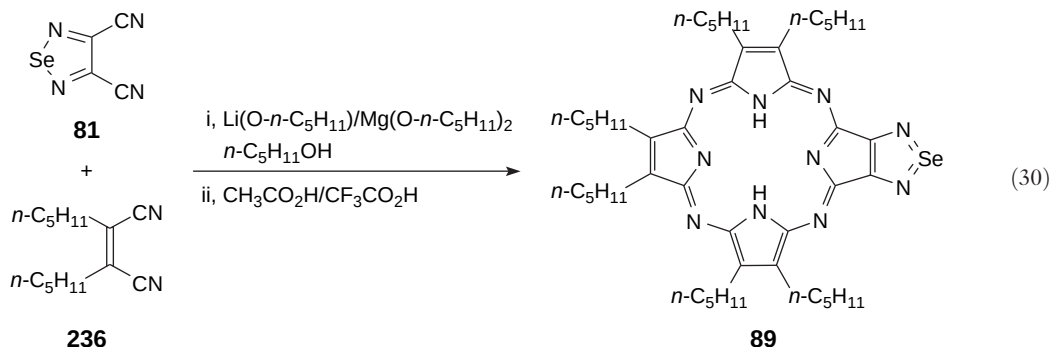


Scheme 29

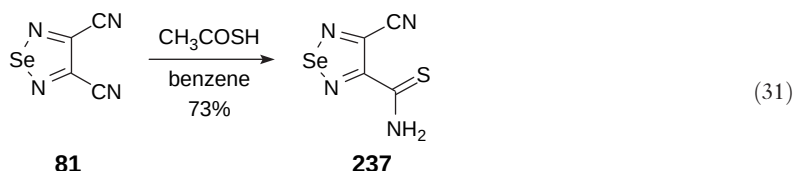
Cocyclization of 3,4-dicyano-1,2,5-selenodiazole **81** and alkene **234** by reaction with Mg(OBu)_2 in BuOH , and subsequent demetalation by trifluoroacetic acid and metalation with MnCl_2 , led to a porphyrazine containing one 1,2,5-selenodiazole ring Mn complex **235** in 59% yield (Equation 29) <2003AGE462, 2003JOC1665>.



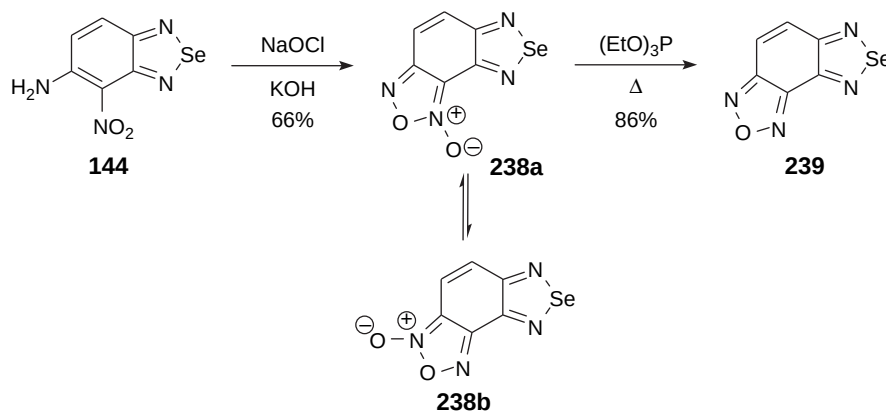
The reaction of 3,4-dicyano-1,2,5-selenodiazole **81** and alkene **236** with Li or Mg(*O-n*-C₅H₁₁)₂ in boiling *n*-pentanol and subsequent demetalation by either acetic acid (Li) or trifluoroacetic acid (Mg) gave unsymmetrical porphyrazine with 1,2,5-selenodiazole **89** (Equation 30) <2001MC45>. The structure of product **89** was elucidated by single crystal X-ray diffraction.



4-Cyano-1,2,5-selenadiazole-3-carbothioamide **237** was obtained by the reaction of 3,4-dicyano-1,2,5-selenadiazole **81** with thioacetic acid in benzene in 73% yield (Equation 31) <1998PCA9021>.

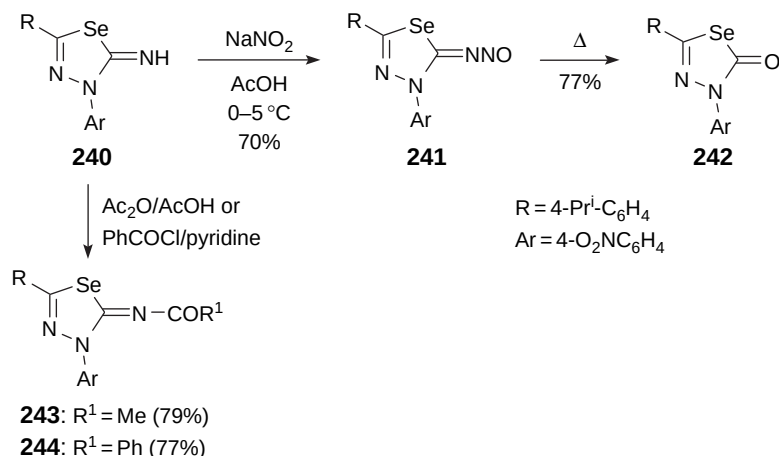


Treatment of nitroamine **144** with sodium hypochlorite and potassium hydroxide in ethanol gave the *N*-oxide **238** in 66% yield (Scheme 30) <2004JHC955>. The compound **238** was deoxygenated with triethyl phosphite to give compound **239** in 86% yield. The overall yield of product **239** from commercially available compound represents improvement over the previous methodology for preparation of compound **239** (final ring closure of selenadiazole ring by SeO₂) <1990HCA902>. The NMR spectra of *N*-oxide **238** showed the presence of two isomers **238a** and **238b** in a ratio of 6:4.



Scheme 30

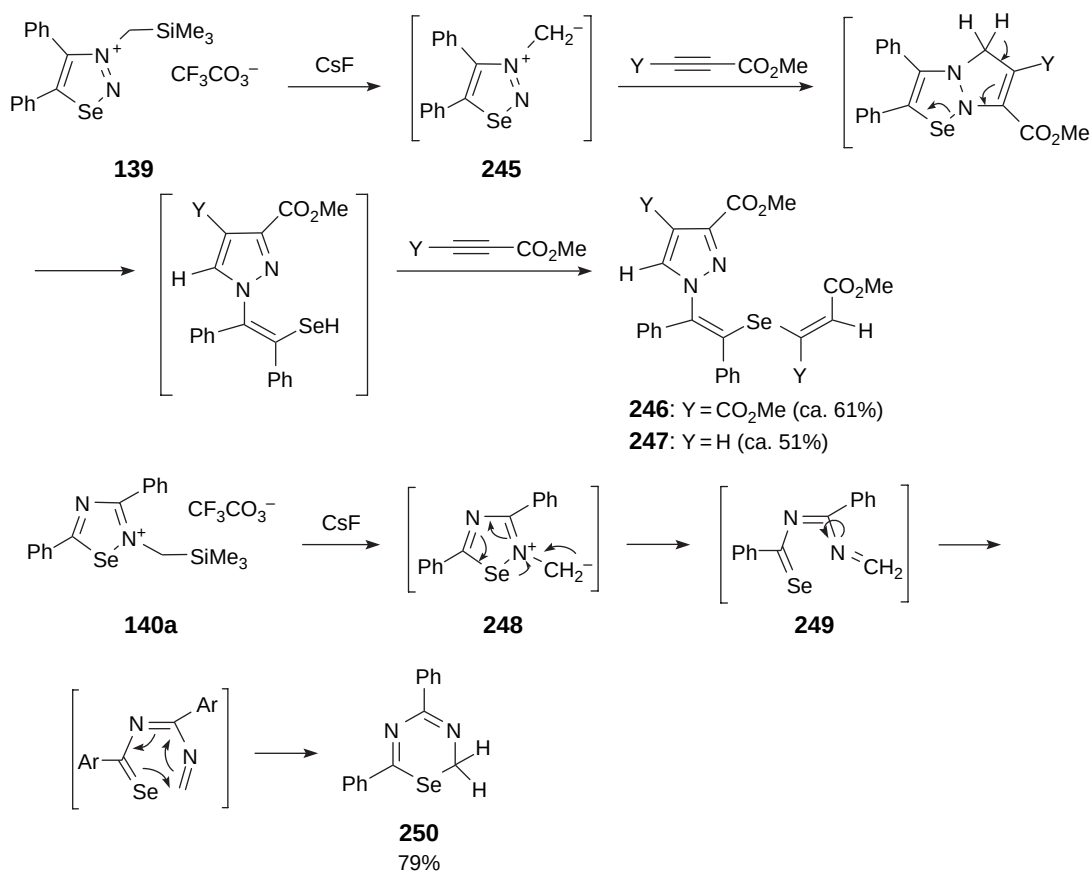
Some chemical transformations of 2,3-dihydro-1,3,4-selenadiazoles were reported <2003HAC421, 2004MI329, 2001HAC468, 1997PS43, 2005PS149>. Nitrosation of compound **240** with sodium nitrite in acetic acid solution gave compound **241** in 70% yield (Scheme 31). Thermal decomposition of compound **241** in boiling xylene gave compound **242** in 77% yield. Acylation of compound **240** with acetic anhydride or benzoyl chloride in pyridine gave *N*-acyl derivatives **243** and **244**, respectively.



Scheme 31

6.12.8 Reactivity of Substituents Attached to Ring Heteroatoms

The salts **139** and **140a** were desilylated with CsF to generate transient selenadiazoliumylmethanide (ylide) intermediates **245** and **248** at ambient temperature in dichloromethane (Scheme 32) <2001J(P1)394>. 4,5-Diphenyl-1,2,3-selenadiazol-3-ium-3-ylmethanide **245** undergoes cycloaddition–rearrangement reaction with excess



Scheme 32

DMAD and methyl propiolate to give the pyrazolylvinyl vinyl selenides **246** (ca. 61% from crude salt **139**) and **247** (ca. 51% from crude **139**). On the other hand, the intramolecular rearrangement of 3,5-diphenyl-1,2,4-selenadiazol-2-ium-2-ylmethanide **248** occurred more rapidly than cycloaddition and no trapping was achieved with up to 20 mol excess of dimethyl acetylenedicarboxylate. The rearrangement gave 4,6-diphenyl-2*H*-1,3,5-selenadiazine **250** in 79% yield.

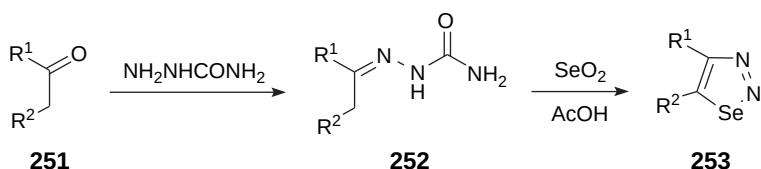
6.12.9 Syntheses

6.12.9.1 1,2,3-Selenadiazoles

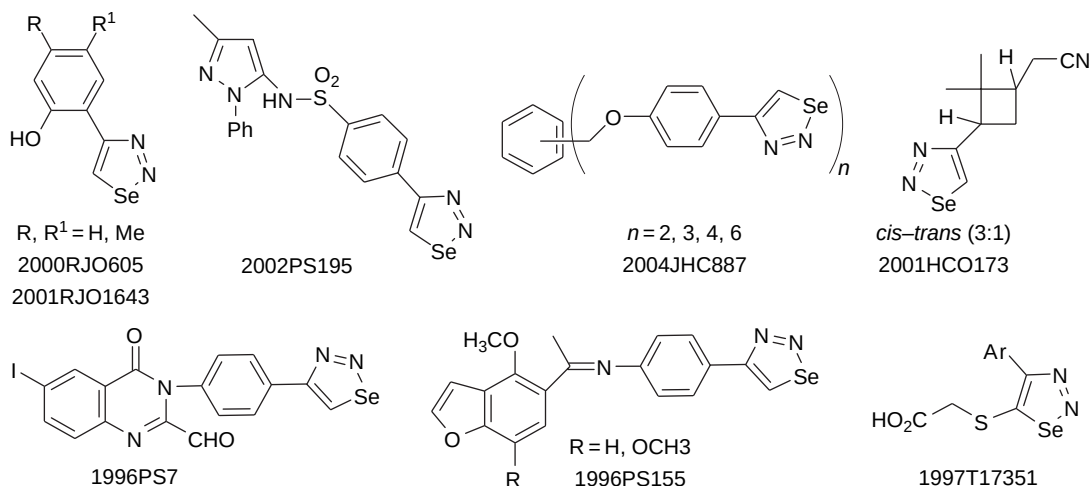
As described in the previous sections, 1,2,3-selenadiazoles are utilized as useful synthetic intermediates through a variety of reactions with the loss of nitrogen and/or selenium. Their biological activities are also of interest.

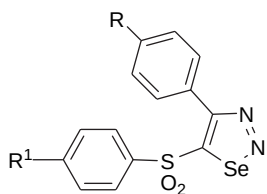
The most widely used method to synthesize 1,2,3-selenadiazoles is the reaction of semicarbazones with selenium dioxide. This reaction has been described in detail <1996CHEC-II(4)743, 1984CHEC(6)333, 2004HOU777>. This method has often been utilized for synthesis of a variety of 1,2,3-selenadiazoles, including carbocyclic and heterocyclic fused systems.

Ketones **251** are transformed to semicarbazones **252** by standard procedure (Scheme 33). Heating semicarbazones **252** with SeO₂ in acetic acid gave 4-substituted, 4,5-disubstituted, and carbocyclic and heterocyclic fused 1,2,3-selenadiazoles **253**. A number of 1,2,3-selenadiazoles prepared by this method are shown below <2000RJO605, 2001RJO1643, 2002PS195, 2004JHC887, 2001HCO173, 1996PS7, 1996PS155, 1997T17351, 1997IJB1062, 1998HCO81, 2004MI659, 2004PS2411, 2002PS1223, 1997IJB923, 1999SC667, 1998JCM784, 2003MAL1464, 2000JHC1325, 2001IJB414, 1997LA1557, 2000HCO271, 1999IJB1342, 2003JHC149, 2001SC3429, 2003IJB189, 1999IJB308, 1999HCO285, 1995OM975, 2002AGE1181, 2000OM1578>.

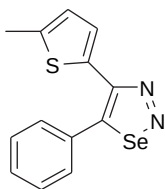


Scheme 33

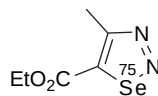




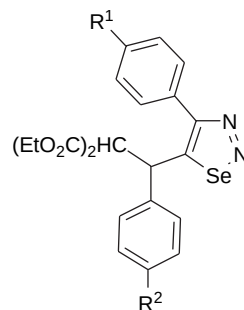
R, R¹ = H, Me, Cl, Br, NO₂, OEt
1997IJB1062



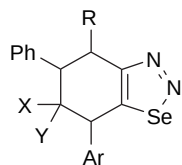
1998HCO81



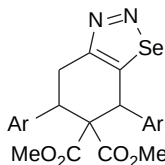
2004MI659



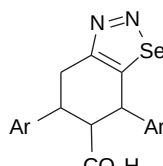
2004PS2411



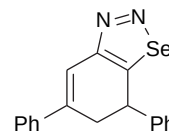
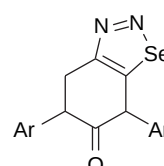
R = Me, Ph
Ar = Ph, 4-MeC₆H₄,
4-MeOC₆H₄, 4-ClC₆H₄
X, Y = CO₂Me, CN
2002PS1223



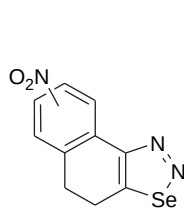
Ar = 3, 4-(MeO)₂-C₆H₃,
4-MeO-3-EtO-C₆H₃,
4-Me₂N-C₆H₄
1997IJB923



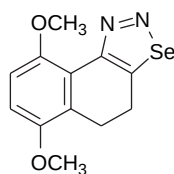
1999SC667



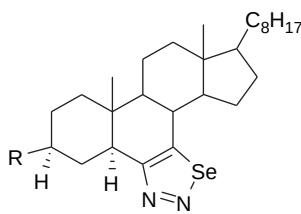
1998JCM784



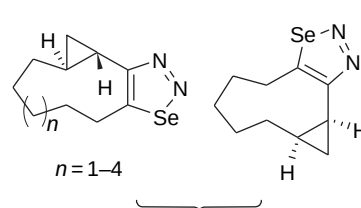
2003FA63



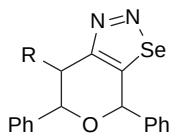
2000JHC1325



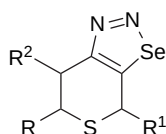
R = OAc, Cl, H
2001IJB414



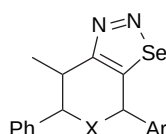
1997LA1557



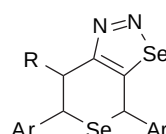
2000HCO271



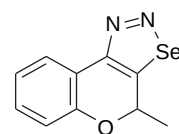
1999IJB1342



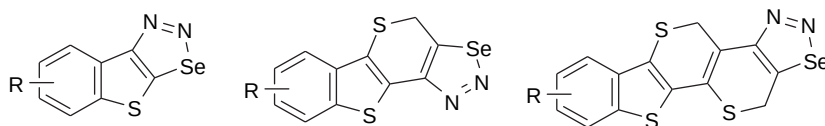
X = NMe; S = O
2003JHC149



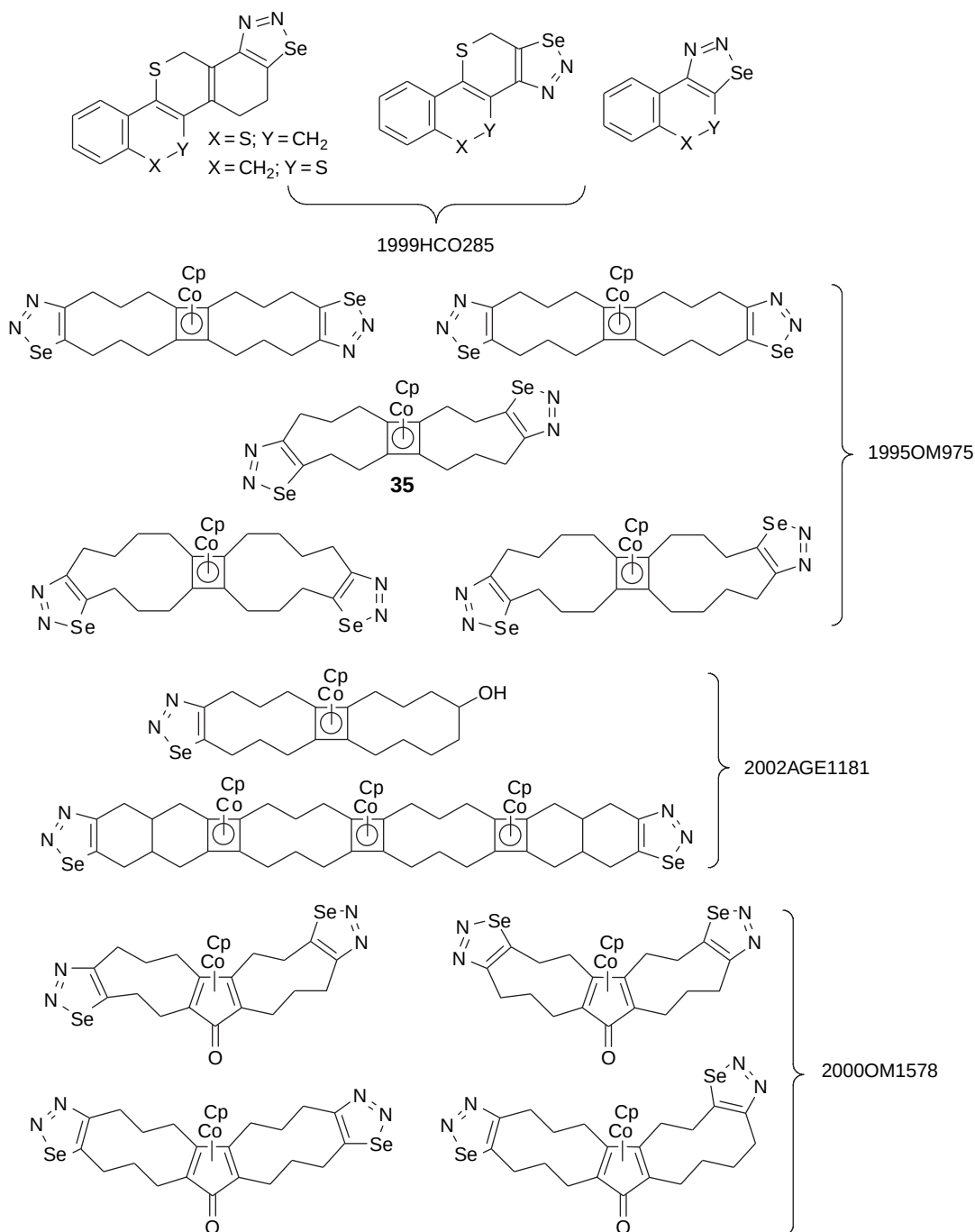
2001SC3429



2003IJB189

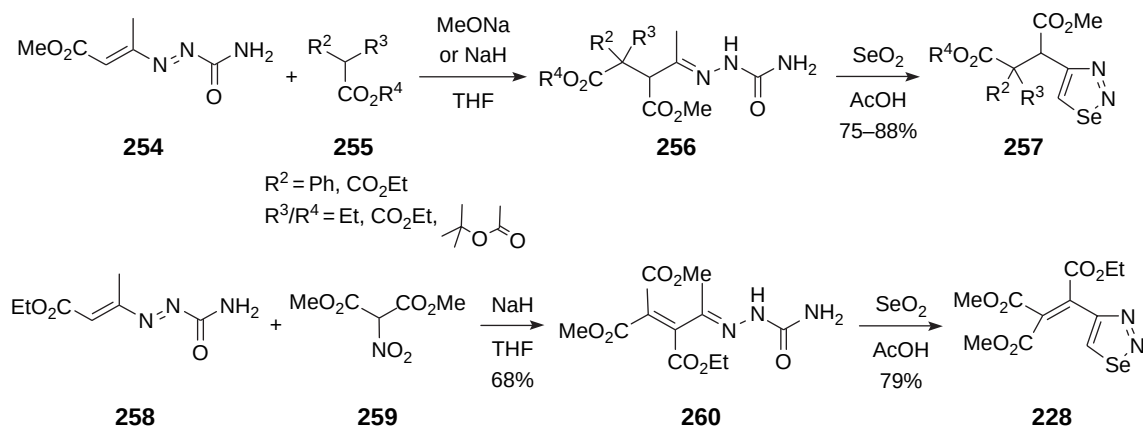


1999IJB308

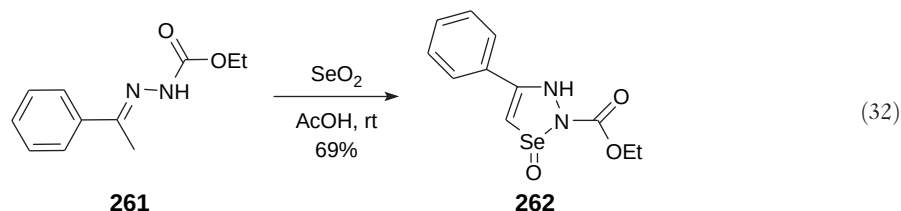


The precursor semicarbazones **256** and **260** were also prepared from the reaction of 1,2-diaza-1,3-butadienes **254** and **258** and activated methinic compounds such as diethylphenylmalonate, trimethylmetanetricarboxylate, 2,2-dimethyl-5-phenyl-1,3-dioxane-4,6-dione, **255**, and dimethyl nitromalonate **259** in the presence of catalytic amount of MeONa or NaH in THF (Scheme 34) <2003JOC1947>.

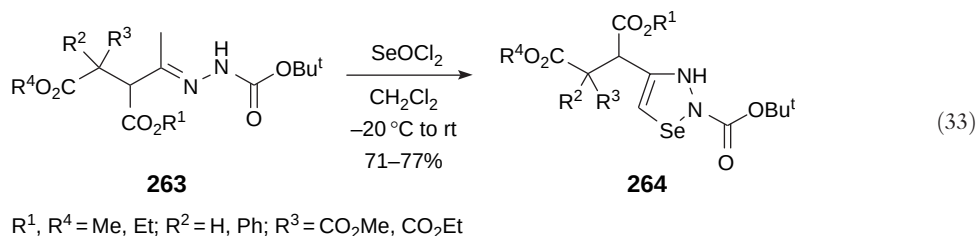
Ethoxycarbonyl hydrazones are also used for the reaction with $SeO_2/AcOH$ leading to 1,2,3-selenadiazoles. The reaction of hydrazone **261** with $SeO_2/AcOH$ at room temperature gave the probable intermediate **262** toward 1,2,3-selenadiazole in 69% yield (Equation 32) <2004MOL957>.



Scheme 34

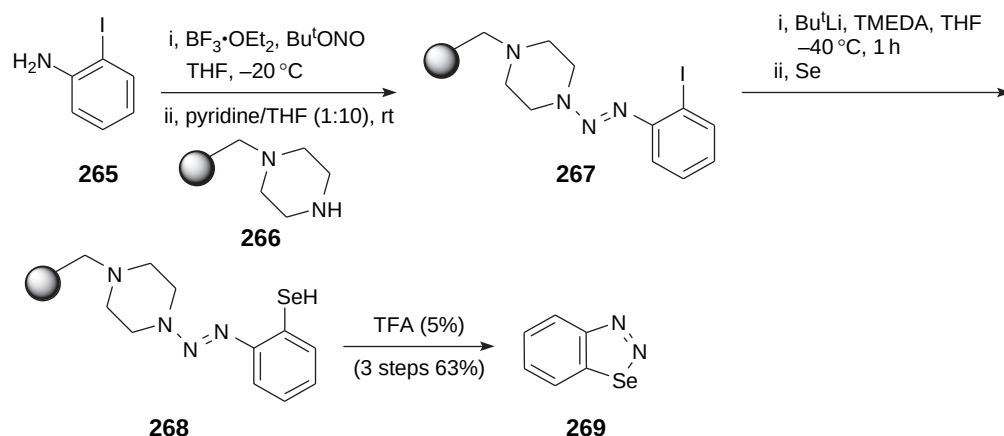


The reaction of *tert*-butoxycarbonyl hydrazones **263** with selenium oxychloride in CH₂Cl₂ from –20 °C to room temperature gave 2,3-dihydro-1,2,3-selenadiazoles **264** in 71–77% yields (Equation 33). Under these mild conditions, the aromatization process did not occur, and only 2,3-dihydro compounds were observed. The advantage of this reaction is the ease of workup. Pure compounds **264** were obtained simply by addition to the reaction mixture of an aqueous saturated solution of NaHCO₃ and subsequent evaporation of the organic solvent <2003JOC1947>.

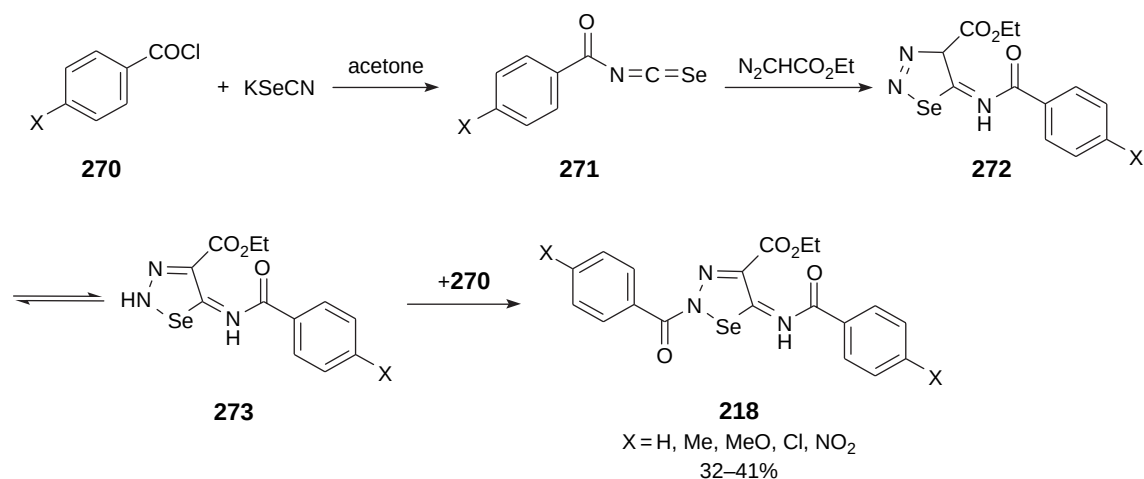


The solid-phase synthesis of benzo[1,2,3]selenadiazole was achieved by starting from resin-bound *ortho*-iodotriazene and using a functionalization upon cleavage <2005OBC1835>. By diazotation of 2-iodoaniline **265** with *t*-butyl nitrite and subsequent coupling to the piperazine resin **266**, triazene iodo aryl resin **267** was prepared on a multigram scale (Scheme 35). The resulting triazene aryl iodide resin **267** was then converted to the corresponding triazene selenol resin **268** by starting with an iodine–lithium exchange with BuⁿLi and tetramethylethylenediamine (TMEDA), followed by treatment with elemental selenium. Cleavage of the resin **268** with dilute trifluoroacetic acid resulted spontaneously in the cyclization reaction, yielding benzo[1,2,3]selenadiazole **269** in 63% yield.

The reaction of aryl chlorides **270** with KSeCN and ethyl diazoacetate in acetone at room temperature yields ethyl 2-aryl-5-(arylimino)-2,5-dihydro-1,2,3-selenadiazole-4-carboxylates **218** in 32–41% yield (Scheme 36) (Section 6.12.3.1) <2000HCA539>. A reaction mechanism via the initial formation of the corresponding aryl isoselenocyanates **271** followed by a 1,3-dipolar cycloaddition of ethyl diazoacetate with the C–Se bond to give ethyl 5-(arylimino)-4,5-dihydro-1,2,3-selenadiazole-4-carboxylates **272** was proposed. The initially formed cycloadduct **272** can tautomerize to isomer **273**, which can be trapped by acylation with aryl chlorides **270**.



Scheme 35

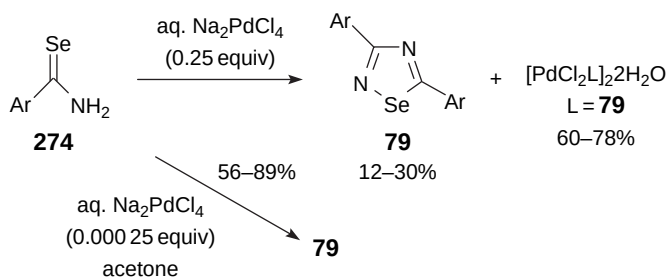


Scheme 36

6.12.9.2 1,2,4-Selenadiazoles

The previously reported synthetic methods for 1,2,4-selenadiazoles have been summarized [<2004HOU777>](#). Reaction of selenoamide with oxidants results in oxidative dimerization with loss of selenium to lead to 1,2,4-selenadiazoles. Some modified methods for the reaction have been reported.

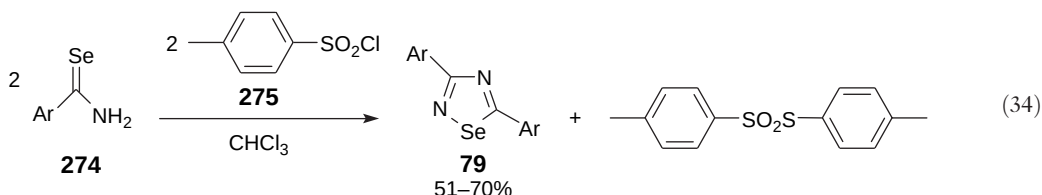
Palladium-catalyzed dimerization of arylselenocarboxamides **274** gave 3,5-diaryl-1,2,4-selenadiazoles **79** under mild reaction conditions (Scheme 37) [<2002JOM274>](#). Treatment of arylselenocarboxamides **274** with aqueous



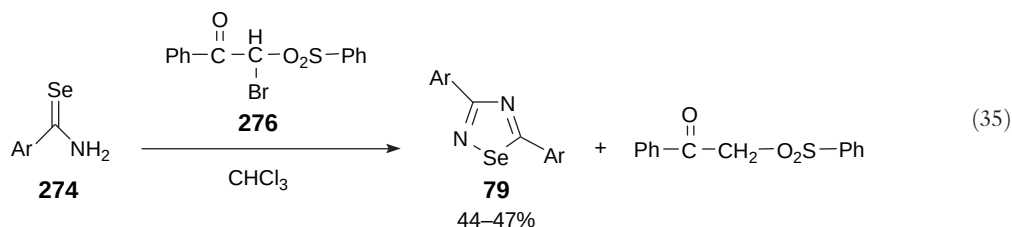
Scheme 37

Na_2PdCl_4 (0.25 equiv) in acetone at room temperature resulted in the formation of 3,5-diaryl-1,2,4-selenadiazoles **79** as unexpected products together with palladium(II) complexes containing 3,5-diaryl-1,2,4-selenadiazoles. Treatment of arylselenocarboxamides with catalytic amounts of Na_2PdCl_4 (0.000 25 equiv) gave only 3,5-diaryl-1,2,4-selenadiazoles **79** in good yields. 3,5-Diaryl-1,2,4-selenodiazoles **79** were also prepared by oxidation of arylselenocarboxamides **274** with iodine for comparison. In general, the synthesis of selenadiazoles **79** using a catalytic amount of Na_2PdCl_4 gave better yields than those prepared by the oxidation with iodine.

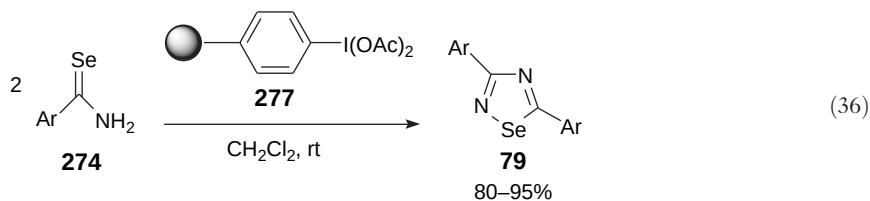
3,5-Diaryl-1,2,4-selenadiazoles **79** were prepared by treatment of aryl selenoamides **274** with *p*-toluenesulfonyl chloride **275** in chloroform in 51–70% yield (Equation 34) <2002CCCL729>.



Reaction of aryl selenoamides **274** with α -arylsulfonyl- α -bromoacetophenone **276** gave compound **79** in 44–47% yield (Equation 35) <1999JHC901>.



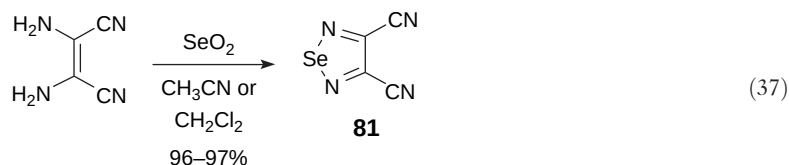
3,5-Diaryl-1,2,4-selenadiazoles **79** were also prepared in 80–95% yield from aryl selenoamides **274** using poly[styrene(iodosodiacetate)] **277** as oxidant (Equation 36). The polymer reagent **277** could be regenerated and reused <2003SC2823>.



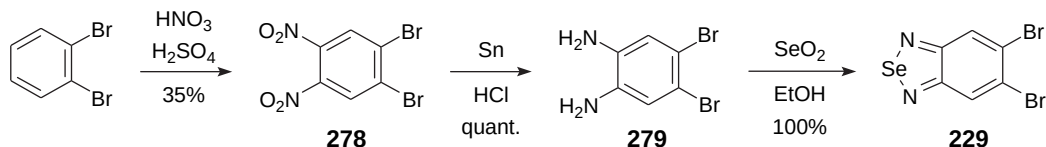
6.12.9.3 1,2,5-Selenadiazoles

In this section, ring synthesis of 1,2,5-selenadiazoles and their fused systems such as 2,1,3-benzoselenadiazoles are described. Most synthetic methods involve the reaction of 1,2-diamines with selenium dioxide or selenium oxychloride. The methodology has been described <2004HOU777, 1996CHEC-II(4)743, 1984CHEC(6)513>. A related investigation toward 2,1,3-benzotelluradiazoles is also described here.

The reaction of diaminomaleodinitrile with SeO_2 in acetonitrile or CH_2Cl_2 gave 3,4-dicyano-1,2,5-selenadiazole **81** in 96–97% yield (Equation 37) <1998PCA9021, 1999MI371>.

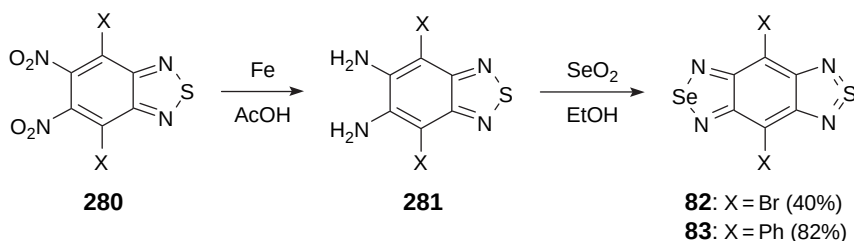


The nitration of 1,2-dibromobenzene, reduction of the resulting 1,2-dibromo-5,6-dinitrobenzene **278**, and subsequent treatment of the diamine **279** with SeO₂ gave 2,1,3-selenadiazole **229** (Scheme 38) <1995ACS658>.



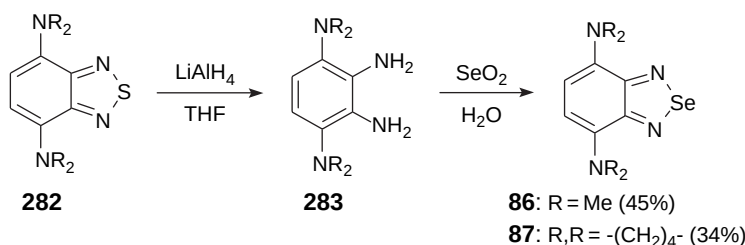
Scheme 38

Reduction of dinitrobenzothiadiazoles **280** with iron dust in acetic acid gave diamines **281** (Scheme 39). The reaction of diamines **281** with selenium dioxide gave [1,2,5]selenadiazolo[4,5-*c*]-2,1,3-benzothiazole derivatives containing a hypervalent sulfur atom **82** and **83** in 40% and 82% yields, respectively <1997T10169>.



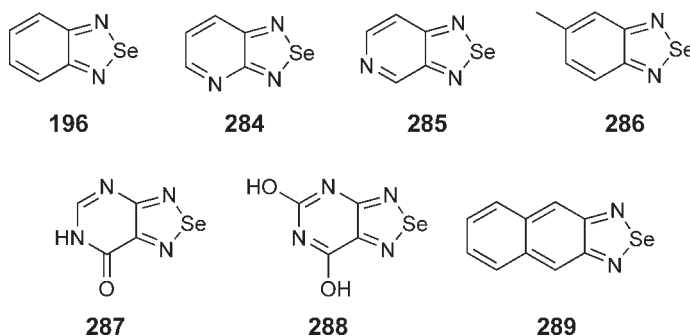
Scheme 39

Reductive ring opening of the thiadiazole ring in compound **282** by LiAlH₄ gave air-sensitive tetramines **283**, from which the selenadiazole derivatives **86** and **87** were prepared by treatment with SeO₂ in yields of 45% and 34% in two steps (Scheme 40) <2001JOC8954>.

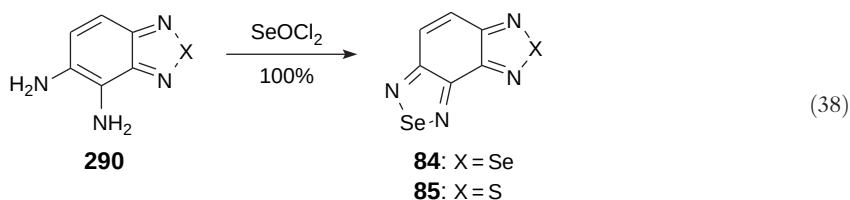


Scheme 40

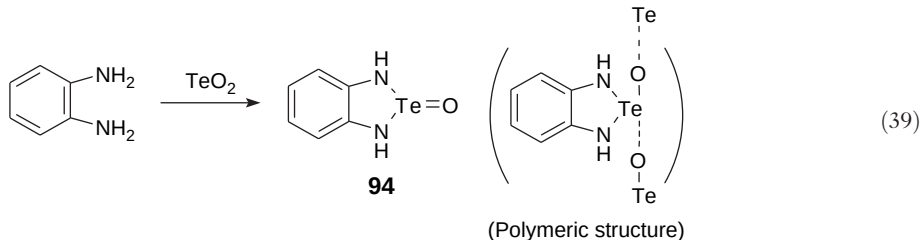
2,1,3-Benzoselenadiazoles were synthesized at room temperature in the solid state with *ortho*-aromatic diamines and selenium dioxide. Diamines and selenium dioxide were ground, respectively, and then were mixed in a ratio of 1:1 in a mortar at room temperature; the process was monitored with X-ray diffraction (XRD) or IR. The results showed that the reactions were completed after 30 min of grinding and the desired products were obtained. The yields of the synthesized compounds are as follows: 2,1,3-benzoselenadiazole **196** 77%; 1,2,5-selenadiazolo-[3,4-*b*]pyridine **284** 44%; 1,2,5-selenadiazolo[3,4-*c*]pyridine **285** 23%; 5-methyl-2,1,3-benzo-[3,4-*c*]selenadiazole **286** 74%; 1,2,5-selenadiazolo[3,4-*d*]pyrimidine-7-(6*H*)-one **287** 50%; 5,7-dihydroxy-1,2,5-selenadiazolo-[3,4-*d*]pyrimidine **288** 19%; and 2,1,3-naphtho-[2,3-*c*]-selenadiazole (**289**) 77% <2004MI1>.



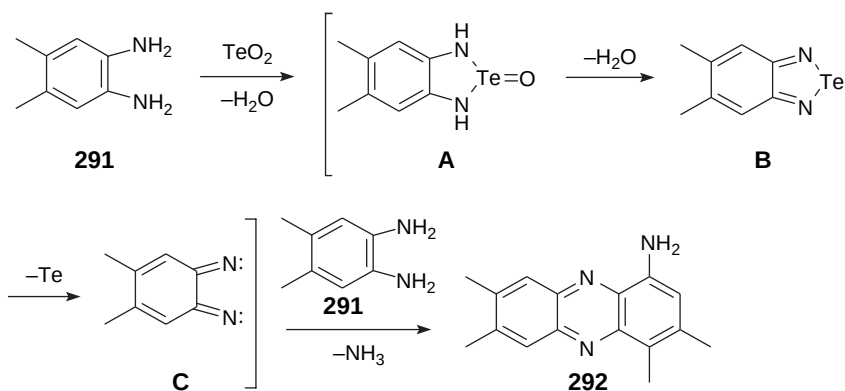
Reaction of diamine **290** with selenium oxychloride in refluxing chloroform–pyridine gave benzo[1,2-*c*:3,4-*c'*]bis[1,2,5]-selenadiazole **84** and [1,2,5]selenadiazolo[3,4-*c*]-2,1,3-benzothiazole **85** in quantitative yields (Equation 38) <2004JHC955>. The yield of product **85** improved compared to the reaction of diamine **290** with SeO₂.



The syntheses of 2,1,3-benzotelluradiazoles were attempted by reaction of diamine with tellurium dioxide <1998PS221>. However, the reaction of 1,2-phenylenediamine with tellurium dioxide gave benzo-2-telluroxo-1,3-dihydrodiazole **94**, which may exist in a polymeric form in the solid state (Equation 39) (Section 6.12.4.1).

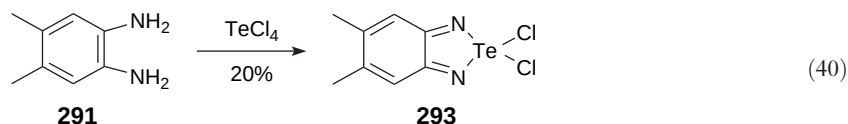


Reaction of 4,5-dimethyl-1,2-phenylenediamine **291** with tellurium dioxide gave 1-amino-3,4,7,8-tetramethylphenazine **292** (Scheme 41). It is postulated that the reaction proceeds via a telluroxodihydrodiazole intermediate **A** which

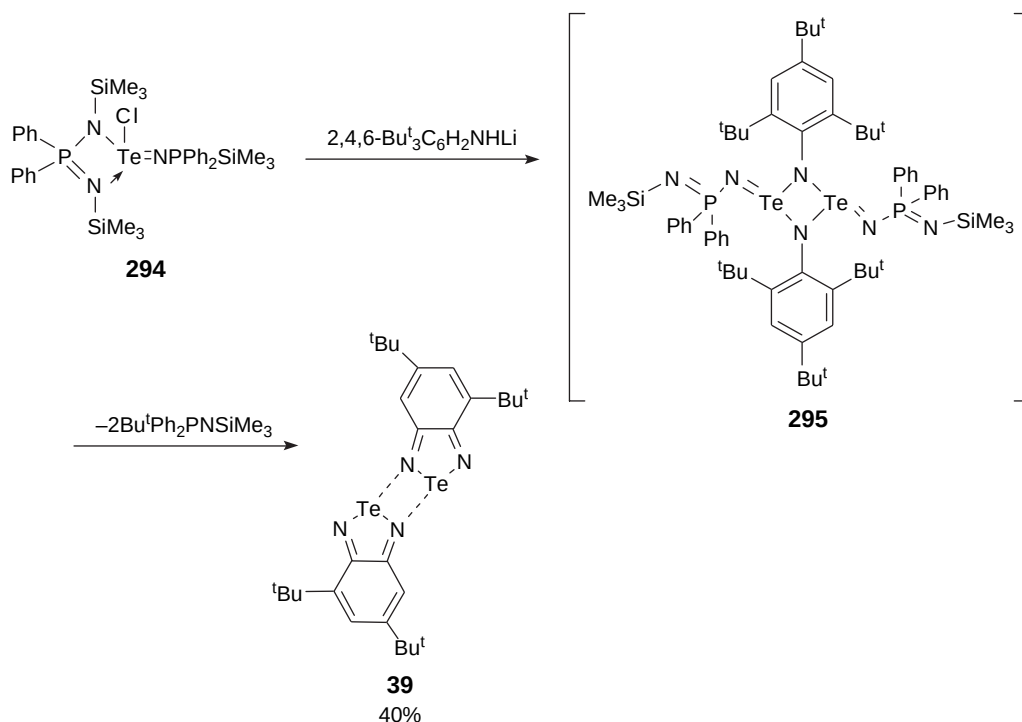


Scheme 41

loses water to give the telluradiazole **B**. Loss of tellurium from **B** gives highly reactive intermediate **C** which attacks a second molecule of the diamine **291**, yielding the product **292**. Reaction of 4,5-dimethyl-1,2-phenylenediamine **291** with TeCl_4 in 1,2-dichlorobenzene (or nitrobenzene) gave 3,4-dimethyl-benzo-2,2-dichloro-2,1,3-telluradiazole **293** in 20% yield (Equation 40).



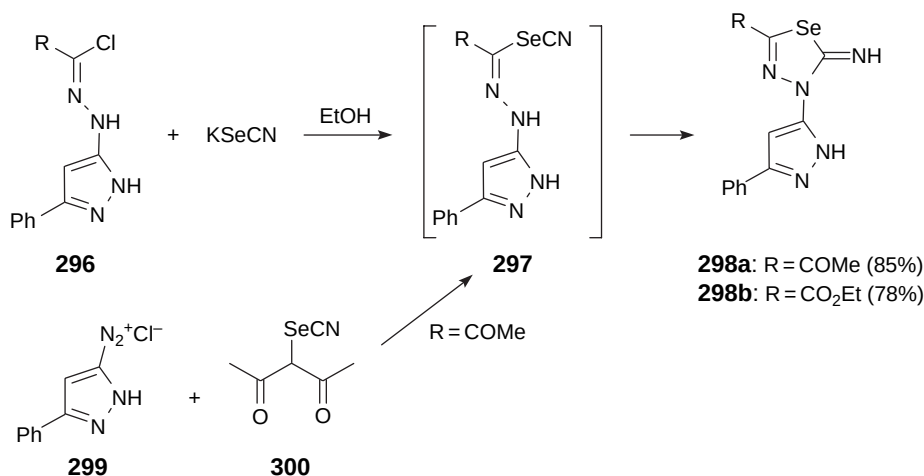
The reactions of the heterocycle **294** with $2,4,6\text{-Bu}^t_3\text{C}_6\text{H}_2\text{NHLi}$ in toluene yielded a telluradiazole $(\text{Bu}^t_2\text{C}_6\text{H}_2\text{N}_2\text{Te})_2$ **39** in 40% yield (Scheme 42). Compound **39** was shown by X-ray crystallography to exist as the dimer in the solid state <1996IC9> (Section 6.12.3.1). The proposed reaction pathway toward compound **39** includes the formation of dimer intermediate **295**, subsequent intramolecular ring closure, and the concomitant cleavage of a $\text{C}(\text{aryl})\text{-C}(\text{CH}_3)_3$ bond leading to compound **39**.



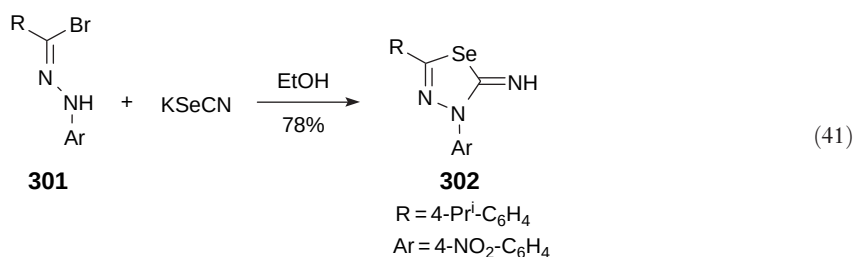
Scheme 42

6.12.9.4 1,3,4-Selenadiazoles

General synthetic methods for the synthesis of 1,3,4-selenadiazoles have been described <2004HOU777, 1996CHEC-II(4)743, 1984CHEC(6)333>. The applications toward new compounds have been reported. A reaction of α -chloro hydrazones **296** with potassium selenocyanate gave 2,3-dihydro-1,3,4-selenadiazoles **298** in 78–85% yield (Scheme 43) <2001HAC468>. Compound **298b** was alternatively prepared from reaction of diazotized aminopyrazole **299** with 3-selenocyanato-2,4-pentane dione **300**. For both reactions, intermediate **297** was proposed. Reaction of α -bromo hydrazones **301** with potassium selenocyanate gave 2,3-dihydro-1,3,4-selenadiazole **302** in 78% yield (Equation 41) <2003HAC421, 2004MI329, 1997PS43, 2005PS149>.

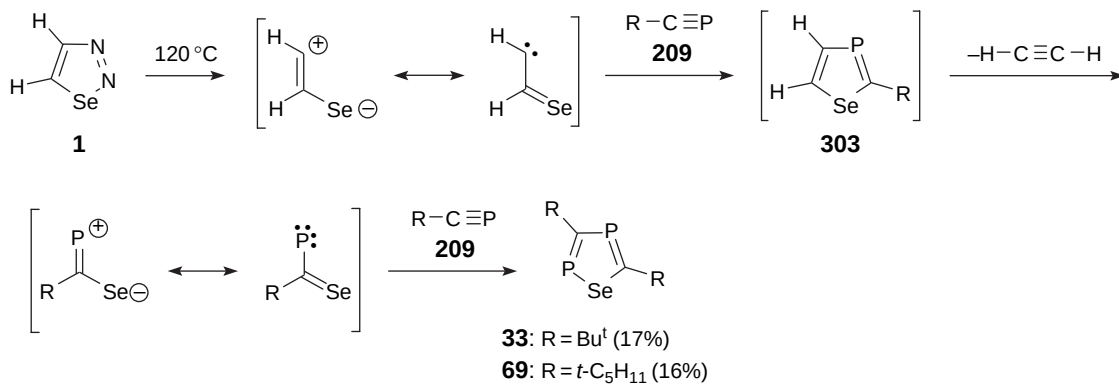


Scheme 43



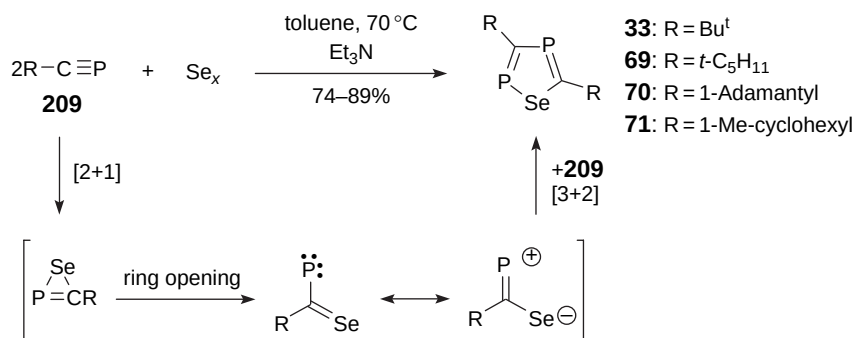
6.12.9.5 1,2,4-Selenadiphospholes, Telluradiphospholes

Members of the previously unknown class of heterocycles, 1,2,4-selenadiphospholes **33** and **69**, have been prepared (Scheme 44). The thermal reaction of 1,2,3-selenadiazole **1** with phosphalkynes **209** gave products **33** and **69** in 17% and 16% yields, respectively <1996PS99>. These compounds are proposed to form by a sequence of [3+2] cycloreversion and cycloaddition reactions (see also Section 6.12.5.9).



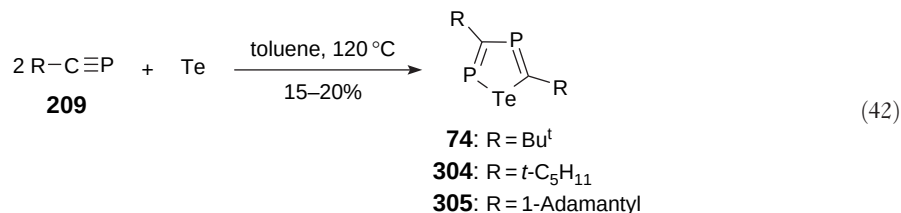
Scheme 44

Reaction of phosphalkynes **209** with elemental selenium in toluene at 70 °C in the presence of triethylamine gave 1,2,4-selenadiphospholes **33** and **69–71** in 74–89% yield (Scheme 45) <1999S1642>.

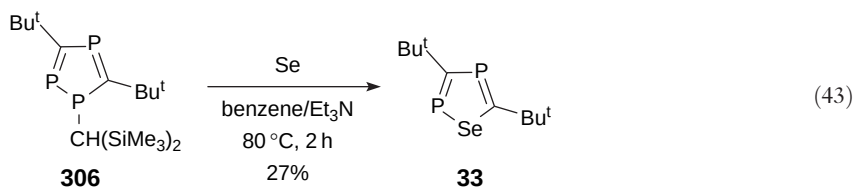


Scheme 45

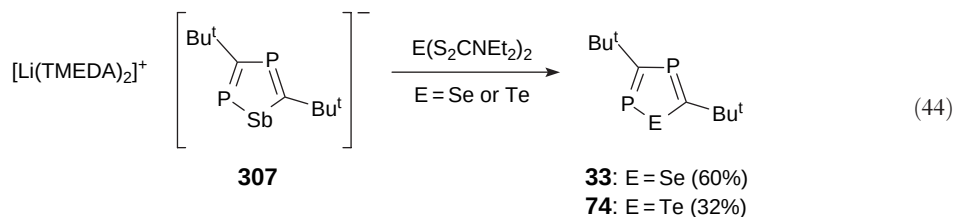
Under harsher conditions (120 °C in toluene) phosphalkynes **209** exhibit an analogous reactivity toward elemental tellurium. The previously unknown 1,2,4-telluradiphospholes **74**, **304**, and **305** were obtained in 15–20% yield along with oligomers of the phosphalkynes (Equation 42). 1,2,4-Telluradiphospholes **74**, **304**, and **305** are thermally labile and decompose on exposure to light with deposition of elemental tellurium.



Reaction of 1,2,4-triphosphole **306** with selenium afforded 1,2,4-selenadiphosphole **33** in 27% yield (Equation 43) <1996BSB675>.

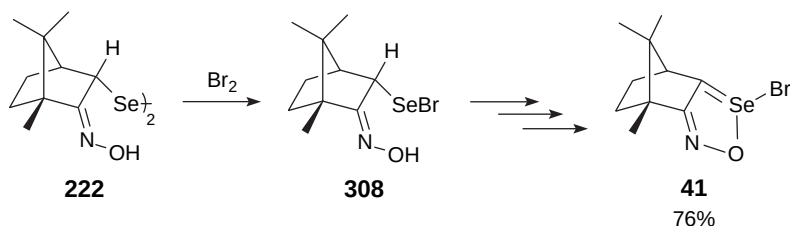


Another route to compounds **33** and **74** was reported (Equation 44) <1999TL3815>. The reaction of [Li(TMEDA)₂][1,4,2-P₂SbC₂Bu^t₂] **307** with E(S₂CNEt₂)₂ (E = Se or Te) leads to 1,2,4-selenadiphosphole **33** and 1,2,4-telluradiphosphole **74** in 60% and 32% yields, respectively. In both reactions, elemental antimony was deposited from the reaction mixture, which suggests that a redox process is occurring. However, the detailed mechanism is not yet clear.



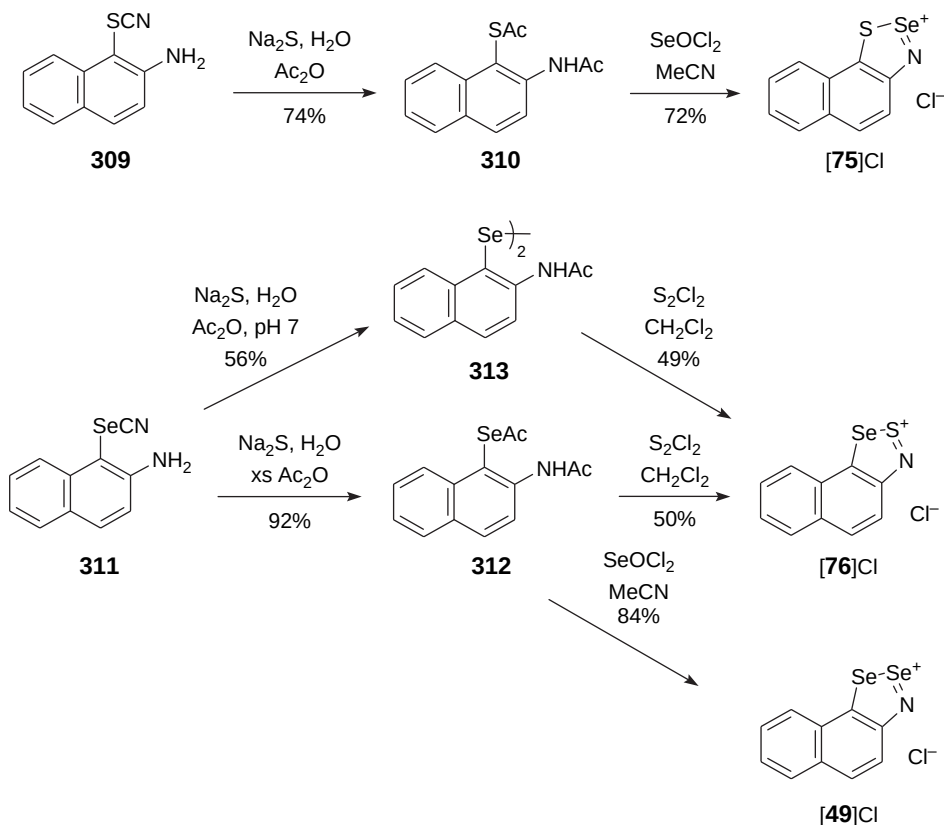
6.12.9.6 Oxaselenazoles, Thiaselenazoles, Diselenazoles

Addition of bromine to diselenide **222** in dichloromethane at –40 °C leads to oxaselenazole **41** in 76% yield (Scheme 46) <2002JOC499>. The structure of compound **41** was determined by X-ray crystallography (Section 6.12.3.1). Conversion of the diselenide **222** to the selenenyl bromide **308** is followed by its transformation to the oxaselenazole **41**.



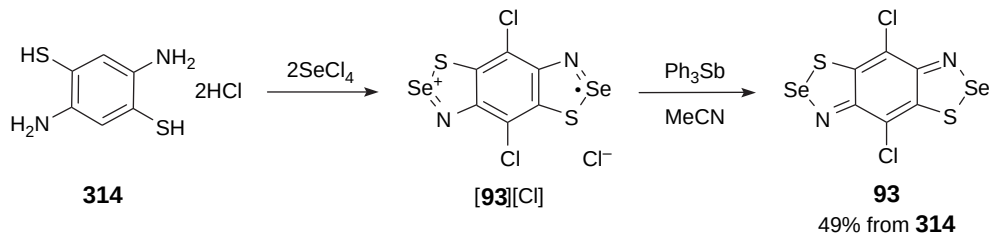
Scheme 46

From the interest in the development of radical-based magnets and conductors, 3*H*-naphtho[1,2-*d*][1,2,3]thiaselenazolylium cation **75** and its variants **76** and **49** have been prepared (Scheme 47) <2005IC1837>. The most efficient and general method involves the intermediacy of bis-acetylated aminothioliates and aminoselenolates. These reagents react smoothly with sulfur and selenium halides to afford the desired ring-closure products. Thus, the intermediate thiolate obtained by the hydrolysis of compound **309** was quenched with acetic anhydride leading to the bis-*N,S*-acetyl derivative **310** as an air-stable crystalline solid in 74% yield. It reacts smoothly with SeOCl_2 to afford 3*H*-naphtho[1,2-*d*][1,2,3]thiaselenazolylium chloride [**75**][Cl] in 72% yield. When 2-aminonaphthalene-1-selenocyanate **311** was hydrolyzed and the resulting selenolate quenched with a large excess of acetic anhydride, an air-stable bis-*N,Se*-acetyl derivative **312** was produced. When the intermediate selenolate was quenched slowly with acetic anhydride so that the pH was not allowed to go below a value of 7, the *N*-acetyl diselenide **313** was produced. The reaction of either compounds **312** or **313** with excess sulfur monochloride afforded the [1,2,5] thiaselenazolylium chloride [**76**][Cl] in 50% and 49% yields, respectively. Treatment of compound **312** with SeOCl_2 at room temperature in MeCN provided the [1,2,3]diselenazolylium chloride [**49**][Cl] in 84% yield.



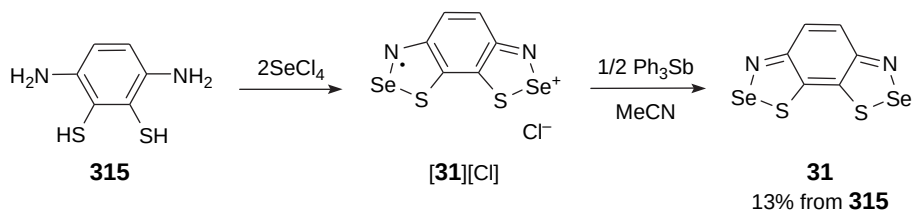
Scheme 47

3,6-Dichlorobenzo[1,2-*d*:4,5-*d'*]bis(1,2,3-thiaselenazole) **93** was prepared using a similar approach (Scheme 48) <1997JA12136>. Reduction of [93][Cl] gave the neutral compound **93** in 49% yield. Chlorination of the benzene ring during the course of the condensations was unavoidable.



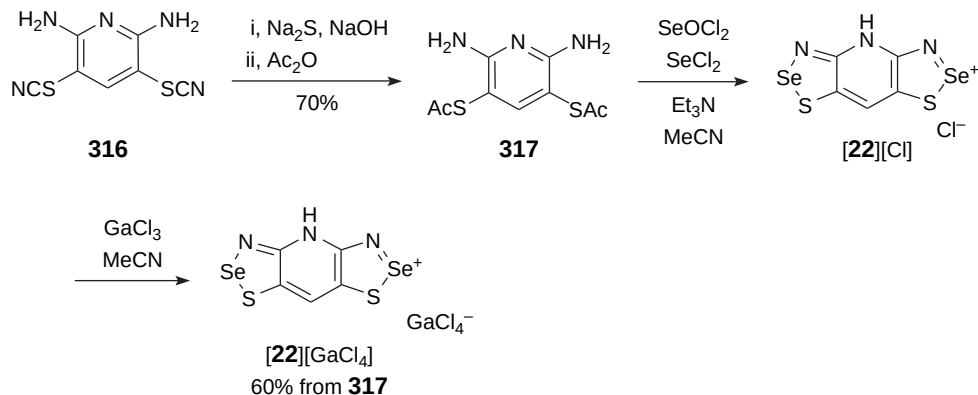
Scheme 48

A preparative method for the synthesis of benzo[2,1-*c*:3,4-*c'*]bis(1,2,3-thiaselenazole) **31** was reported (Scheme 49) <2001IC4705>. When the dihydrochloride of diaminobenzenedithiol **315** and 2 equiv of SeCl_4 is heated in dichloroethane, the crude radical cation salt [31][Cl] is formed. Reduction of the radical cation salt with triphenylantimony affords neutral product **31** in 13% yield from compound **315**.



Scheme 49

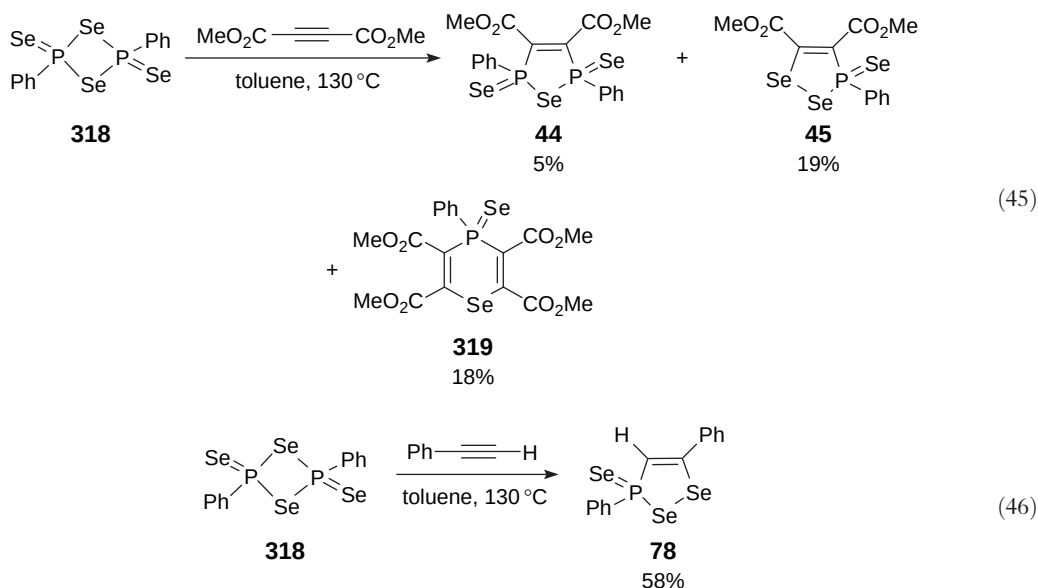
A synthetic sequence leading to salts of N-alkylated pyridine-bridged 1,2,3-thiaselenazolo-1,2,3-thiaselenazolium cations was reported <2005JA18159, 2005CC1543>. The reagent bis-thioacetate **317** is prepared by quenching the intermediate dithiolate (prepared by the hydrolysis of the bis-thiocyanate **316**) with acetic anhydride. Compound [22][Cl] was obtained by mixing **317** with a mixture of 2 molequiv of both SeOCl_2 and SeCl_2 in the presence of triethylamine (Scheme 50). The resulting crude compound [22][Cl] was converted into a soluble tetrachlorogallate [22][GaCl₄] in 60% from compound **317**.



Scheme 50

6.12.9.7 Diselenaphospholes

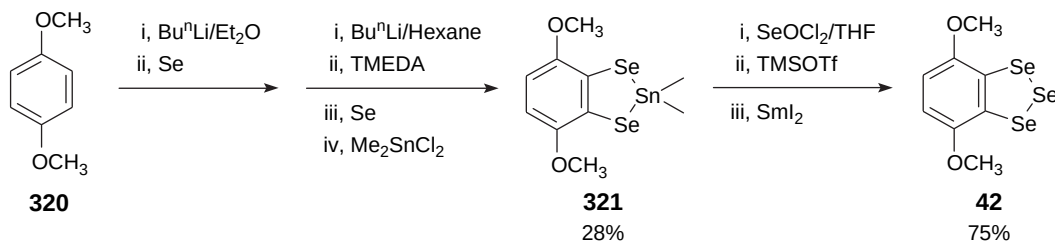
Uncommon heterocycles, diselenaphospholes, and related compounds were reported. Reaction of the four-membered ring compound **318** with DMAD in toluene at 130 °C afforded selenadiphosphole **44**, 1,2,3-diselenaphosphole **45**, and 1,4-phoshaselenin derivative **319** in low yields (5–19% based on **318**) (Equation 45) <2002CEJ2705>. The molecular structures of compounds **44**, **45**, and **319** were determined crystallographically (Section 6.12.3.1). In contrast to the mixture of heterocycles **44**, **45**, and **319** obtained from DMAD, compound **318** reacts with PhC≡CH to give one product, 1,2,3-diselenaphosphole **78**, in 58% yield (Equation 46).



6.12.9.8 Triselenoles

Syntheses of 1,2,3-triselenoles and related compounds are described in this section.

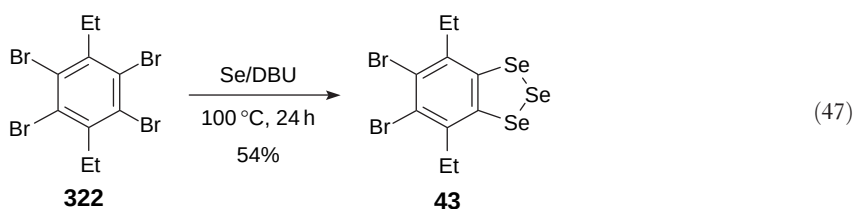
The 4,7-dimethoxy-2,2-dimethyl-1,3,2-benzodiselenastannole **321** was prepared from commercially available 1,4-dimethoxybenzene **320** by a sequence of tandem *ortho*-lithiation and selenation, and followed by dimethyltin protection in 28% yield (Scheme 51). Then, sequential treatment of the stannole **321** in THF with selenyl chloride, trimethylsilyl trifluoromethanesulfonate (TMSOTf), and samarium iodide gave crystalline 4,7-dimethoxybenzotriselenole **42** in 75% yield <1996H(43)1843>. The structure was characterized by X-ray crystallographic analysis (Section 6.12.3.1).



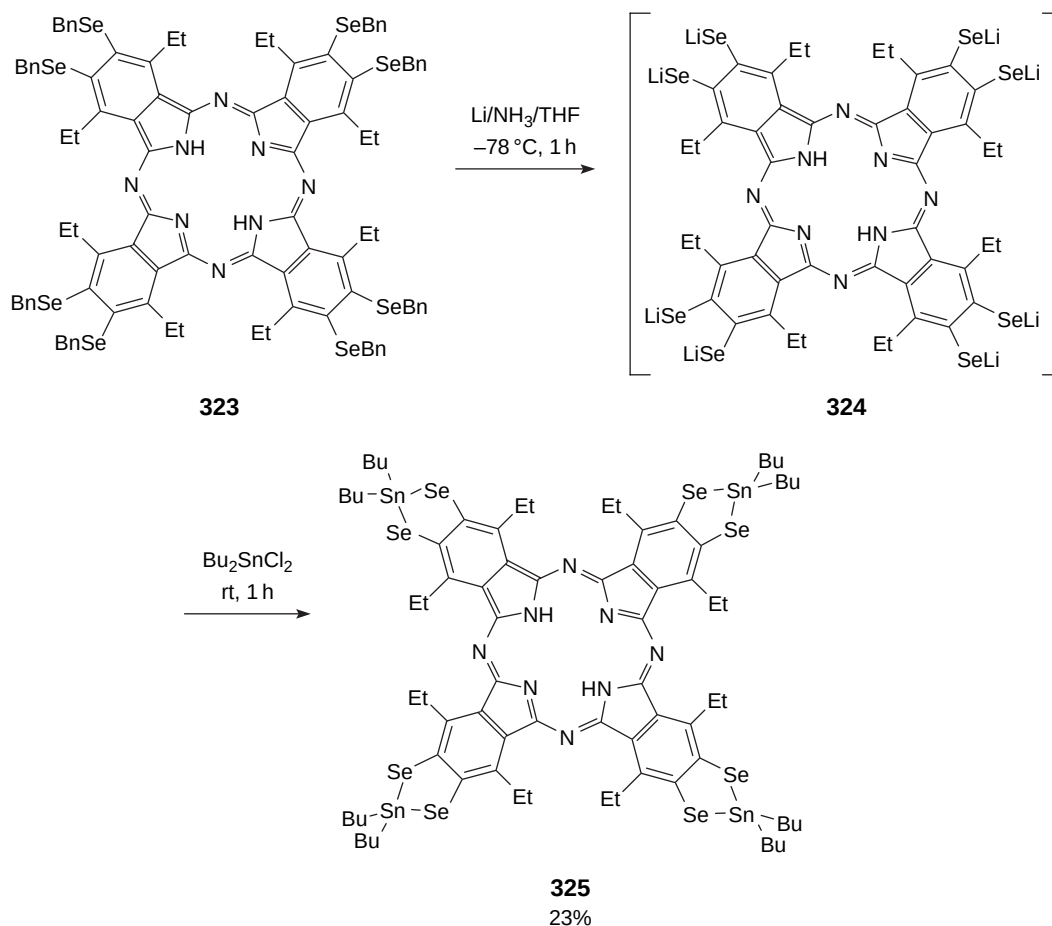
Scheme 51

Direct preparation of a benzo[1,2,3]triselenole derivative by a one-step reaction of 1,2-dibromobenzene with selenium reagents was reported <2004JOC4716>. Benzo[1,2,3]triselenole **43** was obtained in 54% yield by the

reaction of 2,3,5,6-tetrabromo-1,4-diethylbenzene **322** with amorphous selenium in DBU at 100 °C for 24 h (Equation 47). The structure of compound **43** was determined by X-ray crystallographic analysis.



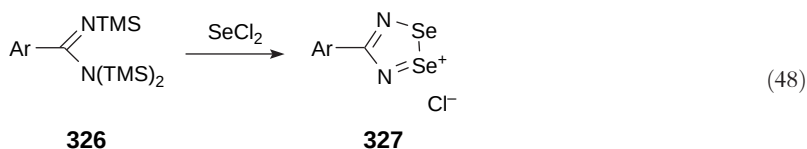
Phthalocyanine derivative **325** with four diselenastannole rings was prepared by the reaction of lithium octaselenolate **324**, which was derived from compound **323** (Scheme 52) <2004JOC4716>. Thus, compound **323** was treated with lithium in THF/NH₃ at –78 °C and then with dibutyltin dichloride to produce compound **325** in 23% yield, by way of intermediate **324**.



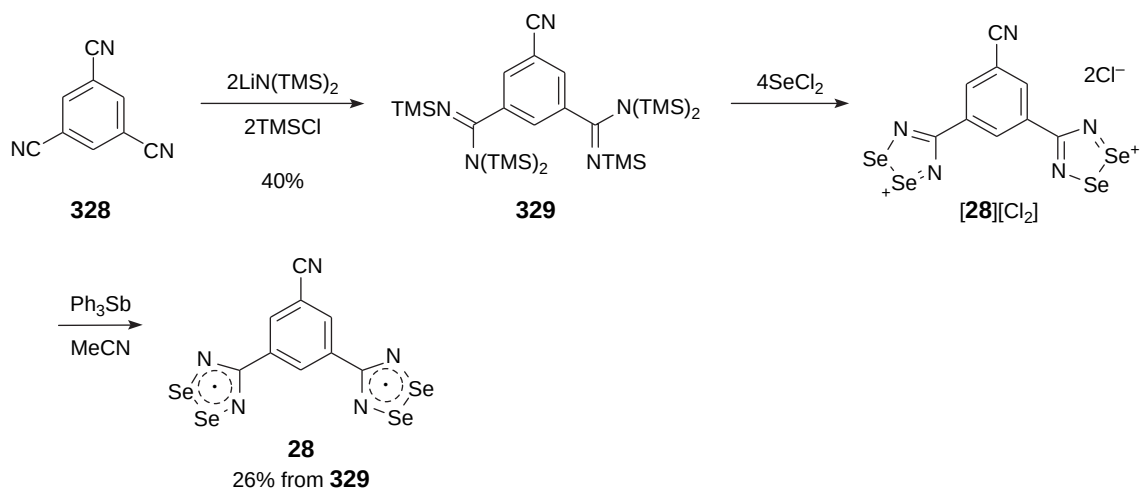
Scheme 52

6.12.9.9 Diselenadiazoles

Synthetic methods toward 1,2,3,5-diselenadiazole rings have been reported <1989JA9276, 1996CHEC-II(4)743, 2004HOU777>. They involve the reaction of tris(trimethylsilyl)amidine **326** with selenium dichloride generated *in situ* from selenium and selenium tetrachloride (Equation 48). A number of new derivatives have been prepared by this method, in order to explore the structural, magnetic, and conductivity properties of the radicals.

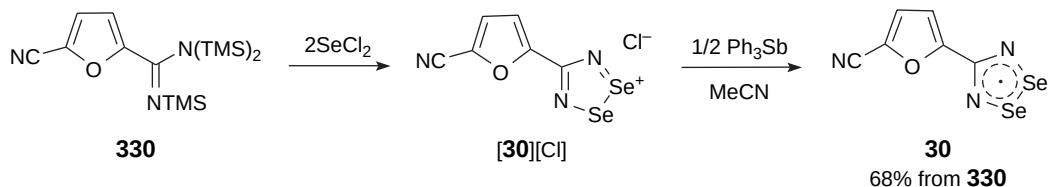


Synthesis of 4,4'-(5-cyanobenzene)-1,3-bis[1,2,3,5-diselenadiazolyl] **28** was reported (Scheme 53) <1993CM820>. The starting material, 5-cyanobenzene-1,3-bis[*N,N,N'*-tris(trimethylsilyl)carboxamidine] **329**, was prepared by treatment of 1,3,5-tricyanobenzene **328** with 2 equiv of lithium bis(trimethylsilyl)amide, followed by transmetalation with trimethylsilyl chloride. Reaction of the bis(amidine) **329** with 4 molar equiv of SeCl₂ affords the bis(1,2,3,5-diselenadiazolium) dication as its dichloride salt [28][Cl₂]. Reduction of the dication with triphenylantimony affords compound **28** in 26% from the bis(amidine) **329**.



Scheme 53

5-Cyanofuran-2-[1,2,3,5-diselenadiazolyl] **30** was prepared similarly (Scheme 54) <2001IC6820>. The cyano-furyl-functionalized persilylated amidine **330**, prepared by the reaction of 2,5-dicyanofuran with lithium bistrimethylsilylamide, was treated with 2 equiv of SeCl₂, which was prepared *in situ* from Se and SeCl₄. The diselenadiazolium chloride [30][Cl] was reduced with triphenylantimony to give the radical **30** in 68% yield from compound **330**.



Scheme 54

6.12.10 Important Compounds and Applications

Biological activities are of interest for 1,2,3-selenadiazoles. 4,5-Dihydronaphtho[1,2-*d'*][1,2,3]selenadiazoles showed antifungal activity <2003FA63>. The antimicrobial and antiaflatoxic activities of 4-substituted-1,2,3-selenadiazoles were investigated <1996PS155>.

1,2,5-Selenadiazoles, 1,2,3,5-diselenadiazoles, 1,2,3,5-thiaselenadiazoles, and 1,2,3-thiaselenazoles have been much studied because of their potential use in conducting materials, organic dyes, and light-emitting diodes, related to their electronic properties and crystal structures. As part of development of molecular conductors based on π -radicals and CT, involvement of 1,2,3,5-diselenadiazoles, 1,2,3,5-thiaselenadiazoles, and 1,2,3-thiaselenazoles has been studied <1989JA9276, 1991JA582, 1992JA1729, 1993JA7232, 1993CM820, 1994CM508, 1996CM762, 1997JA12136, 2001IC6820, 2001IC4705, 2005CC1543, 2005JA18159>. 4,7-Bis(dialkylamino)benzo[*c*][1,2,5]selenadiazoles were studied as a novel class of organic dyes <2001JOC8954>. Incorporation of 1,2,5-selenadiazoles into phthalocyanines and porphyradines has been studied for application toward new materials <1995ACS658, 1999MI371, 2001MC45, 2004JHC955>. The polymer containing 2,1,3-benzoselenadiazole structures has been shown to be a promising candidate for red polymer light-emitting diode (PLED) <2003SM177>.

6.12.11 Further Developments

The structures of benzo-2,1,3-telluradiazole and 3,6-dibromobenzo-2,1,3-telluradiazole were determined crystallographically. The assembled structures were consistent with the computational predictions, explained by Te–N secondary bonding interactions <2006MI181> (see Section 6.12.3.1). A synthetic route to new pyridine-bridged bisthiaselenazolyls and bisdiselenazolyls has been developed. These selenium-based resonance stabilized radicals showed an increase in conductivity and reduction in thermal activation energy relative to sulfur-based radicals <2006JA15080> (see Sections 6.12.9.6 and 6.12.10).

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6.13

Three or Four Heteroatoms including at least One Phosphorus

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6.13.1	Introduction	583
6.13.2	Theoretical Methods	584
6.13.3	Experimental Structural Methods	586
6.13.3.1	X-Ray Diffraction	586
6.13.3.2	NMR Spectroscopy	586
6.13.4	Syntheses and Reactions of Particular Classes of Compounds	588
6.13.4.1	1,2,4-Diaza-, 1,2,4-Oxaza-, and 1,2,4-Thiazaphospholes	588
6.13.4.2	1,4,2-Diazaphospholes and 1,3,4-Thiazaphospholes	589
6.13.4.3	1,2,3-Diazaphospholes	589
6.13.4.4	1,3,2-Diaza-, 1,3,2-Oxaza-, and 1,3,2-Thiazaphospholes	590
6.13.4.5	1,3,2-Dithia- and 1,3,2-Diselenaphospholium Salts	592
6.13.4.6	1,2,3,4-Triazaphospholes	593
6.13.4.7	1,2,4,3-Triazaphospholes and 1,3,4,2-Thiadiazaphospholium Salts	594
6.13.4.8	1,2,3-Azadiphospholes	595
6.13.4.9	1,2,4-Azadiphospholes	596
6.13.4.10	1,2,3,5-Diazadiphospholes	596
6.13.4.11	1,2,4-, 1,2,5-, and 1,3,4-Thiadiphospholes	596
6.13.4.12	1,2,3-Tri-, 1,2,4-Tri-, and Tetraphospholes and Phospholides	597
6.13.5	Important Compounds and Applications	598
6.13.5.1	Applications in Research	598
6.13.5.2	Biological Activity	598
6.13.6	Further Developments	598
References		599

6.13.1 Introduction

The compounds with five-membered rings containing three or four heteroatoms including at least one phosphorus were first systematically reviewed in Chapter 4.22 of CHEC-II(1996) by Schmidpeter <1996CHEC-II(4)771>. In CHEC(1984), only few examples of 2*H*-1,2,3-diazaphospholes were mentioned in the general chapter on phosphorus heterocycles <1984CHEC(1)493>.

A great variety of heterophospholes with three or four heteroatoms incorporating different elements have been reported in the literature. The scope of compounds covered in CHEC-II(1996) <1996CHEC-II(4)771> is limited mainly to structures 1–27 (Figure 1) and the related annelated and nonconjugated systems including oxo derivatives. More recently, several of these structural classes were reviewed in volumes 12 and 13 of Houben-Weyl's *Science of Synthesis* in the following chapters: Product class 6: azaphospholes and azarsoles <2002HOU(12)679>, Product class 7: diphospholes <2002HOU(12)705>, Product class 16: oxazaphospholes and thiazaphospholes <2004HOU(13)647>, Product class 17: oxadiphospholes and their analogs <2004HOU(13)659>, Product class 18: diazaphospholes and diazarsoles <2004HOU(13)689>, Product class 19: azadiphospholes and their analogues <2004HOU(13)717>, Product class

20: triphospholes and diphospharsoles <2004HOU(13)729>, Product class 22: triazaphospholes <2004HOU(13)743>, Product class 23: diazadiphospholes <2004HOU(13)757>, and Product class 24: tetraphospholes <2004HOU(13)763>.

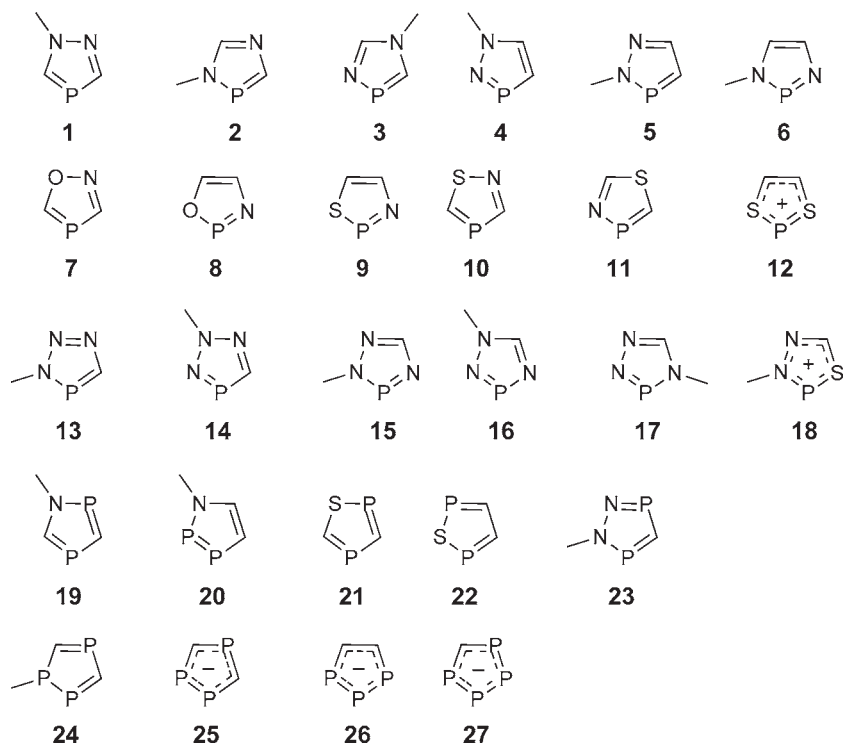


Figure 1 Known phosphole systems with three and four heteroatoms.

This chapter provides an update of Chapter 4.22 published in CHEC-II(1996) <1996CHEC-II(4)771> and overviews recent publications related to the heterocyclic systems of 1,2,4-diazaphospholes **1**, 1*H*-1,4,2-diazaphospholes **2**, 4*H*-1,4,2-diazaphospholes **3**, 1*H*-1,2,3-diazaphospholes **4**, 2*H*-1,2,3-diazaphospholes **5**, 1,3,2-diazaphospholes **6**, 1,2,4-oxazaphospholes **7**, 1,3,2-oxazaphospholes **8**, 1,3,2-thiazaphospholes **9**, 1,2,4-thiazaphospholes **10**, 1,3,4-thiazaphospholes **11**, 3*H*-1,2,3,4-triazaphospholes **13**, 2*H*-1,2,3,4-triazaphospholes **14**, 2*H*-1,2,4,3-triazaphospholes **15**, 1*H*-1,2,4,3-triazaphospholes **16**, 4*H*-1,2,4,3-triazaphospholes **17**, 1,2,4-azadiphospholes **19**, 1,2,3-azadiphospholes **20**, 1,2,4-thiadiphospholes **21**, 1,2,5-thiadiphospholes **22**, 1,2,3,5-diazadiphospholes **23**, 1,2,4-triphospholes **24**, cationic and anionic species **12**, **18**, **25–27**, and the related nonconjugated systems (Figure 1).

The analogous phosphorus heterocyclic systems that include selenium or tellurium are discussed in detail in Chapter 6.12, and the systems incorporating phosphorus and arsenic or antimony are covered in Chapter 6.14. In addition, numerous examples of five-membered heterocyclic systems with phosphorus and elements of group III (B, Al, Ga, In) and group IV (Si, Ge, Sn, Pb) are included in Chapters 6.16 and 6.17 of this volume. The systems with five heteroatoms in a five-membered ring (e.g., pentaphospholide anion and tetrazaphospholium cation) and the fused heterocyclic rings (see Volumes 9–11) are beyond the scope of this chapter and are not covered here.

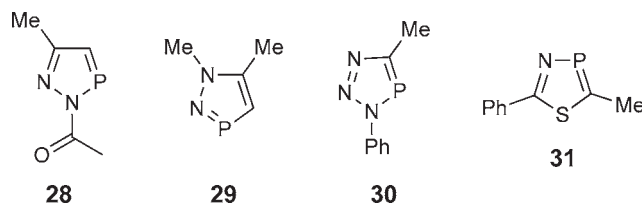
This chapter is structured similarly to the original Chapter 4.22 of CHEC-II(1996) <1996CHEC-II(4)771>, and a brief reference to CHEC-II(1996) is provided at the beginning of each related section. It should be noted that the subdivisions in this chapter do not follow completely the pattern in the rest of this volume, partly because this diverse group of heterocycles does not lend itself fully to those subdivisions. However, it is our belief that all the most important information in the decade since 1996 has been summarized, and leading references have been cited.

6.13.2 Theoretical Methods

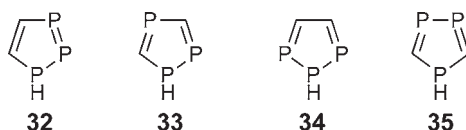
The earlier literature on quantum-chemical calculations at different levels for several classes of heterophospholes (e.g., structures **4**, **6**, **20**, **24–27**) is reviewed in CHEC-II(1996) <1996CHEC-II(4)771>. More recently, several theoretical papers evaluating aromaticity in numerous five-membered heterocyclic systems including heterophospholes shown

in **Figure 1** have been published <1997T2357, 1998IC4413, 2002JOC1333, 2003T1657, 2006OL863, 2007STC25>. In particular, calculated data for aromatic stabilization energies (ASEs), resonance energies (REs), magnetic susceptibility exaltations (Λ), as well as the values of nucleus-independent chemical shift (NICS) and harmonic oscillator model of aromaticity (HOMA) indexes for numerous heterophospholes with three or more heteroatoms were summarized, and the validity of these data as the measure of aromaticity was discussed <2002JOC1333, 2003T1657>.

The molecular geometries and the frontier orbital energies of heterophospholes **28–31** were obtained from density functional theory (DFT) calculations at the B3LYP/6-311+G** level. The 1,3-dipolar cycloaddition reactivity of these heterophospholes in reactions with diazo compounds was evaluated from frontier molecular orbital (FMO) theory. Among the different types of heterophospholes considered, the 2-acyl-1,2,3-diazaphosphole **28**, 3*H*-1,2,3,4-triazaphosphole **30**, and 1,3,4-thiazaphosphole **31** were predicted to have the highest dipolarophilic reactivities. These conclusions are in qualitative agreement with available experimental results <2003JPO504>.



The π - and σ -complexation energy of triphospholes **32–35** with metal ions Li^+ , Na^+ , K^+ , Mg^{2+} , and Ca^{2+} was calculated at the post-Hartree-Fock MP2 level, MP2(FULL)/6-311+G(2d,2p)//MP2/6-31G*. Compared to the analogous azoles, the phospholes were found to have higher π -complexation energy with Li^+ , Mg^{2+} , and Ca^{2+} . The complexation energy of the π - and σ -complexes of phospholes did not vary significantly and the phospholes did not show binding mode preference. In the σ -complexes of phospholes, the metal binds away from the electron-deficient phosphorus center <2006PCA10148>.



Optimized geometries, potential energies, Gibbs free energies, and vibrational frequencies were calculated for all possible tautomers of triphospholes and tetraphosphole molecules at the B3LYP/aug-cc-pVTZ level (**Figure 2**)

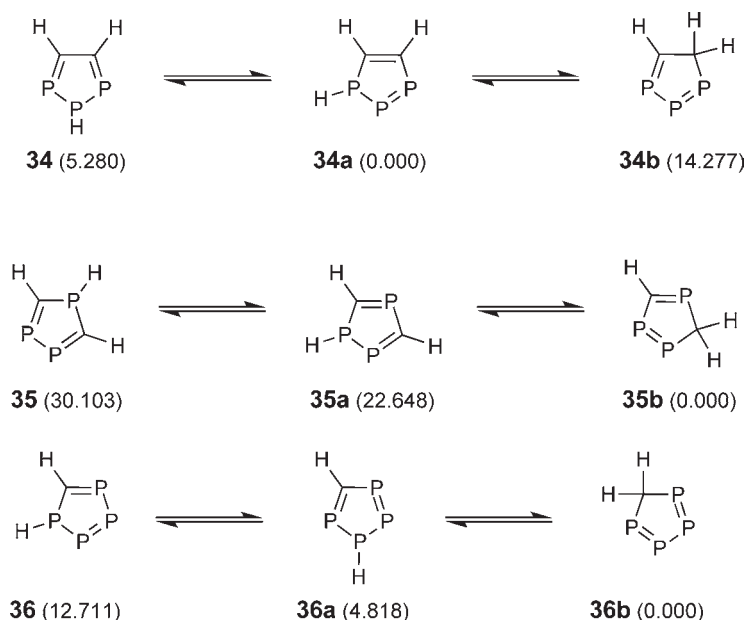


Figure 2 Possible tautomeric forms of triphospholes and tetraphospholes with calculated relative energies (ΔE , kJ mol^{-1}).

<2005CPH(313)123>. For 1,2,3-triphosphole **34**, the most stable phosphole form is the CH₂-tautomer **34b**. For 1,2,4-triphosphole **35**, the energy difference between the tautomers is large and only one tautomer **35** may be observed. For tetraphosphole **36**, two tautomers **36** and **36a** may coexist. Nonplanarity of the five-membered ring is present only for PH-tautomers, while in the CH₂-tautomers the ring is planar <2005CPH(313)123>.

6.13.3 Experimental Structural Methods

6.13.3.1 X-Ray Diffraction

X-Ray crystal structural data for heterophospholes reported up to 1996 were tabulated in CHEC-II(1996) <1996CHEC-II(4)771>. In these tables, bond lengths and bond angles at the phosphorus atom for various conjugated and nonconjugated ring systems of diazaphospholes, thiazaphospholes, dithiaphospholes, triazaphospholes, azadiphospholes, and triphospholes are summarized <1996CHEC-II(4)771>.

The recently reported single crystal X-ray structures of phosphole systems with three and four heteroatoms are shown in **Figure 3** <2006JA3946, 2000CEJ3414, 2007IC1426, 2000AGE3084, 2001JOM(623)116, 2003JOM(682)212, 1999HAC105, 2000T21, 2000T35, 1999ZNB187, 2005POL1855, 2006AGE2598, 2005AGE1700, 1999CC2363, 2003CC1142, 2002JA2506, 1999JOM(580)386, 1999CEJ3143, 1998AGE1083>.

It is difficult to generalize structural features for a variety of compounds shown in **Figure 3**. For aromatic system of 1,2,4-azadiphosphole **50**, the five-membered ring is completely planar and the bond distances P(2)–N (1.715 Å), P(2)–C(1) (1.697 Å), P(1)–C(1) (1.746 Å), P(1)–C(2) (1.740 Å), and C(2)–N (1.366 Å) are all fully consistent with significant electron delocalization <1999CC2363>. The 1,2,4-triphosphole system in structures **54** also features almost planar five-membered ring <1999CEJ3143, 1998AGE1083>. Interestingly, the shortest P–C bond length in structure **54b**, namely P(1)–C(1) (1.684 Å), involves the tricoordinate phosphorus atom P-1, and is significantly shorter than P(2)–C(2) (1.745 Å), P(3)–C(2) (1.715 Å), or P(3)–C(1) (1.743 Å), which all involve dicoordinate phosphorus atoms <1998AGE1083>. The five-membered ring in 2*H*-1,3,2-diazaphospholenes (e.g., structures **37** and **40**) exhibits an envelope conformation in which the phosphorus atom is out of the plane containing the other four ring atoms <2006JA3946, 2000AGE3084>. The five-membered ring in the stable P-heterocyclic carbene **49** (m.p. 123–127 °C) is slightly deviated from planarity (*trans*-arrangement of the 2,4,6-*tert*-butylphenyl substituents), which makes molecule **49** chiral in the solid state <2005AGE1700>. A strong donation of the phosphorus lone pairs to the electron-deficient carbene center in molecule **49** is clearly apparent from the P–C(1) bond lengths (1.673 and 1.710 Å), which are significantly shorter than normal P–C single bonds (>1.80 Å) <2005AGE1700>.

In addition to compounds shown in **Figure 3**, numerous X-ray structures of transition metal complexes with heterophosphole ligands have been reported. Representative examples include 2*H*-1,3,2-diazaphosphole, 2*H*-1,4,2-diazaphosphole, and Δ³-1,3,2-oxazaphospholene tungsten(0) complexes <1998CEJ1542>; 2*H*-1,3,2-diazaphosphole platinum(0) complex <1999IC4056>; iridium complexes with 1,2,3-azadiphosphole ring system <2000CC1659>; 2,3-dihydro-1,2,4-selenadiphosphole complexes of Cr, Mo, and W <2002JOM(659)84>; η¹-W(CO)₅, η⁵-W(CO)₅, and η⁵-Mo(CO)₃ complexes of the 1,2,4-thiadiphosphole ring <2002JOM(655)7>; platinum(II) 1,3,4-thiadiphosphole complex <2000JA4557>; scandium 1,2,4-triphosphole complex <2003AGE1038>; 2,3-dihydro-1*H*-1,2,4-triphosphole tungsten complex <2002JOM(650)198>; gold(I) 1,2,4-triphospholyl complex <2002JOM(643)357>; and zinc and cadmium 1,2,4-triphospholyl complexes <2001JOM(633)143>. Several X-ray structures of 1,2,4-triphospholyl complexes of main group metals, such as complexes of magnesium <2005OM5789>, gallium <2002JOM(646)191>, and thallium <2002JOM(646)191>, were also reported. Structural features of heterophosphole metal complexes were systematized in CHEC-II(1996) <1996CHEC-II(4)771>.

6.13.3.2 NMR Spectroscopy

A detailed discussion on ³¹P, ¹³C, and ¹⁵N nuclear magnetic resonance (NMR) spectra of various heterophospholes can be found in CHEC-II(1996) <1996CHEC-II(4)771>. A low-field chemical shift in ³¹P NMR (δ 50–400 ppm) is characteristic for heterophosphole phosphorus atoms. For example, the following δ³¹P chemical shifts were reported for some of the structures shown in **Figure 3**: diazaphospholene **37** δ³¹P = 71.6 ppm <2006JA3946>, diazaphospholene **39** δ³¹P = 110.7 ppm <2000CEJ3414>, compound **41** δ³¹P = 71 ppm <2001JOM(623)116>, compound **42** δ³¹P = 116.9 ppm <2003JOM(682)212>, compound **48** δ³¹P = 60.0 and 71.5 ppm <2006AGE2598>, stable P-heterocyclic carbene **49** δ³¹P = 73 and 85 ppm <2005AGE1700>, azadiphosphole **50** δ³¹P = 262.5 and 153.5 ppm <1999CC2363>, triphosphole **54a** δ³¹P = 327.4 (1P) and 159.8 (2P) ppm <1999CEJ3143>, triphosphole **54b**

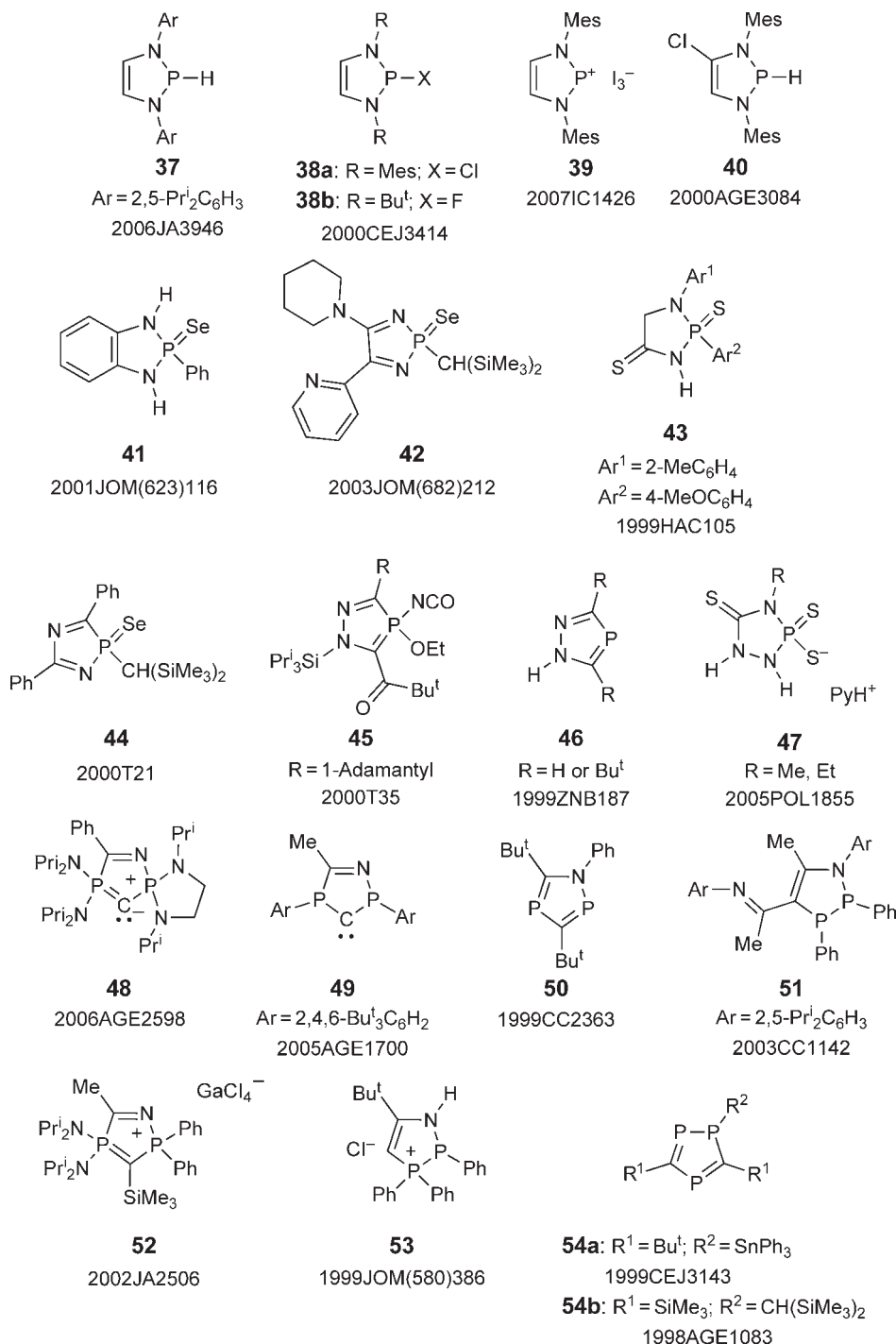


Figure 3 Recently reported single crystal X-ray structures of phosphole systems with three and four heteroatoms (transition metal complexes are not included).

$\delta^{31}\text{P} = 288.3, 180, \text{ and } 179 \text{ ppm}$ <1998AGE1083>. A detailed description of ^{13}C and ^1H NMR spectra for compounds **37–54** can also be found in publications listed in [Figure 3](#).

Detailed multinuclear NMR studies and analysis of coupling constants in various diazaphospholes were reported in several recent publications <2007POL837, 2002HAC340, 2001SPE27>.

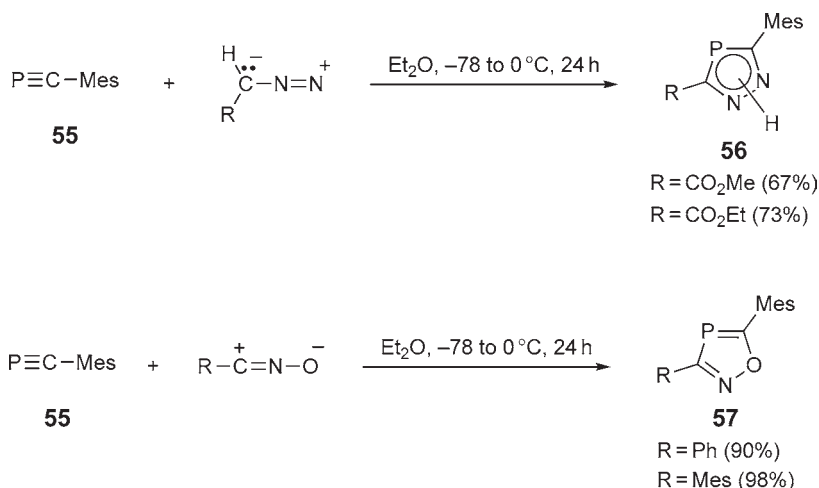
6.13.4 Syntheses and Reactions of Particular Classes of Compounds

This section provides an update on the synthesis, properties, and reactivity of heterophospholes with three or four heteroatoms. The section structure and compound classification are the same as in the original Chapter 4.22 of CHEC-II(1996) <1996CHEC-II(4)771>.

6.13.4.1 1,2,4-Diaza-, 1,2,4-Oxaza-, and 1,2,4-Thiazaphospholes

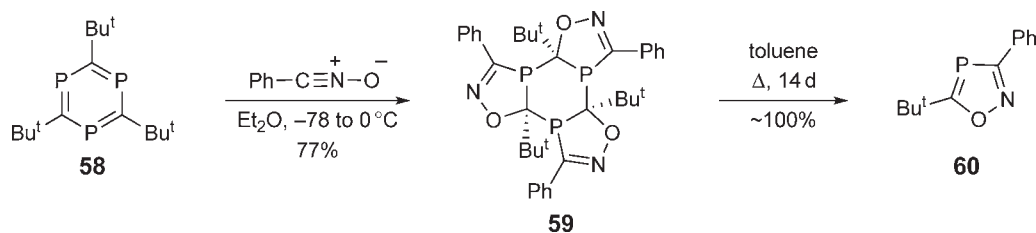
1,2,4-Diaza **1**, 1,2,4-oxaza- **7**, and 1,2,4-thiaza- **10** phospholes are colorless to pale yellow, distillable oils or solids, which may exhibit a characteristic unpleasant penetrating smell <1996CHEC-II(4)771>. Monocyclic 1,2,4-diazaphospholes are fairly unreactive; they are stable to hydrolysis even when by concentrated hydrochloric acid. They are degraded, however, by 30% aqueous hydrogen peroxide and bromine to phosphoric acid and PBr_3 <1996CHEC-II(4)771>. CHEC-II(1996) provides a detailed description of the chemistry of these compounds. Almost no new results have been reported on the chemistry of 1,2,4-diaza-, 1,2,4-oxaza-, and 1,2,4-thiazaphospholes since the publication of CHEC-II(1996).

A new synthetic approach to heterophospholes based on the [3+2] cycloaddition reactions of phosphalkynes has been developed by Regitz and co-workers <1998S1305>. In specific examples, a mixture of tautomeric 1,2,4-diazaphospholes **56** was prepared by cycloaddition of phosphalkyne **55** and diazo compounds, while 1,2,4-oxazaphospholes **57** were prepared similarly from phosphalkyne **55** and appropriate nitrile oxides (Scheme 1) <1998S1305>.



Scheme 1

In a recent publication, the formation of the previously known 1,2,4-oxazaphosphole **60** by a quantitative [2+2+2] cycloreversion reaction of adduct **59**, which was prepared from benzonitrile oxides and triphosphinine **58**, was reported (Scheme 2) <2004S241>.

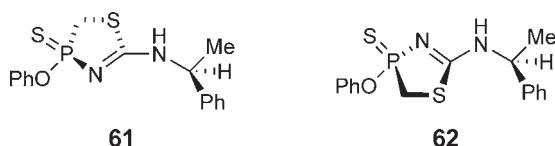


Scheme 2

6.13.4.2 1,4,2-Diazaphospholes and 1,3,4-Thiazaphospholes

A detailed description of the chemistry of 1,4,2-diazaphospholes **2**, **3**, and 1,3,4-thiazaphospholes **11** is provided in CHEC-II(1996) <1996CHEC-II(4)771>. The 1,4,2-diazaphospholes are colorless to pale yellow crystalline solids with a characteristic naphthalene-like smell and are stable toward atmospheric oxygen. They do not react with sulfur, selenium, or methyl iodide but can be alkylated with dimethyl sulfate at the two-coordinate nitrogen atom. Hydrolysis opens the diazaphosphole ring to give a zwitterionic 2-aminopyridinio-methylphosphonite; methanol adds to the P=C bond. The 1,3,4-thiazaphospholes are colorless, yellow, or red crystalline solids; the 2-phenyl derivative is a pale yellow liquid. They are not oxidized by atmospheric oxygen or sulfur, but can be methylated by dimethyl sulfate or trimethyloxonium tetrafluoroborate, which methylates the nitrogen atom <1996CHEC-II(4)771>.

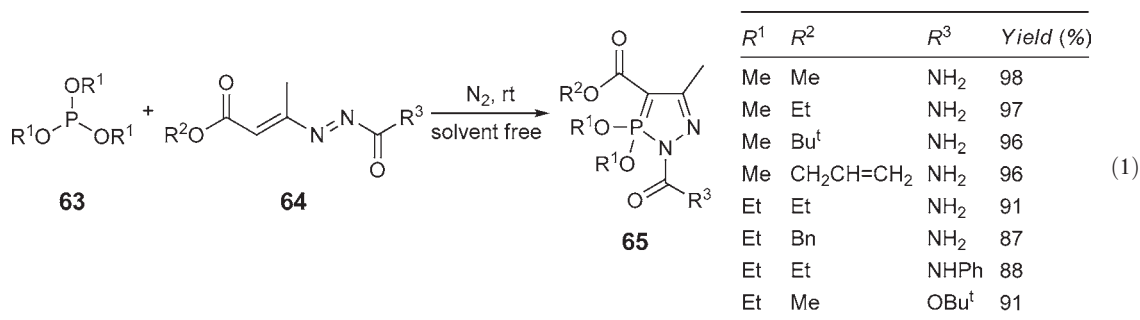
Very little new data have been obtained in this area since the publication of CHEC-II(1996). In a recent work, the optically active enantiomeric 1,3,4-thiazaphospholes **61** and **62** were synthesized by the reaction of *O*-phenyl(chloromethyl)isothiophosphonate with (*R*)-(+)- and (*S*)-(-)-(1-phenyl)ethylamine <2006SL1613>.



6.13.4.3 1,2,3-Diazaphospholes

1,2,3-Diazaphospholes **4** and **5** are colorless to pale yellow distillable liquids or crystalline solids that are stable to oxidation by air and do not react with elemental sulfur. They are readily hydrolyzed to give the hydrazone from which they originate and phosphorus acid. While only a few reactions of 1*H*-1,2,3-diazaphospholes **4** are reported, the chemistry of the 2*H*-isomers **5** is well studied. In CHEC-II(1996), the following reactions of 1,2,3-diazaphospholes are described in detail: N-protonation and alkylation, polar addition to the P=C bond and substitution at C-4, cycloaddition reactions, substituent reactions, and the formation of transition metal complexes <1996CHEC-II(4)771>.

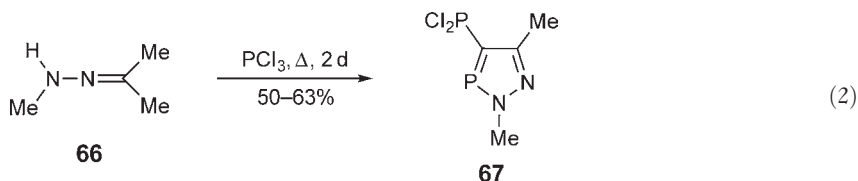
No new results on the chemistry of 1*H*-1,2,3-diazaphospholes **4** have been reported and only few papers on 2*H*-1,2,3-diazaphospholes have appeared since the publication of CHEC-II(1996). A new synthetic approach to alkyl 3,3-dialkoxy-2*H*-1,2,3-diazaphosphole-4-carboxylates **65** by the reaction between trialkyl phosphates **63** and 1,2-diaza-1,3-butadienes **64** and under solvent-free conditions in nitrogen atmosphere was recently reported (Equation 1) <2005JOC4033>.



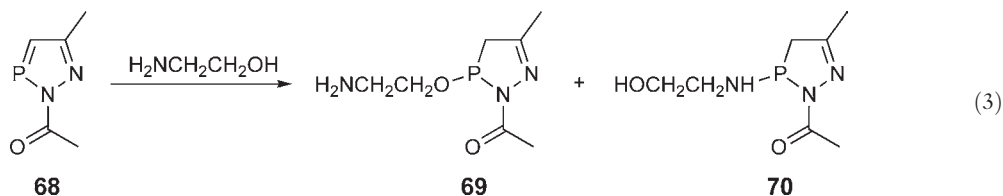
A synthesis of 4-cyano-2,3-dihydro-3-hydroxy-2,5-diphenyl-1*H*-1,2,3-diazaphosphole 3-oxide from hydrazidoyl halide PhC(Cl)=NNHPh and diethylphosphonoacetonitrile in the presence of sodium ethoxide was reported <2004PS(179)521>.

Mikoluk and Cavell have reported an improved preparation of 4-(dichlorophosphino)-2,5-dimethyl-2*H*-1,2,3-diazaphosphole **67** via condensation of acetone methylhydrazone **66** with an excess of phosphorus trichloride (Equation 2) <1999IC1971>. The two chlorine substituents in compound **67** can be replaced with two fluorine,

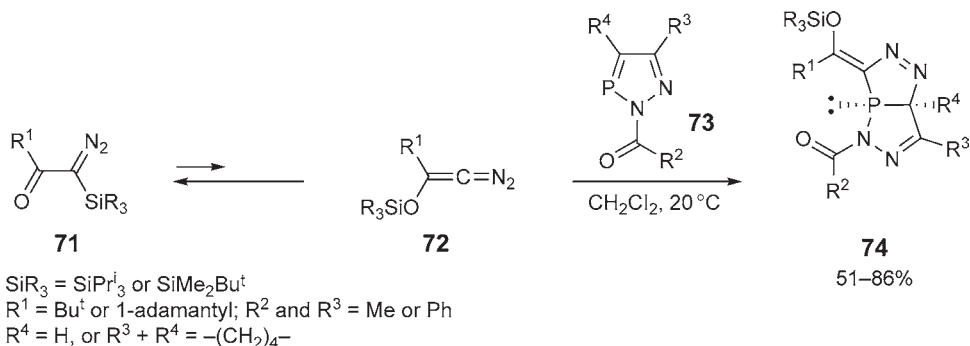
dimethylamino, diethylamino, bis(propyl)amine, pyrazole, 3,5-dimethylpyrazole, 2,2,2-trifluoroethoxy, phenoxy, pentafluorophenoxy, 2,6-difluorophenoxy, and pentafluorobenzoxy substituents via treatment with the appropriate nucleophiles <1999IC1971>.



In a series of publications, Cherkasov and co-workers reported reactions of 2-acetyl-5-methyl-2*H*-1,2,3-diazaphosphole **68** with ethanolamine leading to adducts **69** and **70** (Equation 3) <2006RJC495>, and the addition reactions of diazaphosphole **68** with butane-2,3-diol <2004MC212>, ethanol <2002RJC323>, trichloro(*o*-phenylenedioxy)phosphorane <2000RJC984>, tetrafluoropropanol <2000RJC154>, and phosphorylsulfonyl chlorides <1998RJC1411>.



Kerth and Maas have reported reactions of 2-acyl-1,2,3-diazaphospholes **73** with diazo ketones **71** to form bicyclic compounds **74**, the products of a 1,3-dipolar cycloaddition reaction of diazoalkenes **72**, which are in equilibrium with diazo ketones **71** (Scheme 3) <1999EJO2633>.



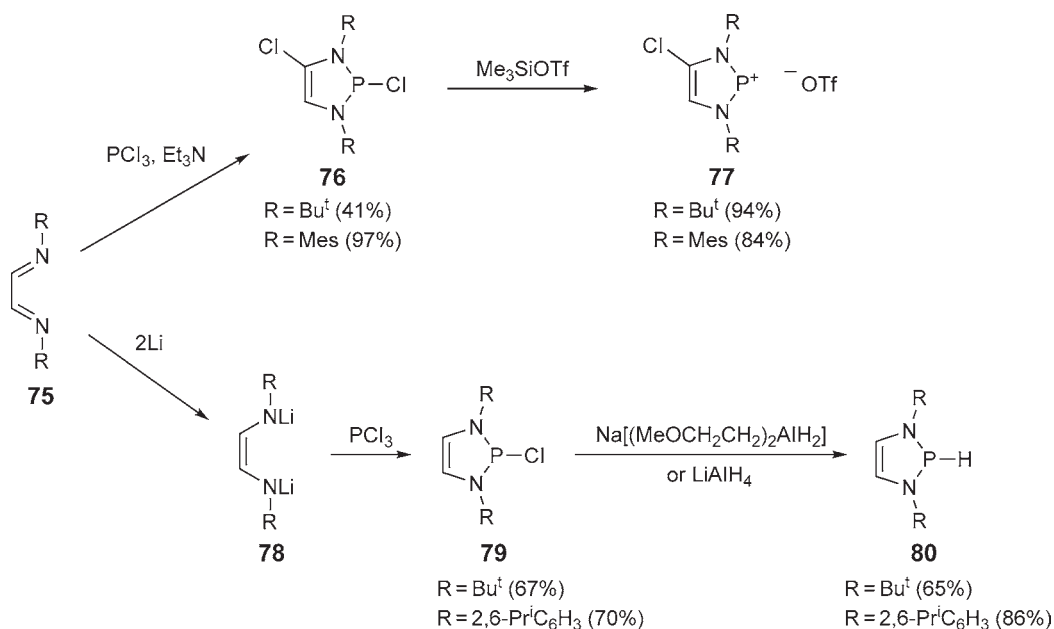
Scheme 3

The preparation of several transition metal complexes with derivatives of 1*H*-1,2,3-diazaphosphole as ligands has also been reported <1999IC4056, 1999OM3306, 1999IC2791>. A detailed description of diazaphosphole complexes including coordination modes with different metals is provided in CHEC-II(1996) <1996CHEC-II(4)771>.

6.13.4.4 1,3,2-Diaza-, 1,3,2-Oxaza-, and 1,3,2-Thiazaphospholes

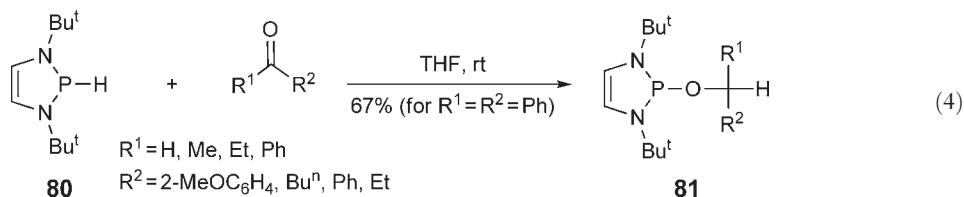
1,3,2-Diazaphospholes **6** are colorless to pale yellow distillable liquids or crystalline solids that are stable to oxidation by air and do not react with elemental sulfur. 1,3,2-Oxazaphospholes **8** and 1,3,2-thiazaphospholes **9** are mainly known as benzo and fused derivatives. In CHEC-II(1996), only the chemistry of 4,5-dicyano-1,3,2-diazaphosphole, 1,3,2-benzodiazaphospholes, 1,3,2-benzoxazaphospholes, and 1,3,2-benzothiazaphospholes is discussed <1996CHEC-II(4)771>. No significant new results on the chemistry of 1,3,2-oxaza- and 1,3,2-thiazaphospholes have been reported since the publication of CHEC-II(1996).

In a series of recent publications, the preparation and structure of various P-substituted 1,3,2-diazaphospholenes and 1,3,2-diazaphospholenium salts **37–40**, **76**, **77**, **79**, and **80** was reported <2006JA3946, 2000CEJ3414, 2007IC1426, 2000AGE3084, 1999EJ141>. The most common synthetic approach to 1,3,2-diazaphospholenes **76** and **79** includes the reaction of phosphorus trichloride with 1,4-diazadienes **75** or its lithium adduct **78** (Scheme 4) <2000CEJ3414, 2006JA3946>. 2-Hydrido-1,3,2-diazaphospholenes **80** and various other substituted 1,3,2-diazaphospholenes and 1,3,2-diazaphospholenium salts (e.g., triflate **77**) can be prepared by exchanging chlorine in the readily available chlorides **76** and **79**. In a recently published procedure, 1,3,2-diazaphospholenium salt **39** (see Figure 3) was prepared in 87% yield by a direct reaction of 1,4-diazadiene **75** (R = Mes) with phosphorus triiodide in dichloromethane solution <2007IC1426>.



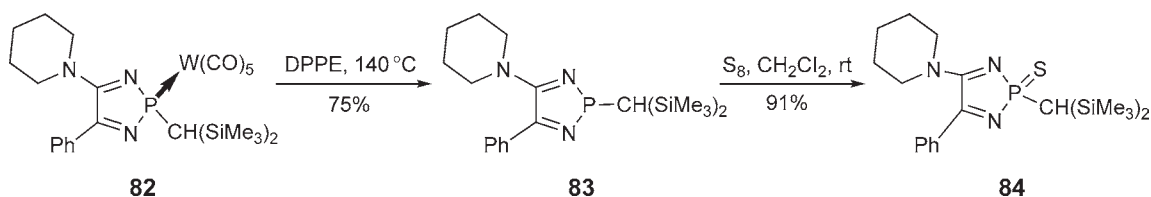
Scheme 4

The pure 2-hydrido-1,3,2-diazaphospholenes **80** are light yellow liquids or solids that are highly air and moisture sensitive. They are highly reactive toward carbonyl compounds; for example, the reaction of compound **80** with ketones and aldehydes is completed in several minutes affording products of reduction of the carbonyl function **81** in high yield (Equation 4) <2006JA3946>.

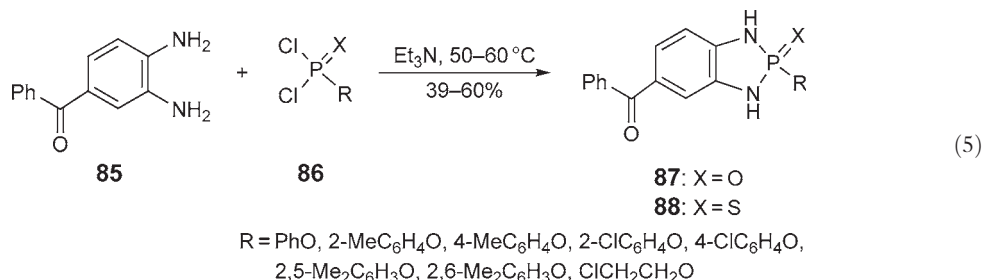


The decomplexation of 2*H*-1,3,2-diazaphosphole complex **82** <1998CEJ1542> by heating to 140 °C for 4 days in the presence of 1,2-bis(diphenylphosphino)ethane (DPPE) afforded 2*H*-1,3,2-diazaphosphole derivative **83** in 75% yield. Derivative **83** reacted with elemental sulfur at room temperature to give the corresponding 2*H*-1,3,2-diazaphosphole *P*-sulfide **84** (Scheme 5) <2000T21>. The analogous 2-pyridyl derivative **42** shown in Figure 3 was prepared by a similar procedure <2003JOM(682)212>.

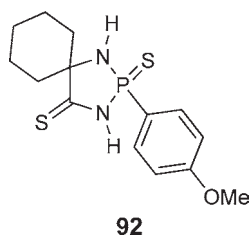
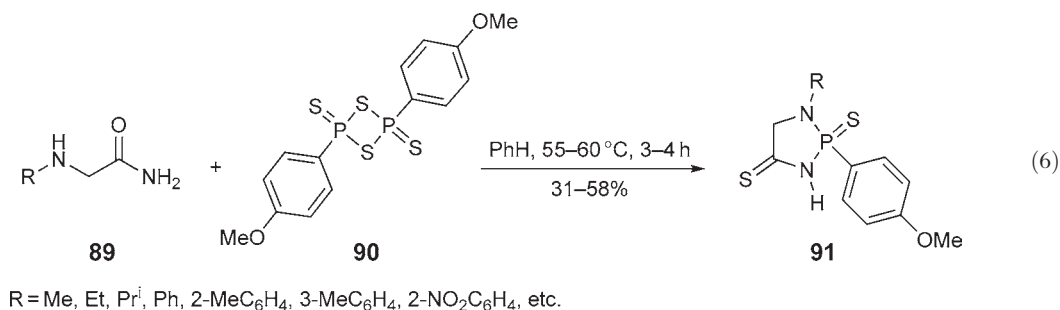
Syntheses of several 2-substituted-2,3-dihydro-5-benzoyl-1*H*-1,3,2-benzodiazaphosphole 2-oxides **87** and 2-sulfides **88** were accomplished by reactions of 3,4-diaminobenzophenone **85** with various phosphorodichloridates **86** in the presence of triethylamine (Equation 5) <2002HAC340>.



Scheme 5



Various 1,3,2-diazaphospholidin-4-thione-2-sulfides **91** were prepared in moderate yield by the reaction of 3-substituted glycinamides **89** with Lawesson's reagent **90** in benzene at 55–60 °C (Equation 6) <1999HAC105, 1997PS(129)111>. A similar procedure based on the reaction of Lawesson's reagent **90** with α -aminonitriles was used for the synthesis of 1,3,2-diazaphospholidine-4-thione-2-sulfide derivative **92** <2001S2445>.



The preparation of several tungsten(0) complexes involving derivatives of 2*H*-1,3,2-diazaphosphole <2001EJI3175, 1998CEJ1542, 2003OM5427> and 1,3,2-thiazaphosphole <2002HAC72, 1999CC499> as ligands has also been reported.

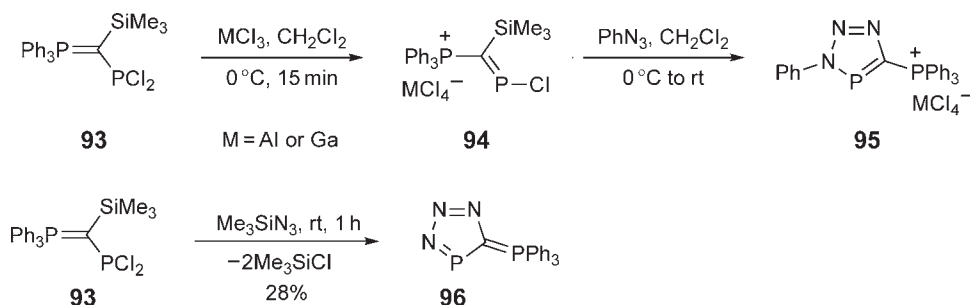
6.13.4.5 1,3,2-Dithia- and 1,3,2-Diselenaphospholium Salts

Only benzo derivatives of 1,3,2-dithiaphospholium salts **12** and the analogous 1,3,2-diselenaphospholium salts are known, and the chemistry of these compounds is covered in a short subsection of Chapter 4.22 of CHEC-II(1996) <1996CHEC-II(4)771>. No significant new results on the chemistry of these compounds have been reported since the publication of CHEC-II(1996).

6.13.4.6 1,2,3,4-Triazaphospholes

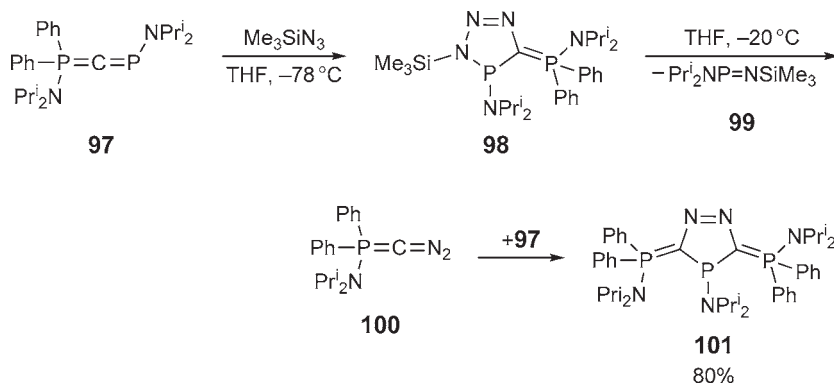
1,2,3,4-Triazaphospholes **13** and **14** are colorless distillable liquids or crystalline solids. The reactivity and synthesis of 1,2,3,4-triazaphospholes and the related triazaphospholium salts are briefly overviewed in CHEC-II(1996) <1996CHEC-II(4)771>. A few new reports on 3*H*-1,2,3,4-triazaphospholes **13** have been published <2005EJI2619, 2000T35, 1998S1305, 1997BSB455, 1997CB89>, and no publications on 2*H*-1,2,3,4-triazaphospholes **14** have appeared in the last decade.

Schroedel and Schmidpeter reported the preparation of triphenylphosphonio-substituted 1,2,3,4-triazaphospholes **95** by cycloaddition reactions of phosphonium salts **94** (generated *in situ* from dichlorophosphane **93**) with phenyl azide (Scheme 6). A novel phosphoniotriazaphospholide **96** was prepared by the reaction of dichlorophosphane **93** with trimethylsilyl azide and isolated in 28% yield as a relatively stable colorless powder with decomposition point above 105 °C <1997CB89>.



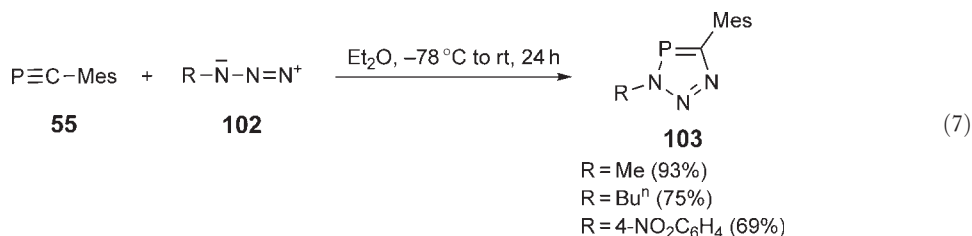
Scheme 6

In a recent work <2005EJI2619>, an unstable phosphoniotriazaphospholide **98** was generated by [3+2] cycloaddition of diphosphaallene **97** with trimethylsilyl azide and identified by low-temperature NMR. Above -20 °C, phosphoniotriazaphospholide **98** undergoes a clean fragmentation into iminophosphane **99** and diazomethylenephosphorane **100**, which can also act as a 1,3-dipole for the diphosphaacumulene **97** to afford heterocycle **101** as the final product (Scheme 7) <2005EJI2619>.

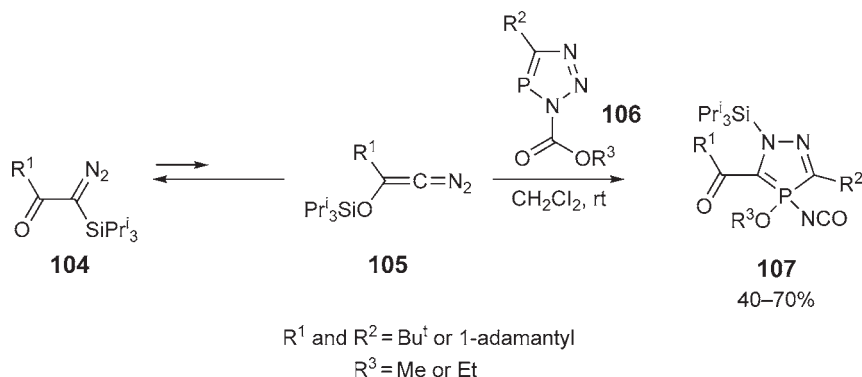


Scheme 7

A synthetic approach to 1,2,3,4-triazaphospholes based on the [3+2] cycloaddition reactions of phosphaaalkynes with azides was developed by Regitz and co-workers <1998S1305, 1997BSB455>. In a specific example, 1,2,3,4-triazaphospholes **103** were prepared in good yields by cycloaddition of phosphaaalkyne **55** and azides **102** under mild reaction conditions (Equation 7) <1998S1305>.



Maas and co-workers have reported reactions of 1,2,3,4-triazaphospholes **106** with diazo ketones **104** to form diazaphospholes **107**, the products of a 1,3-dipolar cycloaddition reaction of diazoalkenes **105**, which are in equilibrium with diazo ketones **104** (Scheme 8) <2000T35>.

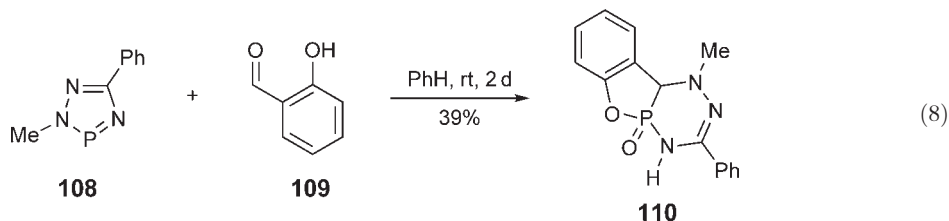


Scheme 8

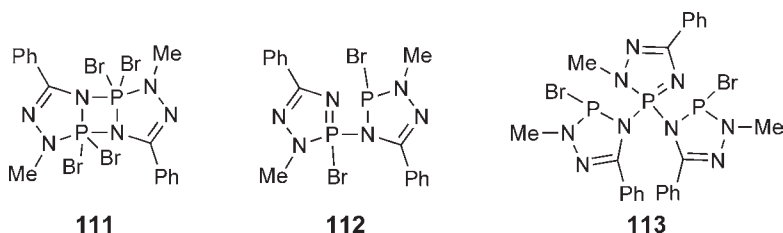
6.13.4.7 1,2,4,3-Triazaphospholes and 1,3,4,2-Thiadiazaphospholium Salts

The 1,2,4,3-triazaphospholes are colorless or pale yellow distillable liquids or crystalline solids. They are not oxidized by air and are reluctant to react with sulfur. Three isomeric heterocyclic systems of 2*H*-1,2,4,3-triazaphospholes **15**, 1*H*-1,2,4,3-triazaphospholes **16**, and 4*H*-1,2,4,3-triazaphospholes **17** are known and they differ considerably in their behavior <1996CHEC-II(4)771>. The synthesis of 1,2,4,3-triazaphospholes and reactivity of different isomers of 1,2,4,3-triazaphospholes in the reactions at a ring nitrogen, in the addition to the P=N bond, oxidative addition to the ring phosphorus, cycloaddition reactions, and the formation of transition metal complexes are systematically covered in CHEC-II(1996) <1996CHEC-II(4)771>. The 1,3,4,2-thiadiazaphospholium ions **18** are only briefly mentioned in CHEC-II(1996) and no new results on their chemistry have been published in the last decade.

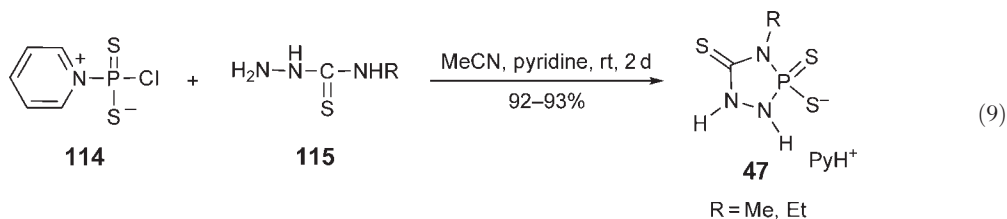
Only few new reports on the chemistry of 1,2,4,3-triazaphospholes have appeared after the publication of CHEC-II(1996). Schmidpeter *et al.* reported several new reactions of 2-methyl-5-phenyl-1,2,4,3-triazaphosphole **108** <1996CB1493, 1996PS(118)129>. In particular, salicylaldehyde **109** adds to triazaphosphole **108** to yield the bicyclic phosphonic amide **110**, whose structure was established by single crystal X-ray analysis. Substituted salicylic aldehydes as well as 2-hydroxyacetophenone and benzophenone react with triazaphosphole **108** in the same way. A stepwise mechanism was proposed for this reaction involving a Michaelis–Arbuzov rearrangement in the penultimate step (Equation 8) <1996CB1493>.



The formation and reactivity of several oligocyclic derivatives **111–113** from the partial bromination of 2-methyl-5-phenyl-1,2,4,3-triazaphosphole **108** was reported by the same group <1996PS(118)129>.



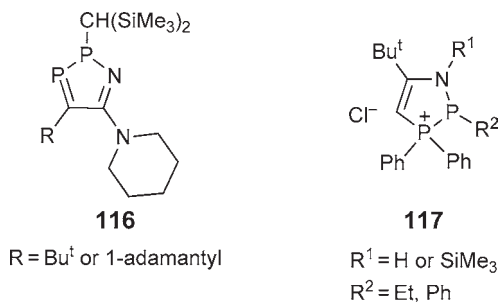
In a recent paper, the preparation of 3-sulfido-3,5-dithioxo-1,2,4,3-triazaphospholidine derivatives **47** by the reaction of chlorodithiophosphoric acid pyridiniumbetaine **114** and monosubstituted thiosemicarbazides **115** was reported (Equation 9) <2005POL1855>.



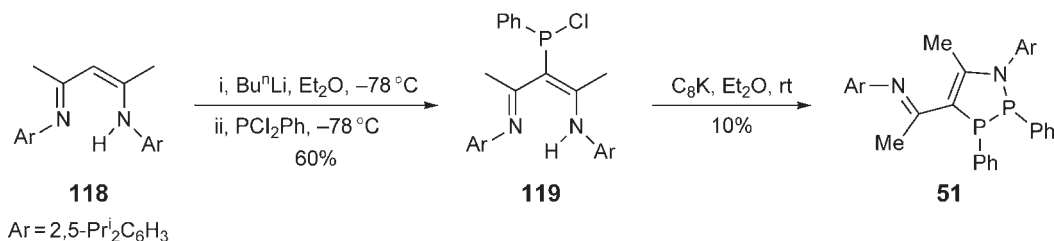
The preparation and alcoholysis of several platinum(II) and palladium(II) complexes involving 2-methyl-5-phenyl-1,2,4,3-triazaphosphole and 1,5-dimethyl-1,2,4,3-triazaphosphole as the ligands has also been reported <1997ICA(265)47>.

6.13.4.8 1,2,3-Azadiphospholes

The heterocyclic system of 1,2,3-azadiphosphole **20** is relatively uncommon. The preparation and properties of the 1,3-diphospholyl-substituted 1,2,3-azadiphospholes and 1,2,3-benzazadiphospholes are briefly discussed in CHEC-II(1996) <1996CHEC-II(4)771>. In a more recent research, several representatives of this structural class (e.g., compounds **116** <2000CC1659> and **117** <2005EJ11955, 1999JOM(580)386, 1997JOM(529)243>) were prepared and used as ligands in the transition metal complexes.



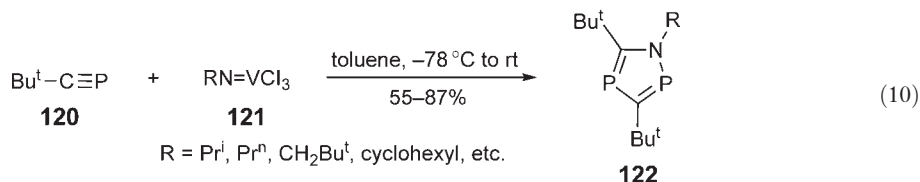
A stable crystalline heterocycle **51** was prepared in two steps by treatment of the β -diketimine **118** with butyllithium and PCl₂Ph followed by the reductive dechlorination of the intermediate product **119** (Scheme 9) <2003CC1142>.



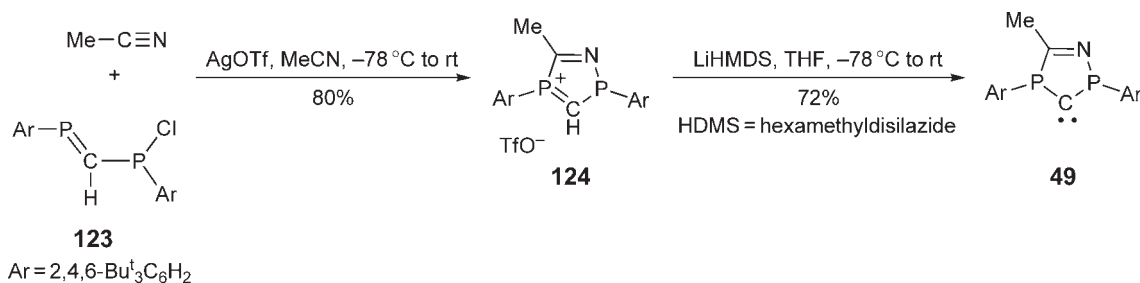
Scheme 9

6.13.4.9 1,2,4-Azadiphospholes

1,2,4-Azadiphospholes **19** are only briefly mentioned in CHEC-II(1996) <1996CHEC-II(4)771>. A new synthetic approach to various substituted 1,2,4-azadiphospholes based on the cycloaddition reaction of the kinetically stabilized phosphalkynes with imidovanadium(v) or imidotitanium(IV) complexes has recently been developed <1999CC2363, 2000CEJ4558>. In a specific example, reactions of an excess of the phosphalkyne **120** with the vanadium complex **121** furnish the corresponding 1,2,4-azadiphospholes **122** in good yields (Equation 10) <2000CEJ4558>.



The synthesis and structural study of the stable P-heterocyclic carbene **49** and related structures (e.g., structures **48** and **52**; see Figure 3) have attracted some recent research activity <2005AGE1700, 2002JA2506, 2006AGE2598, 2006AGE7447>. The synthesis of the stable P-heterocyclic carbene **49** was accomplished in two steps: (1) a formal [3+2] cycloaddition of the readily available phosphalkene **123** with acetonitrile in the presence of silver triflate afforded salt **124**, and (2) the isolated and recrystallized salt **124** was deprotonated by lithium hexamethyldisilazide in tetrahydrofuran (THF) to afford carbene **49** as relatively stable light-yellow crystals (Scheme 10) <2005AGE1700>.



Scheme 10

6.13.4.10 1,2,3,5-Diazadiphospholes

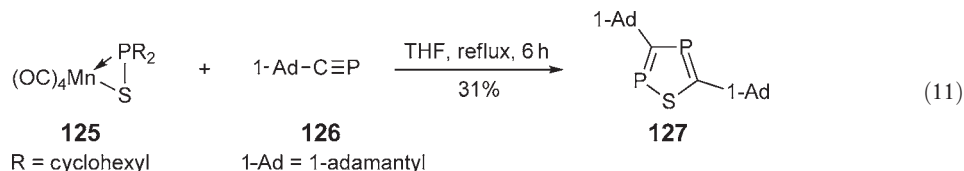
Only few examples of 1,2,3,5-diazadiphospholes **23** were reported in the literature. The preparation of 1-phenyl-1,2,3,5-diazadiphosphole by the condensation of methylene bis(dichlorophosphine) and a hydrazine in the form of a colorless, air-sensitive liquid is described in CHEC-II(1996) <1996CHEC-II(4)771>. No new research on the preparation and chemistry of 1,2,3,5-diazadiphospholes has been published in the last decade.

6.13.4.11 1,2,4-, 1,2,5-, and 1,3,4-Thiadiphospholes

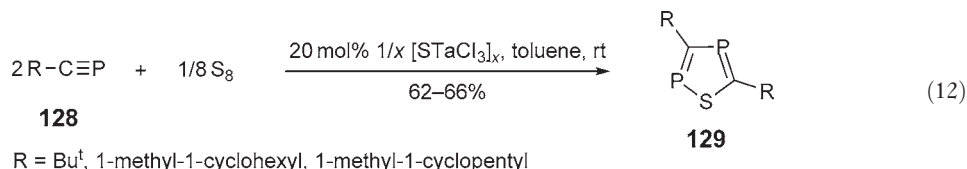
The preparation and chemistry of 1,2,4-thiadiphospholes **21** and 1,2,5-thiadiphospholes **22** are very briefly discussed in CHEC-II(1996) <1996CHEC-II(4)771>. Only one example of a 1,2,5-thiadiphosphole, namely 3,4-bis(trifluoromethyl)-1,2,5-thiadiphosphole, has been reported in the literature as a highly reactive, air-sensitive oil <1996CHEC-II(4)771>. No new research on 1,2,5-thiadiphospholes has been published in the last decade. The heterocyclic system of 1,3,4-thiadiphosphole was unknown at the time of publication of CHEC-II(1996).

3,5-Disubstituted-1,2,4-thiadiphospholes can be prepared by the reaction of thiophosphinato manganese or cobalt complexes with the kinetically stabilized phosphalkynes <1996JOM(524)67, 1996CHEC-II(4)771>. In a specific example, 3,5-di(1-adamantyl)-1,2,4-thiadiphosphole **127** was prepared by the reaction of the (η^2 -thiophosphinito)manganese

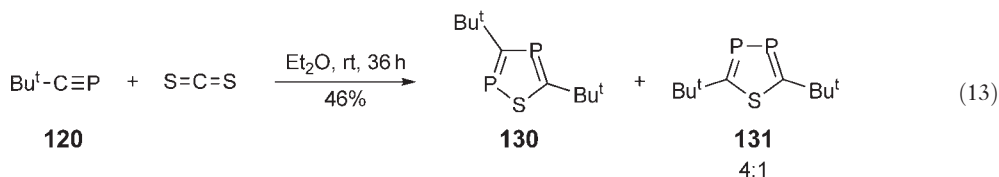
complex **125** with 2 equiv of phosphalkyne **126** (Equation 11). 1,2,4-Thiadiphosphole **127** was isolated as a stable crystalline solid (m.p. 192–195 °C) and its structure was determined by a single crystal X-ray diffraction analysis <1996JOM(524)67>.



A new approach to 1,2,4-thiadiphospholes **129** via a regiospecific reaction of phosphalkynes **128** with sulfur in the presence of the polymeric thiotantalum(v) sulfide [STaCl₃]_x was reported by Regitz and co-workers (Equation 12) <2002EJO1664>.



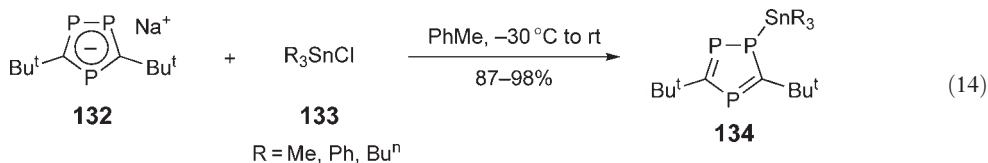
The reaction of phosphalkyne **120** with CS₂ (or its ylide-type complexes) gives a mixture of 3,5-di-*tert*-butyl-1,2,4-thiadiphosphole **130** and 2,5-di-*tert*-butyl-1,3,4-thiadiphosphole **131** (Equation 13), which were characterized by NMR spectroscopy <2000JA4557>. Product **131** belongs to the previously unknown heterocyclic system of 1,3,4-thiadiphosphole; it was also characterized by a single crystal X-ray structure analysis of its bis(platinum(II)) complex <2000JA4557>. In a more recent work, several similar 1,3,4-thiadiphospholes were selectively prepared by the reaction of imidovanadium(v) complex Bu^tN=VCl₃ and the phosphalkynes **128** (R = Bu^t, 1-adamantyl, CMe₂Et, and 1-methyl-1-cyclohexyl) with an excess of elemental sulfur <2003ZNB44>. The preparation of a metal-coordinated 1,3,4-thiadiphosphole was also reported by Weber *et al.* <1997OM3188>.



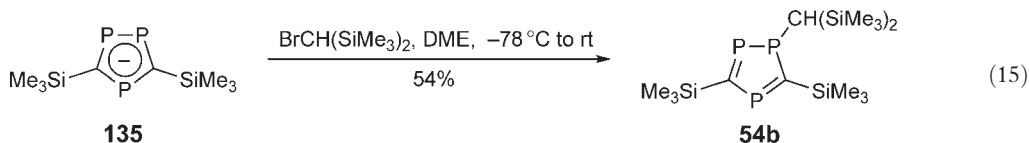
The preparation of several [M(CO)₅] complexes involving 1,2,4-thiadiphospholes as the ligands has also been reported <2002JOM(655)7, 2002JOM(659)84>.

6.13.4.12 1,2,3-Tri-, 1,2,4-Tri-, and Tetraphospholes and Phospholides

In CHEC-II(1996), the chemistry of tri-, tetra-, and pentaphospholide anions is briefly overviewed and the references to earlier reviews are provided <1996CHEC-II(4)771>. Neutral 1,2,3-triphospholes **34**, 1,2,4-triphospholes **24** and **35**, and tetraphospholes **36** usually are unstable compounds, which have been extensively investigated theoretically (see also Section 6.13.2) <2001CRV1229, 1998AGE1083, 1999JOM(588)28, 2004JCD2080, 2004OM5308, 1998IC4413, 2006PCA10148, 2005CPH(313)123>. A few stable neutral triphosphole derivatives were experimentally prepared and described in recent publications <1998AGE1083, 1999CEJ3143>. The stable 1-triorganylstannyl-1,2,4-triphospholes **134** were synthesized by the reaction of sodium triphospholyl derivative **132** (prepared from phosphalkyne **120** and sodium amalgam) with triorganylstannyl chlorides **133** (Equation 14) <1999CEJ3143>. The structure of the triphenylstannyl-1,2,4-triphosphole derivative **134** (R = Ph) was established by single crystal X-ray analysis.



Similarly, 1-[bis(trimethylsilyl)methyl]-3,5-bis(trimethylsilyl)-1,2,4-triphosphole **54b**, whose structure was determined by X-ray diffraction (see [Figure 3](#)), was synthesized by the reaction of 3,5-bis(trimethylsilyl)-1,2,4-triphospholide anion **135** with $(\text{Me}_3\text{Si})_2\text{CHBr}$ ([Equation 15](#)) [<1998AGE1083>](#).



The anionic species and metal complexes of 1,2,3-tri-, 1,2,4-tri-, and tetraphospholides **25–27** are relatively stable and have been extensively investigated. Specific examples of such complexes are listed in [Section 6.13.3.1](#).

6.13.5 Important Compounds and Applications

6.13.5.1 Applications in Research

In CHEC-II(1996), several applications of dihydro-2*H*-1,2,3-diazaphospholes, generated *in situ* from a ketone hydrazone and PCl_3 , as useful intermediates for the synthesis of indoles, pyrroles, pyrrolylacetates, and 1,2-dihydro-2-alkenyl-3*H*-pyrazol-3-ones are listed [<1996CHEC-II\(4\)771>](#).

During the last decade, various heterophospholes have found wide application as ligands for the transition metal complexes. Specific examples of such complexes are listed in [Section 6.13.3.1](#).

6.13.5.2 Biological Activity

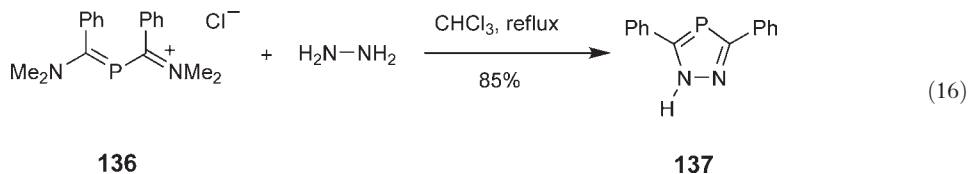
A strong antifungal activity against *Aspergillus flavus*, *Penicillium notatum*, *Helminthosporium anomalum*, and *Fusarium oxysporum* and antibacterial activity (tested on *Bacillus subtilis* and *Klebsiella pneumoniae*) were found for 2,3-dihydro-5-benzoyl-1*H*-1,3,2-benzodiazaphosphole 2-oxides **87** and 2-sulfides **88** (see [Section 6.13.4.4](#)) [<2002HAC340>](#).

A significant antimicrobial activity against *Staphylococcus aureus* and *Escherichia coli* and antifungal activity on *Aspergillus niger* and *Helminthosporium oryzae* were also found for 2-(2-chloroethyl) and 2-allyl-2,3-dihydro-5-benzoyl-1*H*-1,3,2-benzodiazaphosphole 2-oxides [<2004CPB307>](#).

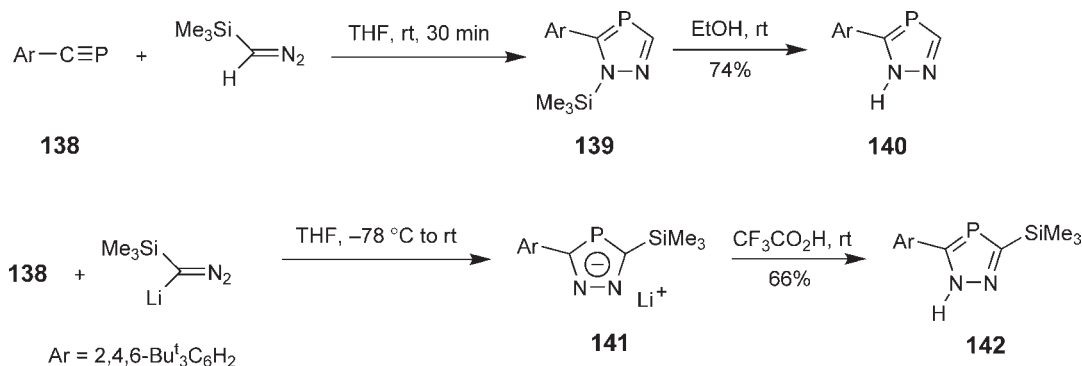
Some of the 1,3,2-diazaphospholidin-4-thione 2-sulfides **91** (see [Section 6.13.4.4](#)) show significant selective herbicidal activity at 3.0 kg ha^{-1} [<1999HAC105>](#).

6.13.6 Further Developments

The preparation, structural characterization, and computational studies of several 1,2,4-diazaphospholes have recently been reported [<2007T9129, 2007EJI3491>](#). 1*H*-3,5-Diphenyl-1,2,4-diazaphosphole **137** was prepared by the reaction of 1,3-bis(dimethylamino)-2-phosphaallyl chloride **136** and hydrazine in chloroform in good yield ([Equation 16](#)) [<2007T9129>](#). The structure of compound **137** was established by X-ray diffraction, and the geometry of this product and several other 1,2,4-diazaphospholes was rationalized by DFT calculations at the B3LYP/6-311++G(d,p) level [<2007T9129>](#).



The extremely sterically hindered 1,2,4-diazaphospholes **139–142** were prepared via [2+3] cycloaddition reaction of 2-(2,4,6-tri-*tert*-butylphenyl)-1-phosphaethyne **138** with trimethylsilyldiazomethane derivatives ([Scheme 11](#)). Structures of 1,2,4-diazaphospholes **140** and **142** were investigated by NMR spectroscopy and X-ray diffraction. The experimental structural studies as well as theoretical calculations confirmed aromatic character of these 1,2,4-diazaphospholes. The crystal structure of compounds **140** and **142** showed remarkable hydrogen bonding character in relation to molecular aggregation due to the presence of the bulky aryl groups [<2007EJI3491>](#).



Scheme 11

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Biographical Sketch



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6.14

Three or Four Heteroatoms including at least One Arsenic or Antimony

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6.14.1	Introduction	603
6.14.2	Spectra, Structure, and Bonding	604
6.14.2.1	Theoretical Methods	604
6.14.2.2	X-Ray Diffraction	604
6.14.2.3	NMR Spectra	606
6.14.3	1,2,4-Diazaarsoles	606
6.14.4	1,4,2-Diazaarsolide Anions	606
6.14.5	1,3,2-Diazaarsolium Cations	607
6.14.5.1	Properties and Reactivity	607
6.14.5.2	Synthesis	607
6.14.6	1,3,2-Diazastibolium Cations	608
6.14.6.1	Properties and Reactivity	608
6.14.6.2	Synthesis	608
6.14.7	1,3,2-Benzodiazaarsolide Anion	608
6.14.8	1,2,4- and 1,4,2-Diphosphaarsolide Anions, 1,2,4- and 1,4,2-Diphosphaarsoles	609
6.14.8.1	Reactivity	609
6.14.8.2	Synthesis	609
6.14.9	1,4,2-Diphosphastibolide Anions	609
6.14.9.1	Properties and Reactivity	609
6.14.9.2	Synthesis	611
6.14.10	Pentaarsolide Complexes	611
	References	611

6.14.1 Introduction

While heteroarsoles and heterostiboles with just one other heteroatom in addition to the As or Sb ring member are covered in Chapters 4.15 and 4.16, those with two nitrogen, sulfur, or phosphorus ring members in addition to the arsenic or antimony atom in the ring are covered in this chapter. The corresponding chapter of CHEC-II(1996) is Chapter 4.23 <1996CHEC-II(4)819>. Again, only 6 π -systems and their anellated derivatives are included and, as has been discussed in the earlier chapters, they generally necessitate two-coordinate arsenic or antimony ring members. All the presently known ring systems are collected in Figure 1. Up to now, no arsoles and stiboles with more than two additional heteroatoms have been reported. They may not have been looked for, but also may not be stable as monomers. A dimerization has been experienced for a 1,2,3-diazaarsole and 1,3,2-benzazaphosphastibole <1996CHEC-II(4)819>. Neither are there arsoles or stiboles yet known with more than one As or Sb ring member. The only exceptions are some pentaarsolide complexes.

Of the systems listed in Figure 1, only those that have been developed or were newly added to the list during the last decade are discussed below. All the other systems can be found in CHEC-II(1996) <1996CHEC-II(4)819>. Their syntheses are also described in volume 13 of *Science of Synthesis* <2004HOU641, 2004HOU689, 2004HOU717, 2004HOU729, 2004HOU771>.

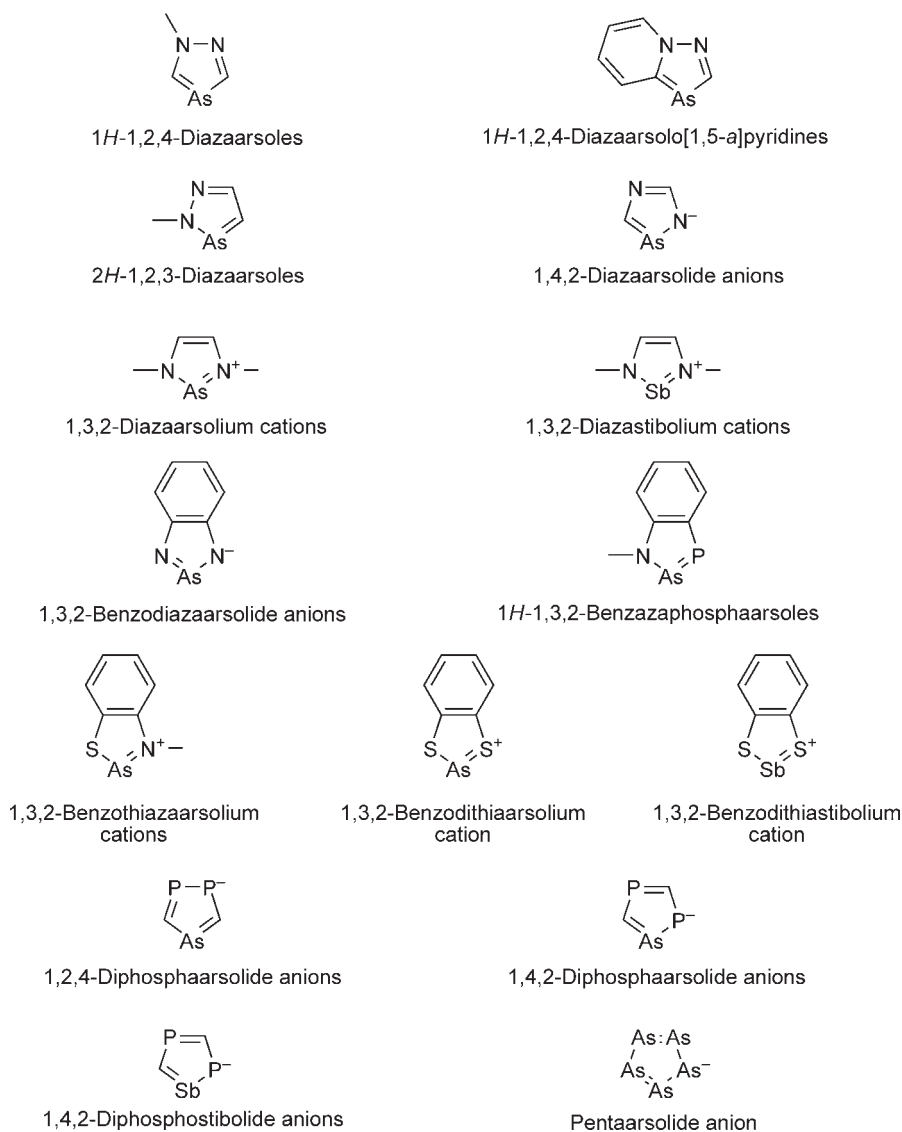


Figure 1 Known arsole and stibole systems with three and more heteroatoms.

6.14.2 Spectra, Structure, and Bonding

6.14.2.1 Theoretical Methods

The interactions of 1,3,2-diazaarsolium and 1,3,2-diazaastibolium ions in halides and in complexes have been calculated <2005HAC327, 2005ZFA1403>.

The calculated relative stability of 1,2,4- and 1,4,2-diphosphaarsoles agree with the experimental results <2002JBS597>.

6.14.2.2 X-Ray Diffraction

The molecular structures of diazaphospholes and diazaastiboles from X-ray diffraction studies are compiled in **Tables 1** and **2**. In every case, the five-membered ring is planar. In compound **10** (Equation 3) also, the tricyclic skeleton of its cation is planar.

Table 1 Arsenic bond angle (°) and bond lengths (pm) in neutral and anionic diazaarsoles from X-ray structure analysis

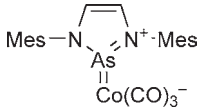
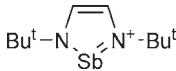
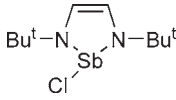
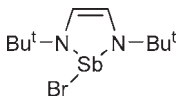
Compound	Angle	Bonds	Reference
	81.1(2)	AsC 182.7(8), 184.7(8)	1999ZNB187
	81.7(7)	AsC 182.1(1), 189(1)	1992HAC151
	84.4(1)	AsC 183.3(3), AsN 184.2(2)	1983DOK(268)885
	80.4(7)	AsC 180(1), AsN 193(1)	1996HAC123
	87.1(1) 86.8(1)	AsC 186.3(3), AsN 182.5(3) AsC 185.1(3), AsN 182.7(3)	2004ZFA1811
	93.9(1)	AsN 178.6(3), 178.9(3)	2001CC2480

Table 2 Bond angles (°) and bond lengths (pm) in 1,3,2-diazaarsolium and 1,3,2-diazastibolium cations and derivatives from X-ray structure analysis (see also <2006JA2800>)

	NAsN	AsN SbN	NC	CC	Reference
	86.2(4)	181.0(9) ^a 181.2(9)	138(1) 138(2)	136(2)	1997CC2095
		183.8(1) ^b 182.7(1)	134.6(2) 135.2(2)	136.2(2)	2005HAC327
	84.9(5)	182.3(10) ^c 183.1(11)	137.2(16) 133.9(16)	137.5(18)	2006CC1784
	85.0(5)	181.8(10) ^c 180.9(10)	135.7(17) 139.3(15)	135.1(18)	
		180.5(1) 180.6(1)	138.2(2) 138.3(2)	134.8(2)	2005HAC327
	85.4(1)	184.6(2) 183.5(2)	139.4(3) 139.6(3)	133.0(3)	2005ZFA1403

(Continued)

Table 2 (Continued)

	<i>NAsN</i>	<i>AsN</i> <i>SbN</i>	<i>NC</i>	<i>CC</i>	<i>Reference</i>
	85.5(1)	181.1(2) 180.7(3)	138.1(4) 138.1(4)	135.5(5)	2005ZFA1403
		201.8(2) ^b 202.0(2)	135.4(3) 134.9(3)	136.4(4)	2005HAC327
		202.3(2) ^d 202.5(2)	135.6(3) 135.3(3)	136.4(4)	2005HAC327
		199.8(4) 200.0(4)	140.7(6) 139.1(6)	134.6(6)	2005HAC327
		199.8(2) 199.4(3)	138.6(4) 139.1(4)	134.6(4)	2005HAC327

^aGeCl₅[−]/Cl[−] anions.^bTfO[−] anion.^cSnCl₅ THF[−] anion.^dSbCl₄[−] anion.

In the 1,4,2-diazaarsolide **1** (Equation 1) and 1,3,2-benzodiazaarsolide **15** (Equation 4), the anion is N-coordinated to the lithium cation, in compound **1** N-1-monodentate, in compound **15** N-1,3-bidentate and chain forming.

While the 1,4,2-diphosphastibolide anion has no contact with the cation in the Li(12-crown-4)₂ and Li(TMEDA)₂ salts **22** (Scheme 7) <1997JOM291>, it is $\mu\text{-}\eta^5\text{:}\eta^5$ -coordinated in the Tl and K(DME) compounds (TMEDA = tetramethylethylenediamine; DME = 1,2-dimethoxyethane) <1998OM3826, 2001JOM61>, and η^5 -coordinated in the (C₅Me₅)Pb compound <1999JCD4057>. The 1,4,2-diphosphastibolide salts and complexes co-crystallize with the corresponding 1,2,4-triphospholide compounds. Because of the site disorder at Sb they are not valid for comment on the bond lengths and angles.

6.14.2.3 NMR Spectra

In their ³¹P{¹H} nuclear magnetic resonance (NMR) spectra, the 1,4,2-diphosphastibolide salts display an AX spin system ($\delta_A = 278$ ppm, $\delta_X = 309$ ppm, $J_{AX} = 55$ Hz) with the low field signal considerably broadened, which suggests that it originates from the phosphorus atom adjacent to the quadrupolar antimony center <1997JOM291, 2001JOM61>.

6.14.3 1,2,4-Diazaarsoles

N-unsubstituted 1,2,4-diazaarsoles are obtained from the condensation of 1,3-bis(dimethylamino) 2-arsaallylic chlorides with hydrazine <1986TL2957> or by the cycloaddition of ethyl diazoacetate to *in situ*-generated chloroarsaalkenes <1989TL349, 2002HC(59)539>. Due to their high proton mobility they readily undergo N-alkylation <1995HAC403>. In the solid state, the molecules of the parent compound are connected to each other by NH⋯N hydrogen bonds forming a helix along a crystallographic axis (Figure 2); for other structural features, see Table 1 <1999ZNB187>.

6.14.4 1,4,2-Diazaarsolide Anions

Treatment of benzonitrile with Bu^tAsLi₂ in tetrahydrofuran (THF) gives the lithium 1,4,2-diazaarsolide **1** formally by the loss of Bu^tLi (Equation 1). On the addition of diglyme and TMEDA, crystals of product **1** are obtained in which

the lithium cations are tetrahedrally coordinated either by two diglyme molecules or by a TMEDA molecule and two diazaarsolide anions. The latter coordinate monodentate by N-1 <2004ZFA1811>.

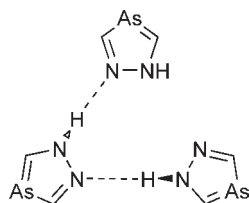
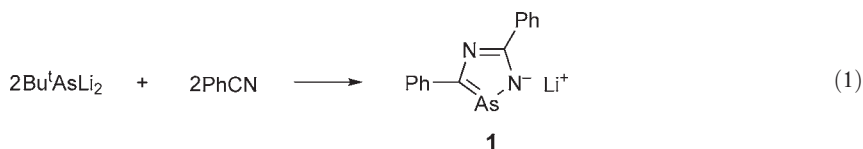


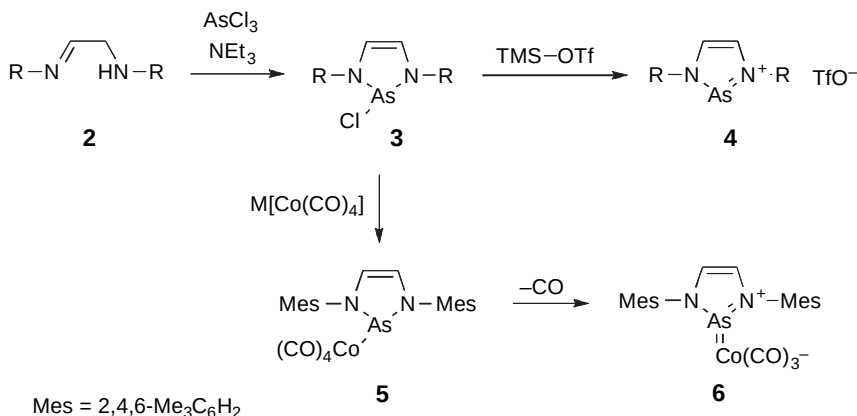
Figure 2 Crystal structure of N-unsubstituted 1,2,4-diazaarsoles.



6.14.5 1,3,2-Diazaarsolium Cations

6.14.5.1 Properties and Reactivity

The 1,3,2-diazaarsolium triflates **4** ($\text{R} = \text{Bu}^t$, Mes) are obtained as colorless, air- and moisture-sensitive crystals from $\text{Et}_2\text{O}/\text{MeCN}$. The respective chlorides **3** are regarded as covalent compounds. The association of the chloride ion is accompanied by an ^{15}N shielding of ~ 110 ppm <2005HAC327>. The 1,3,2-diazaarsolium $\text{Co}(\text{CO})_3$ complex **6** has been obtained from the chloride **3** and $\text{Tl}[\text{Co}(\text{CO})_4]$ via the tetracarbonyl complex **5** and loss of CO (Scheme 1) <2005ZFA1403>.



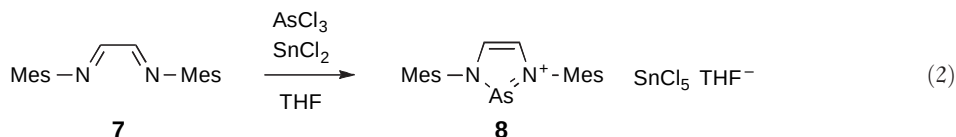
Scheme 1

6.14.5.2 Synthesis

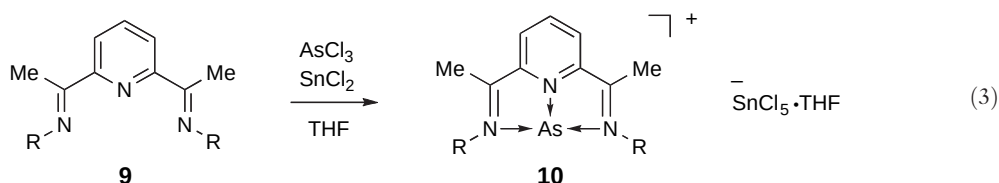
The reaction of α -amino aldimines **2** ($\text{R} = \text{Bu}^t$, Mes) in toluene with AsCl_3 in presence of NEt_3 as acid scavenger gives the 2-chloro-1,3,2-diazaarsolenes **3** (Scheme 1). With trimethylsilyl triflate, they are converted to the 1,3,2-diazaarsolium triflates **4** <2005HAC327>.

Originally, 1,3,2-diazaarsolium salts, $\text{R} = \text{Bu}^t$, were prepared by reacting a cyclic diaminogermylene or a bis(lithio-amino)ethylene with AsCl_3 <1997CC2095>.

Treatment of an equimolar mixture of AsCl_3 and SnCl_2 with the 1,4-dimesityl diimine **7** resulted in 84% yield of the 1,3,2-diazaarsolium pentachlorostannate **8** (Equation 2). The reaction is interpreted as reduction of AsCl_3 to arsenic(i) and its oxidative trapping by the diimine **7** <2006CC1784, 2006JA2800, 2007ICA329>.



The same treatment, but using the diiminopyridine **9**, $\text{R} = 2,6\text{-diisopropylphenyl}$, as trapping ligand, yielded the salt **10**, the cation of which may be regarded a 1,3,2-diazaarsolium derivative (Equation 3). Its metrical parameters indicate however that As(i) has not been oxidized by the ligand in this case. From the reaction of the diiminopyridine **9** with AsI_3 a salt like **10**, but with $\text{As}_2\text{I}_8^{2-}$ as the counterion, has been isolated <2006CC1784>.



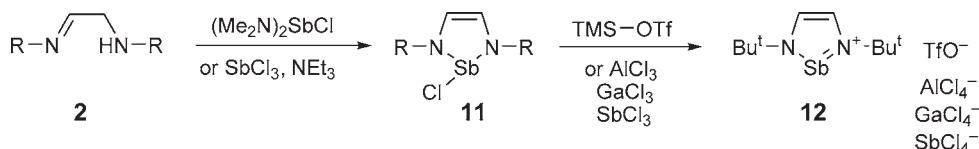
6.14.6 1,3,2-Diazaastibolium Cations

6.14.6.1 Properties and Reactivity

The 1,3,2-diazaastibolium salts **12** ($\text{R} = \text{Bu}^t$, Mes) are obtained as yellow, air- and moisture-sensitive crystals from $\text{Et}_2\text{O}/\text{MeCN}$. The 1,3,2-diazaastibolium chloride, bromide, and iodide are regarded as covalent compounds. The association of the chloride ion is accompanied by a ^{15}N shielding of some 120 ppm and by an additional Raman band assigned to the $\nu(\text{Sb}-\text{Cl})$ stretch mode <2005HAC327>.

6.14.6.2 Synthesis

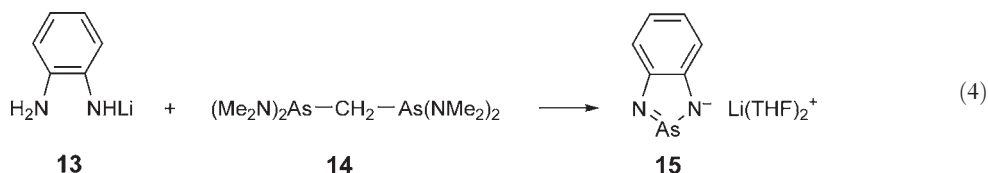
Similar to the corresponding arsolenes, the 2-chloro-1,3,2-diazaastibolenes **11** are prepared from α -amino aldimines **2** ($\text{R} = \text{Bu}^t$, Mes) by transamination with $(\text{Me}_2\text{N})_2\text{SbCl}$ or by condensation with $\text{SbCl}_3/\text{NEt}_3$ (Scheme 2). The 2-bromo derivative is obtained in an analogous way. Conversion of chloride **11** ($\text{R} = \text{Bu}^t$) into the 1,3,2-diazaastibolium salts **12** can be achieved with different chloride acceptors <2004CC2434, 2005HAC327>.



Scheme 2

6.14.7 1,3,2-Benzodiazaarsolide Anion

The reaction of lithiated 1,2-diaminobenzene **13** with the methylene diarsane **14** (4:1 ratio) in toluene unexpectedly yielded the lithium 1,3,2-benzodiazaarsolide **15**, isolated as coordination polymer (Equation 4). Attempts to prepare the 1,3,2-benzodiazaarsolide **15** from $\text{As}(\text{NMe}_2)_3$ failed <2001CC2480>.



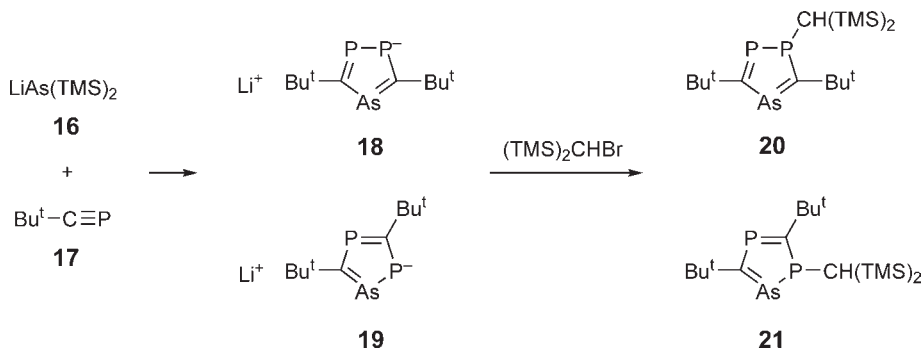
6.14.8 1,2,4- and 1,4,2-Diphosphaarsolide Anions, 1,2,4- and 1,4,2-Diphosphaarsoles

6.14.8.1 Reactivity

The then known complex chemistry of the diphosphaarsolides has been mentioned in CHEC-II(1996) <1996CHEC-II(4)819>.

6.14.8.2 Synthesis

The reaction of lithium bis(trimethylsilyl)arsenide **16** with the phosphaaalkyne **17** yields an approximately equimolar mixture of lithium 1,2,4- and 1,4,2-diphosphaarsolide **18** and **19** as has been reported in CHEC-II <1994JOM45, 1995OM4382, 1996CHEC-II(4)819>. Alkylation of this mixture with bis(trimethylsilyl)bromomethane in DME gives exclusively the 1*H*-1,2,4- and 1*H*-1,4,2-diphosphaarsoles **20** and **21** (Scheme 3). The two isomers could not be separated <2002JBS597>.



Scheme 3

Calculations explain the preferential alkylation of phosphorus. The calculated inversion barrier of a pyramidal phosphorus atom in the ring is low compared to that for a pyramidal arsenic atom <2002JBS597>.

6.14.9 1,4,2-Diphosphastibolide Anions

6.14.9.1 Properties and Reactivity

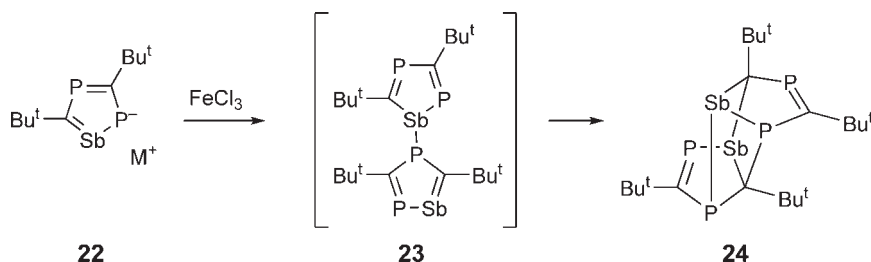
By slow crystallization from petroleum spirit, pure 1,4,2-diphosphastibolide **22** ($\text{M} = \text{Li}(\text{TMEDA})_2$) is obtained as yellow crystals and has been structurally characterized <2000OM1713>.

The reaction of 1,4,2-diphosphastibolide **22** ($\text{M} = \text{Li}(\text{TMEDA})_2$) with TlCl affords the thallium(I) 1,4,2-diphosphastibolide with $\mu-\eta^5:\eta^5$ coordinated rings <1998OM3826>. Also, the $\text{C}_5\text{Me}_5\text{Pb}$ -1,4,2-diphosphastibolide complex has been prepared <1999JCD4057>.

The 1,4,2-diphosphastibolide ring has been incorporated into a series of organometallic complexes <2003AHC1>. Examples of its η^5 -coordination <1996CC1591, 1997JCD2183, 1997JOM89, 1999JCD4057, 2000OM1713>.

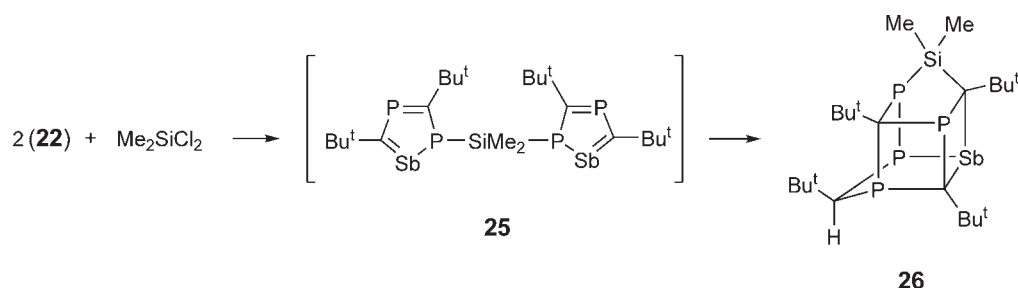
η^2 -coordination <2000OM1713>, and η^1 -coordination <1997JCD2183, 1997JCD4321> are known, as well as η^4 -coordination with simultaneous protonation of the anion at the 3-position <1997JOM89>.

Treatment of a DME solution of FeCl_3 with 1 equiv of 1,4,2-diphosphastibolide **22** ($\text{M} = \text{Li}(\text{TMEDA})_2$) leads to the formation of the air- and moisture-stable cage compound **24** in 61% yield. The reaction probably involves an initial oxidation to give the intermediate **23** which then undergoes a [4+2] cycloaddition reaction to give the tetracyclic product **24** (Scheme 4). InCl_3 , PbCl_2 , or SbF_3 can also be used as the oxidants in this reaction <1997CC305, 1997JCD4321, 1999JCD4057>.



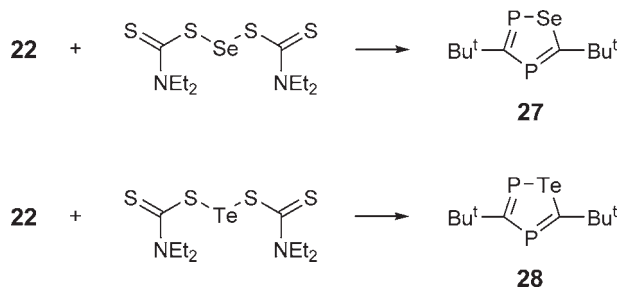
Scheme 4

The reaction of 2 equiv of 1,4,2-diphosphastibolide **22** ($\text{M} = \text{K}(\text{DME})_2$) with Me_2SiCl_2 leads to the formation of the hexahetero-1,3-bishomocubane **26**, presumably via compound **25** as an intermediate (Scheme 5) <2001JOM61>.



Scheme 5

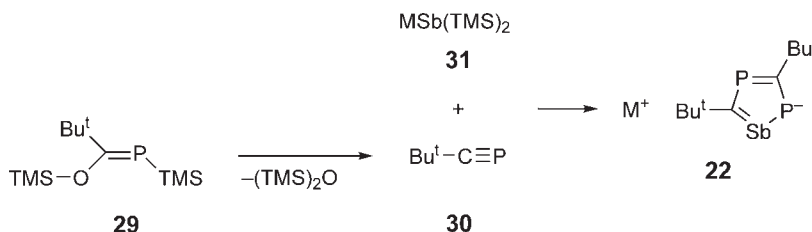
The 1,4,2-diphosphastibolides also open a novel synthetic route to chalcogenadipospholes (Chapter 6.13). Treatment of 2 equiv of 1,4,2-diphosphastibolide **22** ($\text{M} = \text{Li}(\text{TMEDA})_2$) with selenium or tellurium diethyldithiocarbamate leads to the formation of 1,2,4-selenadiposphole **27** or 1,2,4-telluradiposphole **28** in 60% and 32% yield, respectively (Scheme 6) <1999TL3815>.



Scheme 6

6.14.9.2 Synthesis

The synthesis of alkali metal 1,4,2-diphosphastibolides parallels that of the 1,4,2-diphosphaarsolides **18** and **19**. It is however regiospecific and no 1,2,4-isomer is formed. For the synthesis, a DME solution of lithium bis(trimethylsilyl)antimonide **31** ($M = \text{Li}$) is treated with 3 equiv of the phosphalkene **29**. In the course of the reaction, the phosphalkene **29** is converted to the phosphalkyne **30** via the base-catalyzed elimination of hexamethyl disiloxane (Scheme 7). Alternatively, the phosphalkyne **30** can be used directly in place of the phosphalkene. After addition of TMEDA or 12-crown-4, the lithium 1,4,2-diphosphastibolide **22** ($M = \text{Li}(\text{TMEDA})_2$ or $\text{Li}(12\text{-crown-4})_2$) is isolated <1997JOM291>.



Scheme 7

Starting from the potassium bis(trimethylsilyl)antimonide **31** ($M = \text{K}$) prepared *in situ* from the reaction of KOBu^t and $\text{Sb}(\text{TMS})_3$, the potassium 1,4,2-diphosphastibolide **22** ($M = \text{K}(\text{DME})_2$) is formed in the same way <2001JOM61>. In every case, the 1,4,2-diphosphastibolide is contaminated with ca. 25% of the corresponding 1,2,4-triphospholide (see Chapter 6.13). The components of this mixture cannot be separated by fractional crystallization.

6.14.10 Pentaarsolide Complexes

For the pentaarsolide ring in complexes, η^5 - and $\mu\text{-}\eta^5\text{:}\eta^2$ -coordination has been observed <1990JOMC21, 1995AGE1321>.

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Biographical Sketch



Alfred Schmidpeter took his PhD at Munich University in 1960 with Egon Wiberg. His research contributions since then have been in different fields of organophosphorus and organoarsenic chemistry, such as phosphazenes, aminophosphine tautomers, oligocyclic phosphoranes, azaphospholes, two-coordinate phosphorus and arsenic in conjugated cyclic and acyclic systems. He was Professor of Inorganic Chemistry at the University of Munich since 1975 and retired in 1997.



Konstantin Karaghiosoff received his PhD in 1986 from Munich University under the supervision of Alfred Schmidpeter. In his Thesis he developed the synthesis of many new heterophospholes. Further interests of him include phosphorus selenide derived anions and cations, as well as the analysis of NMR spectra of high order. He is Professor of Chemistry at the University of Munich.

6.15

Three or Four Heteroatoms including at least One Boron

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6.15.1	Introduction	616
6.15.2	Theoretical Methods	616
6.15.3	Experimental Structural Methods	617
6.15.4	Thermodynamic Aspects	618
6.15.5	Reactivity of Fully Conjugated Rings	619
6.15.6	Reactivity of Nonconjugated Rings	619
6.15.7	Reactivity of Substituents Attached to Ring Carbon Atoms	620
6.15.8	Reactivity of Substituents Attached to Ring Heteroatoms	620
6.15.8.1	Reactions of B–H bond: Hydroboration	620
6.15.8.1.1	Hydroboration of alkenes and alkynes	620
6.15.8.1.2	Transition metal-catalyzed hydroboration	621
6.15.8.1.3	Hydroboration of fluoroalkenes	623
6.15.8.1.4	Chiral hydroboration of alkenes	623
6.15.8.1.5	<i>trans</i> -Hydroboration of terminal alkynes	624
6.15.8.2	Reactions of B–H bond: Reduction	624
6.15.8.2.1	Asymmetric reduction of ketones	624
6.15.8.2.2	Chiral hydroxythiol-catalyzed reduction of ketones	625
6.15.8.2.3	Reduction of ketophosphonates	625
6.15.8.2.4	Reduction of β -hydroxysulfinylimines	626
6.15.8.2.5	Reduction of tosylhydrazones	626
6.15.8.2.6	Reduction of sulfoxides to sulfides	627
6.15.8.3	Reactions of B–H and B–C: Cross-Coupling	627
6.15.8.3.1	Transition metal-catalyzed cross-coupling	627
6.15.8.3.2	Borylation of aryl halides	627
6.15.8.3.3	Dehydrogenative borylation	628
6.15.8.4	Reactions of B–C: Stereoselective Allylation/Alkylation	630
6.15.8.4.1	Racemic allyl boronates	630
6.15.8.4.2	Chiral allyl boronates	631
6.15.8.4.3	Allylboration of imines	633
6.15.8.4.4	Allylboration of α -ketoesters	633
6.15.8.4.5	Allylboration of vinylnitrones	633
6.15.8.4.6	Bora-ene reaction of SO ₂ and allyl boronates	634
6.15.8.4.7	Lewis acid-assisted allylboration of aldehydes	635
6.15.8.4.8	Transfer aminoallylation	635
6.15.8.4.9	Palladium-catalyzed allylation	636
6.15.8.4.10	Lewis acid-catalyzed allylation of 2-vinylloxiranes	637
6.15.8.5	Reactions of B–C: Diels–Alder Reactions	637
6.15.8.6	Reactions of B–C: Cycloadditions	637
6.15.8.7	Reactions of B–C: Radical Conjugate Additions	638
6.15.8.8	Reactions of B–X	638
6.15.8.9	Reactions of B–Si	640

6.15.8.10	Reactions of B–Cu	642
6.15.9	Ring Syntheses from Acyclic Compounds Classified by Number of Ring Atoms Contributed by Each Compound	644
6.15.10	Ring Syntheses by Transformations of Another Ring	645
6.15.11	Syntheses of Particular Classes of Compounds and Critical Comparison of the Various Routes Available	645
6.15.11.1	Ring Systems Containing Boron and Two Oxygen Atoms	645
6.15.11.2	Ring Systems Containing Boron, Oxygen, and Nitrogen Atoms	646
6.15.11.3	Ring Systems Containing Boron and Two Nitrogen Atoms	646
6.15.11.4	Ring Systems Containing Boron and Other Heteroatoms	647
6.15.11.5	Ring Systems Containing Boron and Multiple Heteroatoms	647
6.15.12	Important Compounds and Applications	648
6.15.13	Further Developments	649
6.15.13.1	Theoretical Methods	649
6.15.13.2	Thermodynamic Aspects	649
6.15.13.3	Reactivity of Fully Conjugated Rings	649
6.15.13.4	Reactions of B–X	649
6.15.13.5	Reactions of B–Si	649
6.15.13.6	Ring Systems Containing Boron and Multiple Heteroatoms	651
	References	651

6.15.1 Introduction

For the last four decades, there has been an exponential increase in the synthesis and usage of a number of organic and inorganic boron compounds in industry and academia. Due to the explosive growth of heterocyclic boron-containing compounds, this topic is covered as a separate chapter here. Previously, the subject of this chapter was covered in a subsection of Chapter 4.24 in CHEC-II(1996) (Sections 4.24.1.3.6 and 4.24.1.3.7). This chapter covers as much literature as possible, but the space restraints did not permit a comprehensive coverage of all literature.

The pioneering research by Nobel Laureate Herbert C. Brown and several others led to the discovery of numerous protocols available for the preparation of several boron-containing molecules as well as a new continent of boron chemistry. One of the important methods for the synthesis of the organoboranes involves the hydroboration of alkenes. A variety of functional groups such as alcohols, amines, aldehydes, ketones, carboxylic acids, etc., are readily obtained by further transformations of organoboranes. Accordingly, the rapid increase of boronated molecules in general and heterocyclic (boracyclic) compounds in particular has led to the addition of this section involving five-membered heterocycles with three or four heteroatoms including at least one boron atom as a separate chapter in CHEC-III. Asymmetric reductions, transition metal-catalyzed cross-couplings, and stereoselective C–C bond-forming reactions such as allylation are among the key reactions that are covered in detail in this chapter.

6.15.2 Theoretical Methods

Extensive electron correlated *ab initio* calculations of the equilibrium geometries, ground state energies, relative stabilities, vibrational frequencies, and dipole moments were carried out on a large group of azaboroles and oxazaboroles. The results demonstrated that the most stable isomers have the structure corresponding to 1,3,2-oxazaborolidines and 1,3,2-diazaborolidines. The stable conformer of the five-membered ring for a vast majority of azaboroles and oxazaboroles was found to be planar in geometry. Although the presence of boron causes scattering of the polarizabilities of isomers, thereby lowering the accuracy of the empirical calculations, Doerksen and Thakkar were able to confirm theoretically that the most stable isomers tended to be the least polarizable. They also determined that the polarizability was highly dependent on the nature of bonds. Boroles with higher number of B–B bonds are highly polarizable, while the diazaboroles and oxazaboroles with more carbon–carbon bonds undergo least polarization. As the polarizability of oxygen

is much smaller than nitrogen, which in turn is smaller than carbon, the replacement of NH by oxygen or CH by nitrogen in the ring invariably reduces the polarizability <1999PCA2141>.

6.15.3 Experimental Structural Methods

One of the widely used techniques for the characterization of boron-containing molecules is the ^{11}B nuclear magnetic resonance (NMR). The typical diagnostic chemical shift values (δ , ppm) for the boroles include δ 80 (trialkylborane R_3B), δ 55 (dialkyl borinate R_2BO), δ 35 (alkyl boronate RBO_2), δ 18 (trialkoxaborate BO_3), and δ 0 (tetrahedral 'ate' complexes BR_4). Various substituents on boron have a significant effect in changing the chemical shift values. The two types of boron atoms in boronate **1** show δ values corresponding to borate (δ 22.6) and boronate (δ 32.7) <2006JA11036>. Replacing oxygen with sulfur leads to deshielding as evidenced by a change in δ for 1,3,2-dioxaborolane **2a** (δ 24) to 1,3,2-oxathiaborolane **2b** (δ 38), and 1,3,2-dithiaborolane **2c** (δ 48) <2004EJI4223>. The diazaborole **3** with two nitrogen substituents shows δ 35.9 <2004EJI3629>, while the tetrahedral boron center with two oxygen and two nitrogen substituents on borole **3** shows δ 13.4, and with four oxygen substituents as in borate **4** shows a peak at δ 12.3 <2004EJI1115>. The presence of two isothiocyanate groups on boron in compound **5** changes the chemical shift to δ -0.1 (Figure 1).

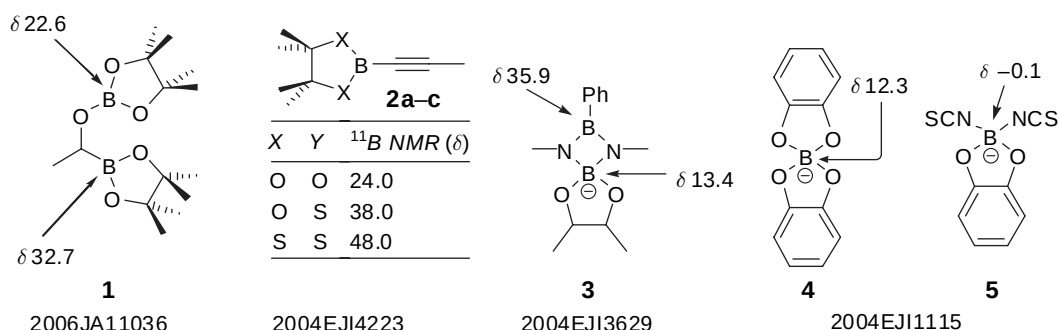


Figure 1 ^{11}B NMR chemical shift values for typical boronates.

1,3,2-Oxazaborolidines **6a-f** show NMR values similar to dioxaborolanes ($\sim\delta$ 35). Boroles **6a-f** with different substituents show different chemical shifts F (δ 22.3), Br (δ 26.0), NH_2 (δ 25.2), SnMe_3 (δ 38.2), etc. <2000OM5791>. Diazaborolines **7a-f** also show similar chemical shifts to those of oxazaborolidines. The presence of iodine (δ 11.8), cyanide (δ 12.0), and isothiocyanate (δ 14.7) leads to further shielding (Figure 2) <1998EJI1145>.

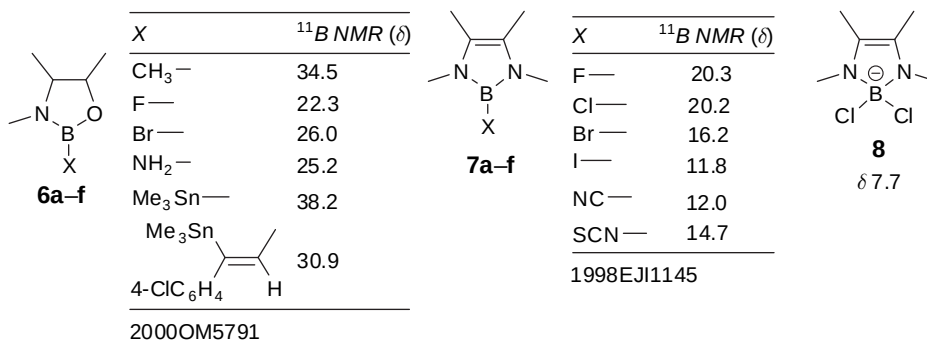


Figure 2 Effect of substituents on ^{11}B NMR chemical shifts of oxaza- and diazaboroles.

The presence of different elements attached to boron atom does not significantly alter the chemical shifts. Diazaboroles **9a-e** substituted with carbon (δ 29.5), silicon (δ 29.9), germanium (δ 30.5), tin (δ 32.8), and lead (δ 39.6) <2003AOM525>, as well as dioxaborolanes **10a-g** substituted with sulfur (δ 34.3), selenium (δ 35.3), silicon

(δ 31.7), germanium (δ 31.5), and tin (δ 31.2) <2006WO2006089402>, show closely comparable ^{11}B NMR spectra. Boronate **11** attached to copper shows a chemical shift of δ 41.7, while boronates **12** and **13** attached to oxygen and carbon show expected values at δ 21 and δ 33, respectively (Figure 3) <2005JA17196, 2006OM2405>.

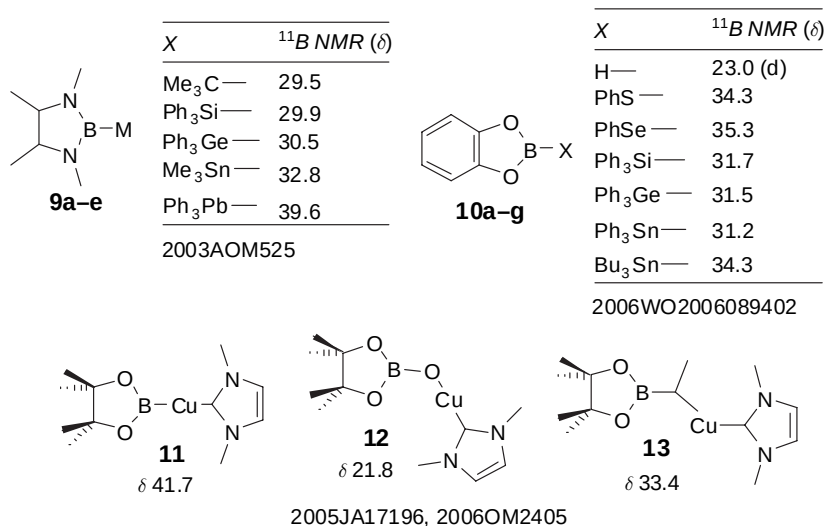


Figure 3 Effect of substituents on ^{11}B NMR chemical shifts of diox- and diazaboroles.

Other miscellaneous heterocyclic boron-containing compounds **14–21** and their chemical shift values are depicted in Figure 4 <2002MRC406, 2004ZFA508, 1995JOM197, 2003JOM188, 1999JOM93, 2002MRC406>.

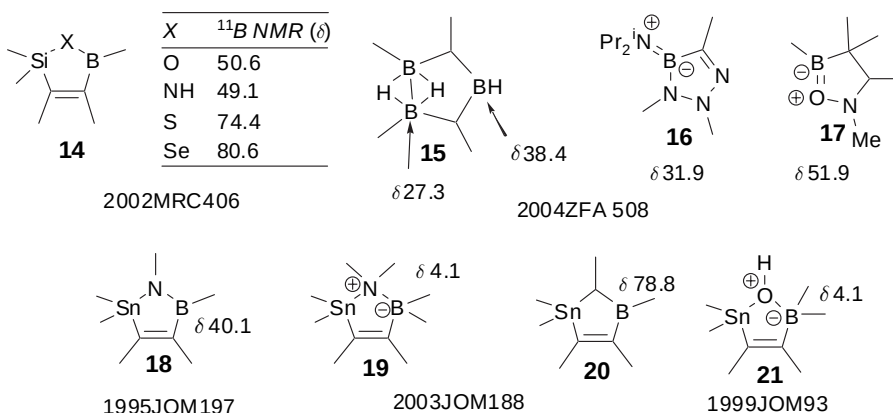
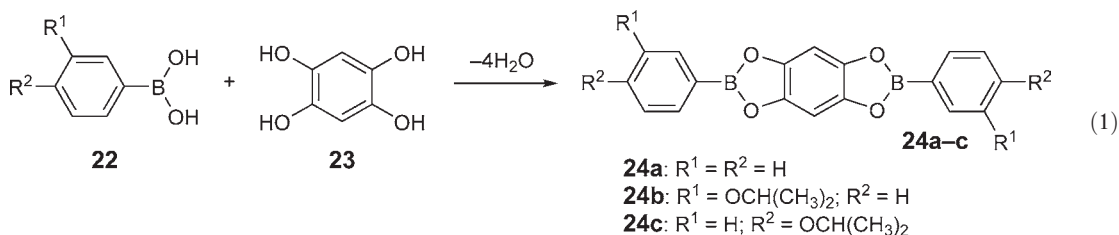


Figure 4 ^{11}B NMR chemical shifts of miscellaneous boroles.

6.15.4 Thermodynamic Aspects

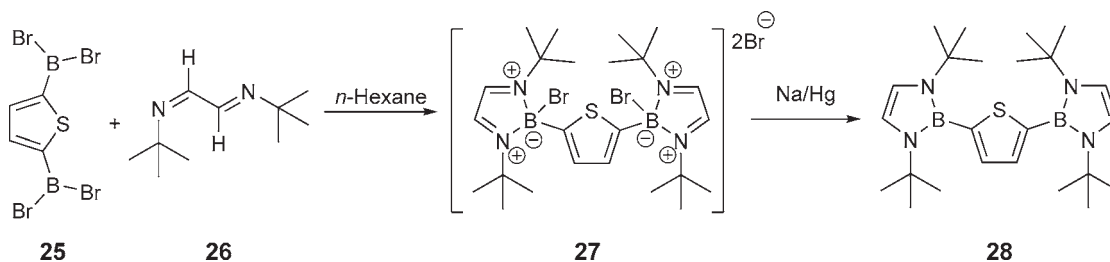
Bis(dioxaboroles) **24** derived from the condensation of 1,2,4,5-tetrahydroxybenzene **23** and substituted phenylboronic acids **22** are crystalline solids and are planar in conformation through an extended π stacking (Equation 1). Lavigne and co-workers demonstrated that the substituents on the phenyl ring did not affect the planarity of the π -system through the boroles, but exerted a profound influence on the intermolecular arrangement of these compounds. The bis(dioxaborole) **24a** was observed to be centrosymmetric and planar with a small dihedral angle between the central phenyl ring and the external phenyl ring. These boronates assume a supramolecular column like structures with the electron-deficient boron moieties efficiently sandwiched between the π -clouds of the central

and terminal phenyl rings of adjacent layers. The bulkier substituents (e.g., isopropoxyl **24b** and **24c**) on the external phenyl ring change the supramolecular secondary arrangement and also increase the distance between the adjacent layers in the solid state <2005CC5166, 2006CGD1274>.



6.15.5 Reactivity of Fully Conjugated Rings

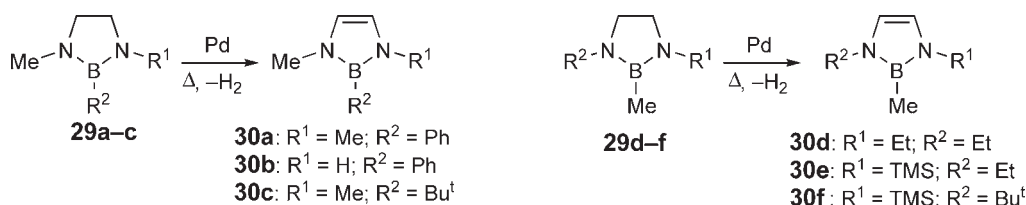
Boron halides **25** react with 1,2-diimines such as *N,N'*-di-*tert*-butylethylidenediimine **26** and furnish fully conjugated diazaborolium salts **27**. These salts are highly reactive and readily undergo reduction with sodium amalgam providing the diazaboroles **28** in high yield (Scheme 1) <2006JCD3777>.



Scheme 1

6.15.6 Reactivity of Nonconjugated Rings

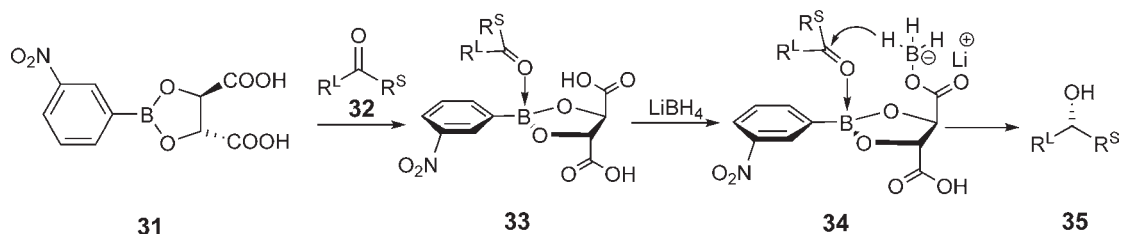
1,3,2-Diazaborolines can be synthesized in three general strategies involving catalytic dehydrogenation of diazaborolidines, alkali metal reduction of the corresponding *B*-halo-diazaborolidines, and the cyclocondensation of boron halides with dilithiated amines <2005EJI4715>. Saturated 1,3,2-diazaborolidines **29a-f** were treated with palladium over charcoal at high temperatures under argon atmosphere for several weeks resulting in the dehydrogenation to furnish the unsaturated 1,3,2-diazaborolines **30a-f** (Scheme 2) <2001CCR39>. The complete consumption of the starting material was highly essential for the successful isolation of products due to the close range of boiling points between the reactants and products. The presence of trimethylsilyl groups on nitrogen (compounds **29e** and **29f**) led to increase in reactivity and the dehydrogenation was complete in 1–3 days.



Scheme 2

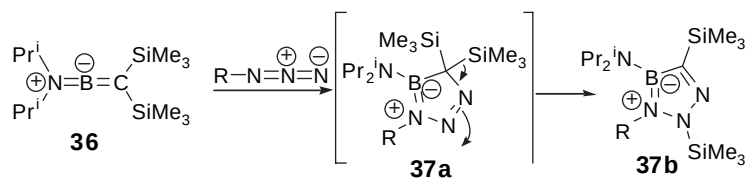
6.15.7 Reactivity of Substituents Attached to Ring Carbon Atoms

The boron atom dominates the reactivity of the boracyclic compounds because of its inherent Lewis acidity. Consequently, there have been very few reports on the reactivity of substituents attached to the ring carbon atoms in the five-membered boronated cyclic systems. Singaram and co-workers developed a novel catalyst **31** based on dicarboxylic acid derivative of 1,3,2-dioxaborolane for the asymmetric reduction of prochiral ketones **32**. This catalyst reduces a wide variety of ketones enantioselectively in the presence of a co-reductant such as LiBH_4 . The mechanism involves the coordination of ketone **32** with the chiral boronate **31** and the conjugation of borohydride with carboxylic acid to furnish the chiral borohydride complex **34**. Subsequent transfer of hydride from the least hindered face of the ketone yields the corresponding alcohol **35** in high ee (Scheme 3) <2006OPD949>.



Scheme 3

The [2+3] cycloaddition of methyldiene borane **36** with alkyl azides furnishes the intermediate triazaboroles **37a**, which further undergoes silicon migration from carbon to nitrogen resulting in the formation of **37b**. The driving force for the reaction is the stabilization of the ring system due to aromatization (6π electrons) (Scheme 4) <2004ZFA508>.



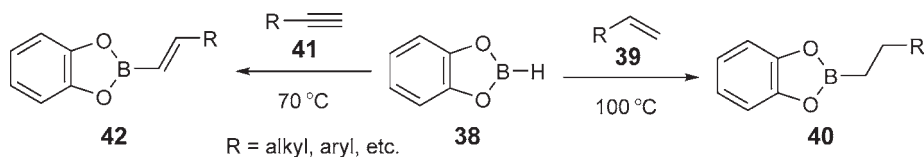
Scheme 4

6.15.8 Reactivity of Substituents Attached to Ring Heteroatoms

6.15.8.1 Reactions of B–H bond: Hydroboration

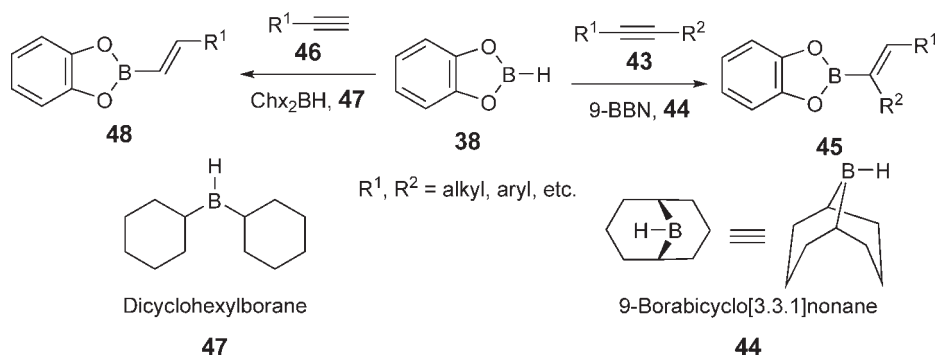
6.15.8.1.1 Hydroboration of alkenes and alkynes

The reactivity of the substituents attached to the boron atom varies greatly depending on the type of substituents present. For example, when a transferable group like hydrogen is attached to boron, it readily adds in a 1,2-fashion across a double ($\text{C}=\text{C}$) or triple ($\text{C}\equiv\text{C}$) bond. Conventional boranes such as $\text{BH}_3\cdot\text{THF}$, 9-borabicyclo[3.3.1]nonane (9-BBN), dicyclohexylborane (Chx_2BH), etc., readily undergo hydroboration at room temperature because of the Lewis acidity of boron (THF = tetrahydrofuran). The presence of electron-rich heteroatoms such as oxygen and nitrogen on boron considerably reduces its reactivity toward hydroboration. Five-membered heterocyclic borolanes such as catecholborane **38** undergo addition to unsaturated compounds (such as alkenes **39** and alkynes **41**) yielding the corresponding hydroboration products **40** and **42**, respectively; (Scheme 5) <1995SC1957>.



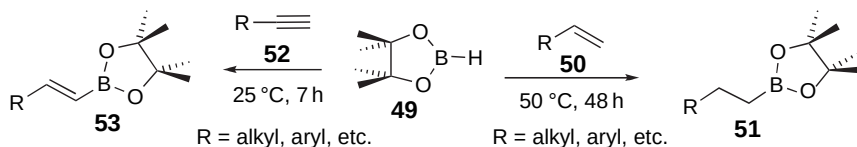
Scheme 5

Hydroboration of alkenes and alkynes with catecholborane is very sluggish, especially in organic solvents. The reaction is performed neat at elevated temperatures. However, the addition of catalytic dialkylboranes such as 9-BBN **44** or Chx_2BH **47** increases the rate of hydroboration with catecholborane. Since dialkylboranes hydroborate much faster than catecholborane, alkynes undergo initial hydroboration with 9-BBN or Chx_2BH to yield the alkenyldialkylborane, which then transfers the alkenyl group to catecholborane furnishing the alkenyl boronate. Typically, Chx_2BH is used as the catalyst for the hydroboration of terminal alkynes **46** and 9-BBN is used for hydroboration of internal alkynes **43** (Scheme 6).



Scheme 6

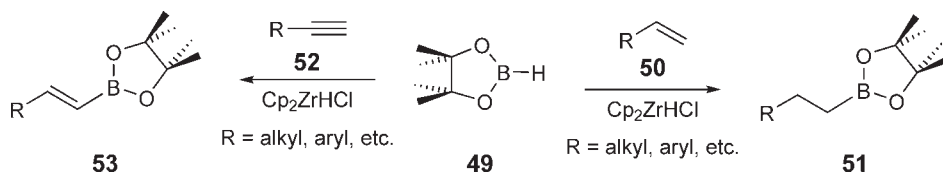
Pinacolborane **49** is a highly stable hydroborating agent. It can be easily prepared and stored without decomposition. Pinacolborane **49** reacts with alkenes and alkynes under relatively milder conditions unlike catecholborane **38**. Alkenes **50** react slower than alkynes and usually undergo hydroboration in 2–3 days at 50°C furnishing the terminal pinacol boronates **51** as the major regioisomer (>98%). Hydroboration of terminal alkynes **52** with pinacolborane proceeds at room temperature with an excellent level of regioselectivity to yield the terminal vinyl boronates **53** (Scheme 7).



Scheme 7

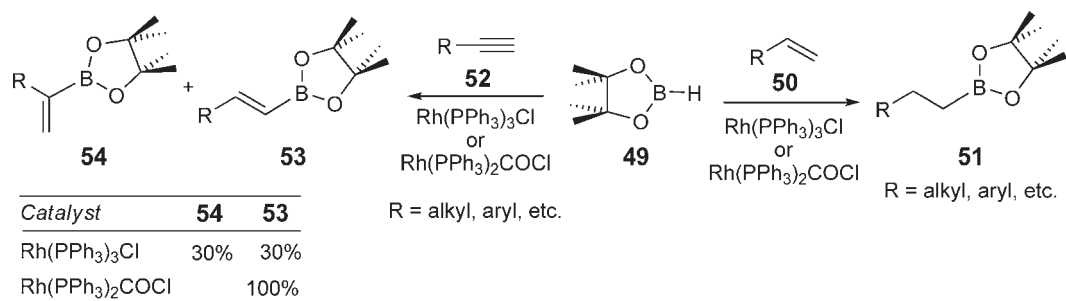
6.15.8.1.2 Transition metal-catalyzed hydroboration

The rate of hydroboration with catecholborane and pinacolborane can be tremendously increased by the addition of transition metal catalysts. Hydroboration of pinacolborane **49** with alkenes **50** <1996JA909> and terminal alkynes **52** <1995OM3127> proceeds with high regioselectivity in the presence of catalytic HZrCp_2Cl furnishing the terminal boronates **51** and vinylboronates **53**, respectively (Scheme 8).



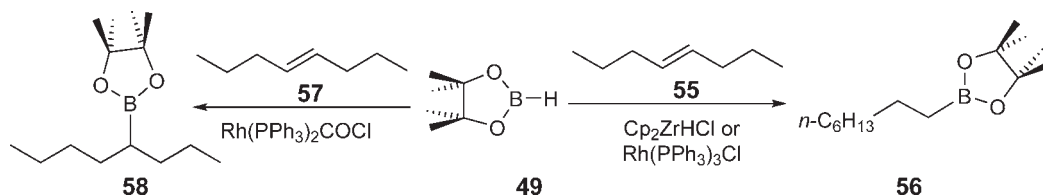
Scheme 8

However, HZrCp_2Cl is not compatible with many functional groups and hence several other catalysts, such as $\text{Rh}(\text{PPh}_3)_3\text{Cl}$ and $\text{Rh}(\text{PPh}_3)_2(\text{CO})\text{Cl}$, have also been employed for hydroboration. Wilkinson's catalyst $\text{Rh}(\text{PPh}_3)_3\text{Cl}$ hydroborates alkynes **52** yielding the regioisomeric mixture of terminal and internal vinyl boronates **53** and **54**. However, by changing the catalyst to $\text{Rh}(\text{PPh}_3)_2(\text{CO})\text{Cl}$, an increase in regioselectivity has been observed for the hydroboration of alkynes [<1996JA909>](#). Terminal alkenes **50** undergo facile hydroboration with $\text{Rh}(\text{PPh}_3)_3\text{Cl}$ and $\text{Rh}(\text{PPh}_3)_2(\text{CO})\text{Cl}$, yielding product **51** as a single isomer ([Scheme 9](#)).



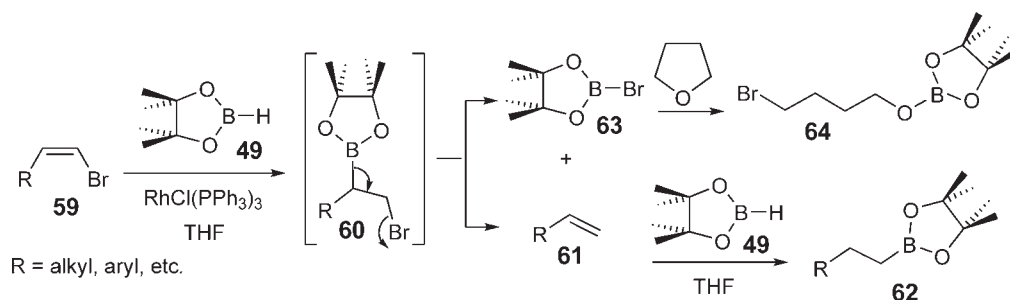
Scheme 9

Internal alkenes **55** undergo isomerization with pinacolborane in the presence of HZrCp_2Cl or $\text{Rh}(\text{PPh}_3)_3\text{Cl}$ furnishing the terminal pinacol boronates **56** [<1995OM3127>](#). Replacing one of the PPh_3 groups in Wilkinson's catalyst by a CO ligand [<1995OM3127>](#) enables the formation of the expected internal boronate **58** as the major product ([Scheme 10](#)). The $\text{Pt}(\text{DBA})_2/\text{P}(2,4,6\text{-MeO-C}_6\text{H}_2)_3$ catalyst system (DBA = dibenzylideneacetone) was also observed to be an efficient catalyst for hydroboration of alkynes with pinacolborane [<1999CL1069, 2003T537>](#).



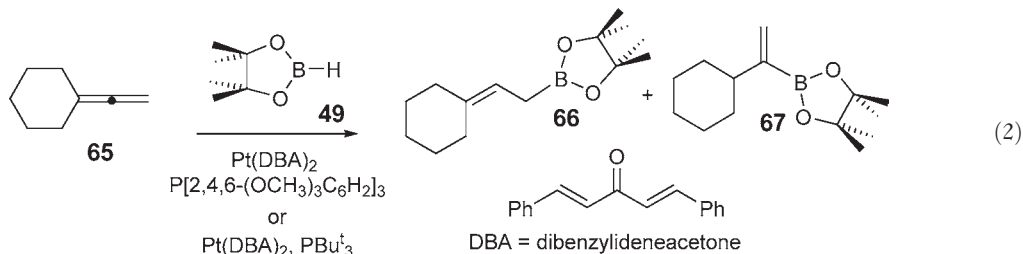
Scheme 10

Catalytic hydroboration of vinylic ethers, acetals, and esters with pinacolborane takes place smoothly in the presence of transition metal catalysts. However, a noticeable exception is the catalytic hydroboration of vinyl bromides **59** which do not furnish the expected hydroborated product under these conditions. The reaction of vinyl bromides with pinacolborane initially affords the expected β -boronoalkylbromide **60**. A fast *syn*-elimination ensues to furnish the terminal alkene **61** and *B*-bromopinacolborane **63**. The alkene **61** undergoes hydroboration with unreacted pinacolborane to provide the debrominated boronate **62**. The intermediate *B*-bromopinacolborane **63** cleaves the ethereal C–O bond in the solvent (THF) to provide 4-bromobutyl borate **64** as a side product ([Scheme 11](#)) [<1996JA909, 2000CSP14505>](#).



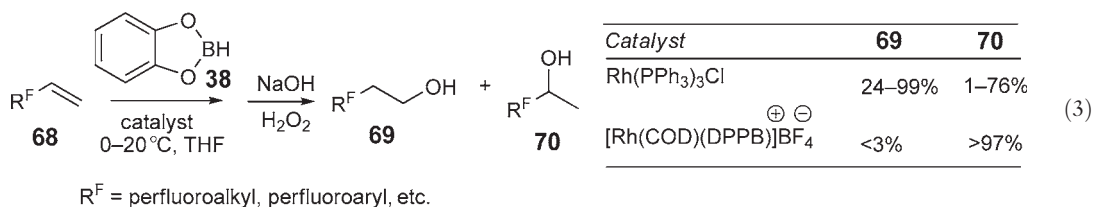
Scheme 11

Hydroboration of allenes **65** with pinacolborane in the presence of $\text{Pt}(\text{DBA})_2$ and a trialkylphosphine provides either the allyl boronate **66** or the vinyl boronate **67** regioselectively, depending on the stereoelectronic factors of the phosphine employed (Equation 2) <1999CL1069>. Allyl and vinyl boronates are synthetically important because of their ability to undergo nucleophilic addition to carbonyl compounds as well as transition metal-catalyzed cross-coupling.



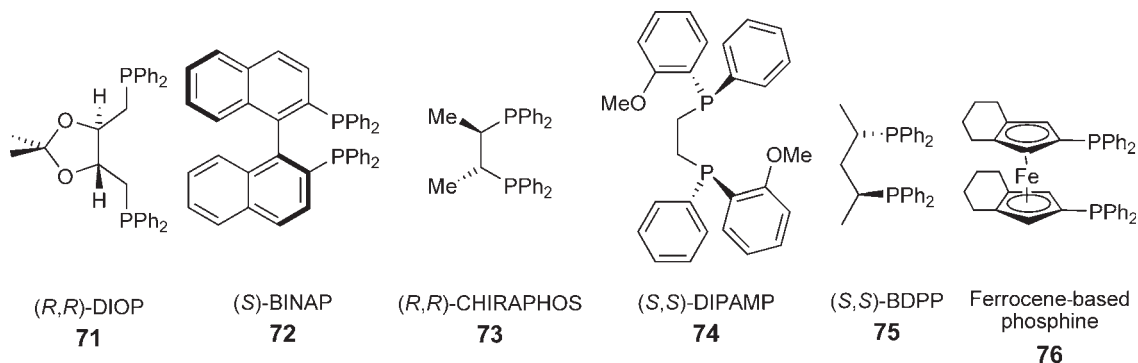
6.15.8.1.3 Hydroboration of fluoroalkenes

Catalytic hydroboration of perfluoroalkenes **68** with catecholborane provides either terminal **69** or internal alcohols **70** regioselectively <1999OL1399>. The regioselectivity is controlled by a judicious choice of catalyst. The *anti*-Markovnikov alcohol can be obtained with very high selectivity by using cationic rhodium catalysts such as $\text{Rh}(\text{COD})(\text{DPPB})^+\text{BF}_4^-$, while neutral Rh catalysts such as Wilkinson's catalyst provide the Markovnikov product (COD = cyclooctadiene; Equation 3) <1999OL1399>.

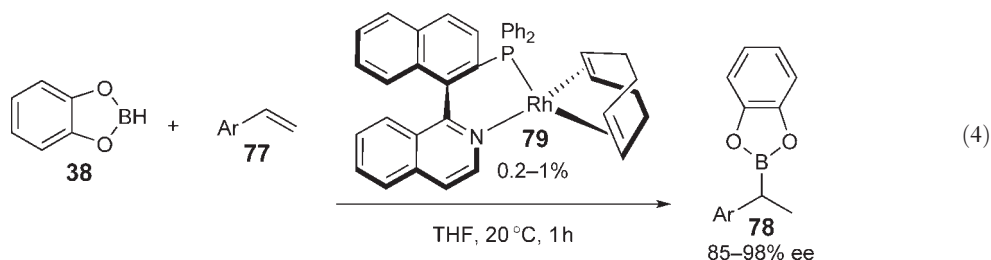


6.15.8.1.4 Chiral hydroboration of alkenes

Asymmetric hydroboration of prochiral alkenes has been achieved using transition metal catalysts and chiral phosphines as ligands to obtain enantiomerically pure alkyl boronates <1997CC173>. Catalysts such as $\text{Rh}(\text{COD})_2^+\text{BF}_4^-$, $\text{Rh}(\text{COD})_2^+\text{Cl}^-$, Rh^+BF_4^- , etc., in combination with chiral phosphines like DIOP **71**, BINAP **72**, CHIRAPHOS **73**, DIPAMP **74**, BDPP **75**, ferrocene-based diphosphines **76** <1999TL4977>, etc., have been employed for the asymmetric hydroboration of prochiral alkenes with moderate to high ee (DIOP = 2,3-*O*-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane; BINAP = 2,2-bis(diphenylphosphanyl)-1,1-binaphthyl; CHIRAPHOS = 2,3-bis(diphenylphosphino)butane; DIPAMP = 1,2-bis[(2-methoxyphenyl)phenylphosphino]ethane; BDPP = 2,4-bis(diphenylphosphino)pentane).

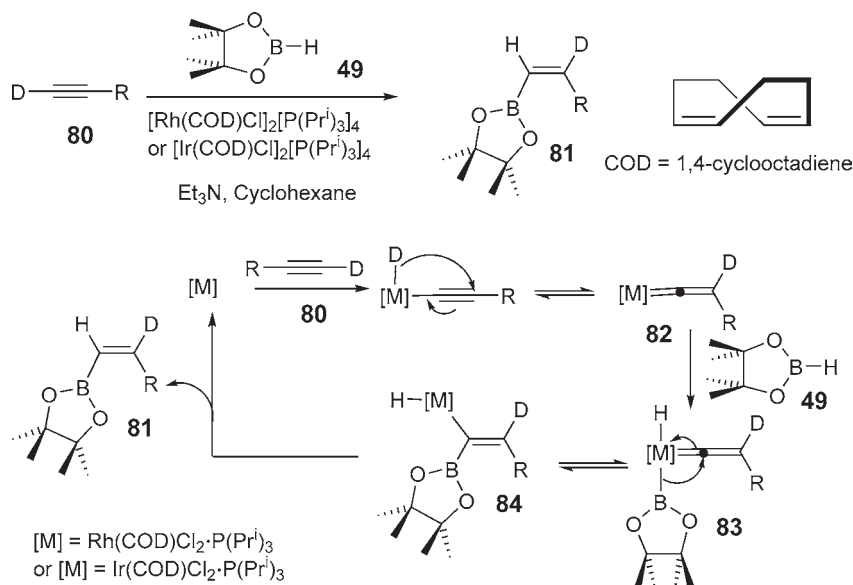


[1-(2-Diphenylphosphino-1-naphthyl)-isoquinoline](cyclooctadiene) rhodium triflate **79** has also been utilized as a catalyst for the chiral hydroboration of vinyl arenes **77** to yield the boronates **78** with high ee (Equation 4) <2000CEJ1840>.



6.15.8.1.5 *trans*-Hydroboration of terminal alkynes

A *trans*-hydroboration of terminal alkynes **80** using $[\text{Rh}(\text{COD})\text{Cl}]_2[\text{P}(\text{Pr}^i)_3]_4$ and $[\text{Ir}(\text{COD})\text{Cl}]_2[\text{P}(\text{Pr}^i)_3]_4$ has been reported by Miyaura and co-workers. Deuterium labeling studies show that the oxidative addition of the alkyne to the metal is followed by the acetylenic deuterium migration to the β -carbon resulting in the formation of a vinylidene metal complex **82**. Insertion of pinacolborane to the complex **82** and 1,2-boryl migration to the α -carbon results in the stereospecific formation of thermodynamically stable alkenylmetal complex **84**, which subsequently undergoes reductive elimination to provide the (*Z*)-vinyl boronate **81** as a single isomer (Scheme 12) <2000JA4990>.

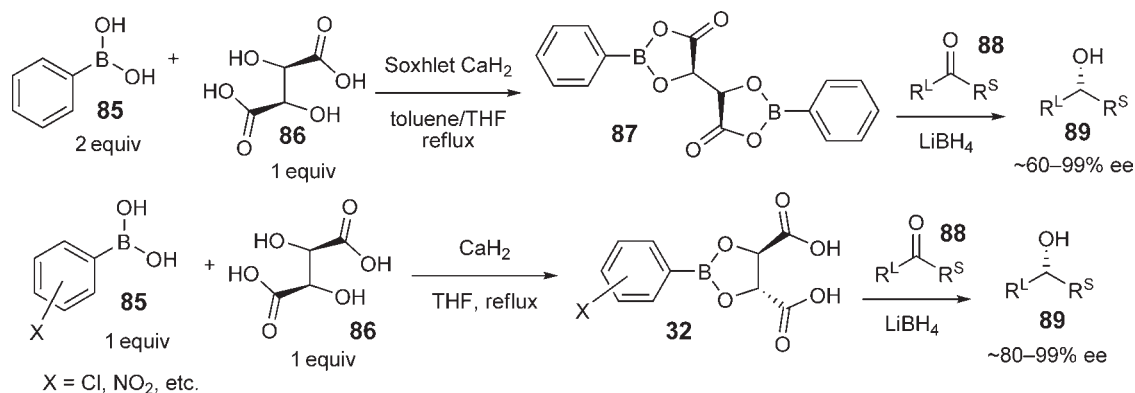


Scheme 12

6.15.8.2 Reactions of B–H bond: Reduction

6.15.8.2.1 Asymmetric reduction of ketones

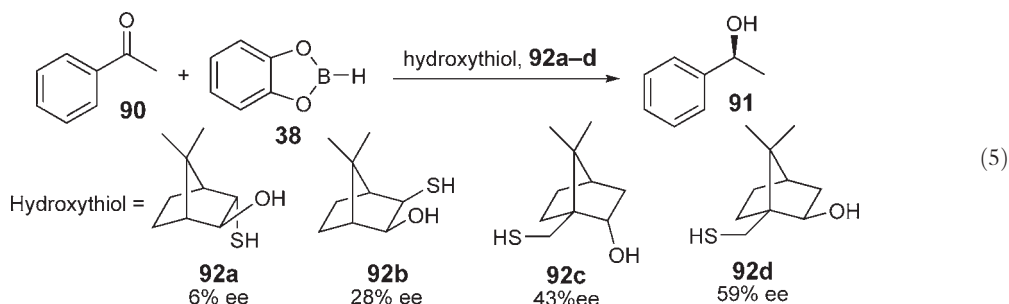
Asymmetric reduction of ketones is one of the most fundamental methods for the stereoselective formation of chiral secondary alcohols. Nozaki *et al.* developed a highly selective catalyst **87** for the asymmetric reduction of ketones, based on arylboronic acid and tartaric acid. The catalyst was prepared readily via transesterification of 2 equiv of phenylboronic acid **85** with tartaric acid **86** under Soxhlet extraction conditions <1999BCJ1109>. Singaram and co-workers were successful in further enhancing the efficacy of the reduction via a modified catalyst (Tar-BNO₂ **32**) starting from 1 equiv of nitrophenylboronic acid **85** and tartaric acid **86**. These catalysts were highly useful for the reduction of ketones in the presence of borohydride as a co-reductant. The catalysts **87** and **32** provided moderate to high ee for the reduction of a wide variety of ketones (Scheme 13) <2006OPD949>.



Scheme 13

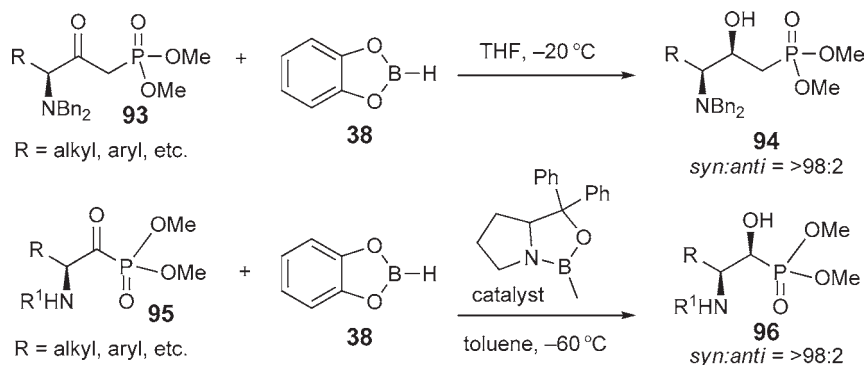
6.15.8.2.2 Chiral hydroxythiol-catalyzed reduction of ketones

Amino alcohols have been extensively utilized as chiral auxiliaries for the chiral reduction of prochiral ketones. Kagan and co-workers employed chiral hydroxythiols **92a–d** derived from camphor in combination with catecholborane for the stereoselective reduction of acetophenone **90** to phenethylalcohol **91** with moderate to low ee (Equation 5) <1998TA3647>. The main benefits of using hydroxythiols over amino alcohols are twofold: (1) nitrogen has only one lone pair while sulfur has two lone pairs, thus enabling higher coordination capability for sulfur; and (2) nitrogen is a hard Lewis base while sulfur is a soft base, which renders the binding of sulfur with the soft Lewis acid borane to be very strong compared to a B–N bond. This exploratory work has shown that hydroxythiols could be successfully employed for the stereoselective reduction of ketones with boranes.



6.15.8.2.3 Reduction of ketophosphonates

Catecholborane stereoselectively reduces chiral γ -amino- β -ketophosphonates **93** and β -amino- α -ketophosphonates **95** yielding the 1,2-*syn*-aminoalcohols **94** and **96** in high selectivity (Scheme 14) <1999TL7705, 2002TA559>.

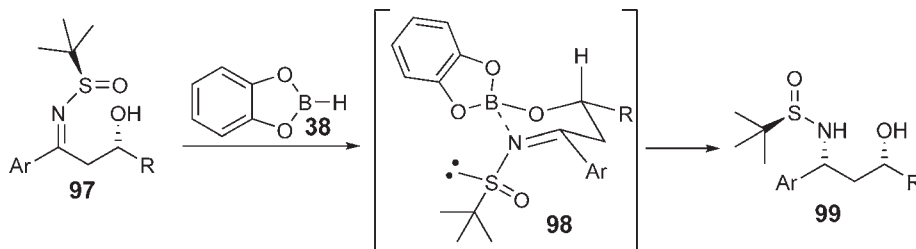


Scheme 14

These products are biologically significant as some of these phosphonates have been observed to be potent inhibitors of proteolytic enzymes such as rennin and HIV protease. Stereoselective reduction of aminoketophosphonates using catecholborane provides a facile access to these biologically important molecules.

6.15.8.2.4 Reduction of β -hydroxysulfinylimines

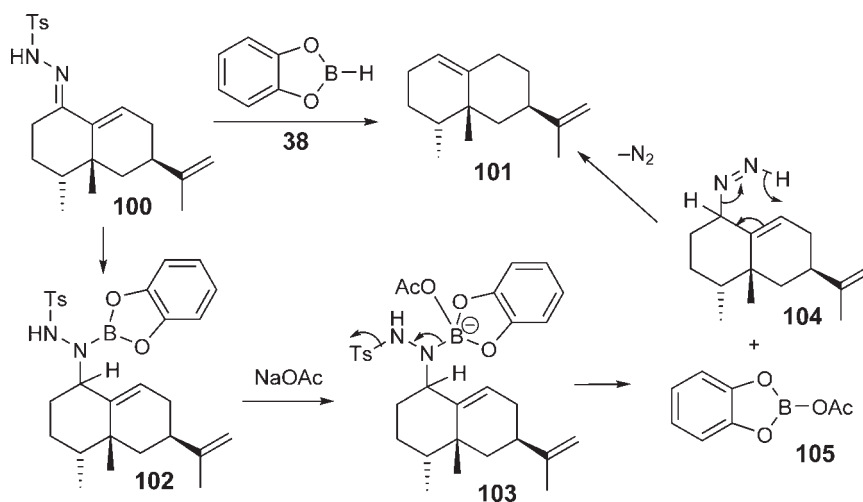
β -Hydroxy-*N*-sulfinylimines **97** undergo highly diastereoselective reduction with excess catecholborane yielding the 1,3-*syn*-*N*-sulfinyl amino alcohols **99** in high yield. Initial deprotonation of alcohol by catecholborane and the coordination of boron with the imine nitrogen results in a six-membered transition state **98**. Subsequent intermolecular hydride addition takes place from the least hindered face of the imine resulting in the stereoselective formation of *syn*- β -hydroxy-*N*-sulfinylamines **99** (Scheme 15) <2002JA6518>. The corresponding *anti*-amino alcohols can be obtained stereoselectively by reduction of the hydroxysulfinyl imines with lithium triethyl borohydride.



Scheme 15

6.15.8.2.5 Reduction of tosylhydrazones

There are very limited procedures for the direct conversion of carbonyl ($C=O$) to methylene (CH_2) group. The typical reduction protocols utilize strongly alkaline (Wolf-Kishner reduction) or strongly acidic (Clemmensen reduction) conditions for the reduction of $C=O$ to CH_2 and hence are not compatible with a variety of acid- and base-sensitive substrates. The above transformation can be realized in a two-step reduction sequence involving the condensation of ketones to the corresponding tosylhydrazones which then undergo reduction with catecholborane. An extension of the above protocol involves the reaction of tosylhydrazones of α,β -unsaturated ketones **100**, which undergo highly chemoselective conjugate reduction with catecholborane furnishing the isomerized alkene **101** (Scheme 16). The mechanism for the conjugate reduction involves the initial reduction of the tosylhydrazone **100** to the corresponding hydrazine **102**, which subsequently reacts with sodium acetate yielding the 'ate' complex **103**. Concomitant elimination of borate and

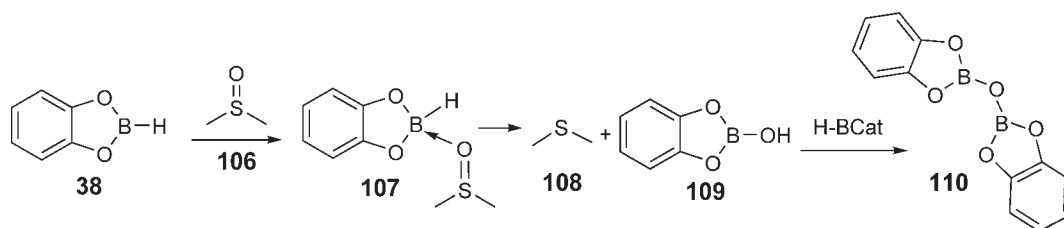


Scheme 16

tosyl groups yields *B*-acetoxy catecholborane **105** and the hydrazide **104**, followed by a thermal [3,3]-sigmatropic rearrangement yielding the conjugate reduction product **101** (Scheme 16) <2004JOC7428>.

6.15.8.2.6 Reduction of sulfoxides to sulfides

Recently, catecholborane has been utilized for the reduction of sulfoxides **106** to the corresponding sulfides **108**. The mechanism is believed to involve the coordination of sulfoxide oxygen to boron, subsequent proton migration, and elimination of dialkyl sulfide yielding benzodioxaborolol **109**. Reaction of borate **109** with another equivalent of catecholborane yields the corresponding dimer **110** (Scheme 17). Although several methods exist for the reduction of sulfoxides, many of them suffer from serious disadvantages such as expensive reagents, functional group incompatibility, difficulty in isolation, etc. Catecholborane affords a mild and practical alternative protocol for the reduction of sulfoxides to sulfides <2004TL8493>.

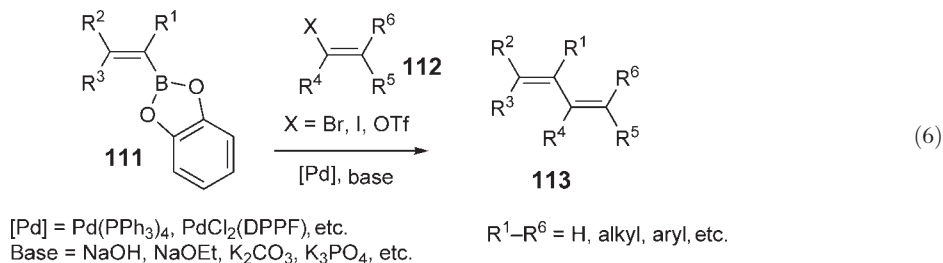


Scheme 17

6.15.8.3 Reactions of B–H and B–C: Cross-Coupling

6.15.8.3.1 Transition metal-catalyzed cross-coupling

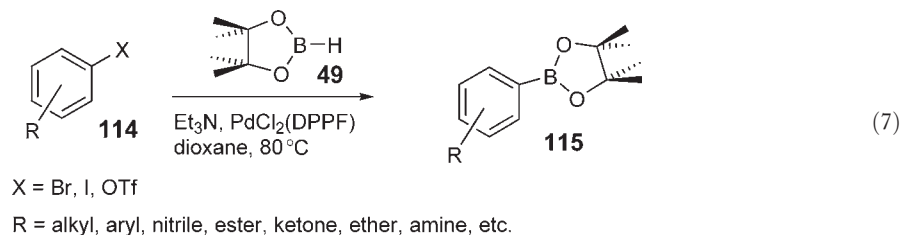
The stereoselective syntheses of conjugated dienes are of great importance in organic chemistry. They serve as precursors for key C–C bond-forming reactions, including Diels–Alder reactions. The diene moieties are found as a common structural motif in a plethora of natural products with interesting biological properties. Transition metal-catalyzed cross-coupling between alkenyl boronates and stereodefined haloalkenes, commonly referred to as Suzuki–Miyaura cross-coupling, results in the formation of dienes in high selectivity. Due to the mild reaction conditions employed, a wide variety of substrates such as aryl and vinyl triflates, iodides, and bromides undergo facile coupling under these conditions. The reaction of vinyl-substituted dioxaborolanes **111** with vinylic halides **112** in the presence of transition metal catalysts affords the cross-coupled products **113** in a highly stereoselective fashion <1995CRV2457>. Vinylic pinacol and catechol boronates are the most widely employed reagents owing to their functional group compatibility, air and moisture stabilities, as well as the ease of preparation (Equation 6) <1999JOM147, 1995CRV2457>.



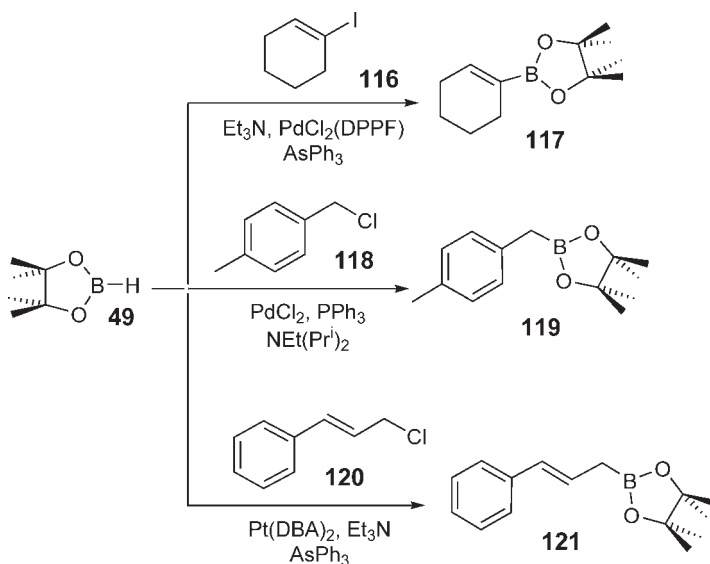
6.15.8.3.2 Borylation of aryl halides

Pinacolborane is extensively used in the borylation of aryl halides **114** in the presence of a base (typically pyridine or Et_3N or KOAc) and catalytic amount of $\text{PdCl}_2(\text{DPPF})$ to furnish aryl boronates **115** (DPPF = 1,1'-bis(diphenylphosphino)ferrocene; Equation 7) <1997JOC6458, 2000JOC164>. Pinacolborane is compatible with esters, ketones,

ethers, tertiary amines, nitriles, etc. The resulting pinacol boronates **115** are highly stable and can be readily purified by silica gel column chromatography. Hence this reaction has broad scope and can be used on a variety of substrates. Aryl iodides react faster than bromides or triflates.



Miyaura and co-workers were able to expand the scope of borylation to include aryl chlorides, which are otherwise inert under standard conditions. Successful borylation was achieved by changing the catalyst system to $\text{Pd}(\text{DBA})_2$ and PCy_3 and replacing pinacolborane with bis(pinacolato)diboron <2001T9813>. Replacing tricyclohexylphosphine with triphenylarsine leads to a facile coupling of vinyl iodides **116** and triflates with pinacolborane yielding the vinyl boronates **117** <2000S778>. Borylation of allylic halides **120** under similar conditions furnishes the allyl boronates **121** in good yield <2000TL5877>. Pinacolborane reacts with benzylic halides **118** in the presence of PdCl_2 , PPh_3 , and *N,N*-diisopropylethylamine providing the benzyl boronates **119** (Scheme 18) <2002SC2513>.



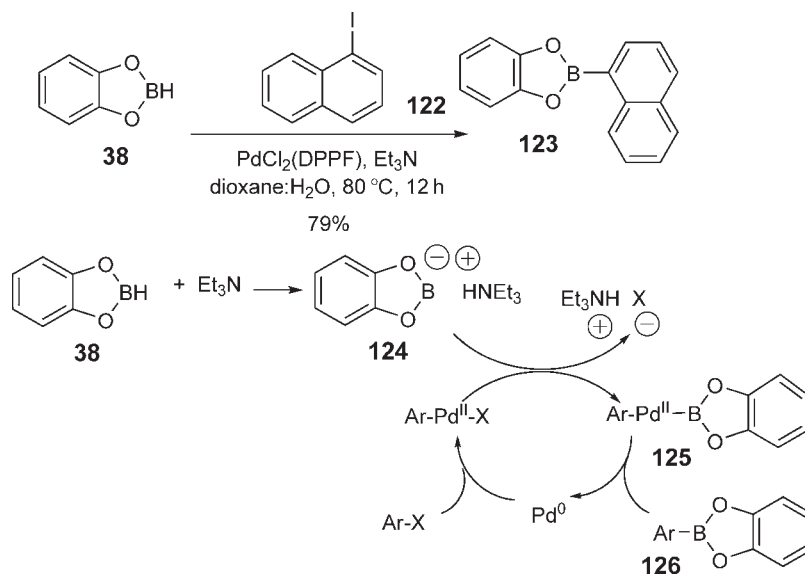
Scheme 18

Borylation of catecholborane with aryl halides **122** is catalyzed by $\text{PdCl}_2(\text{DPPF})$ and Et_3N to yield the corresponding aryl boronates **123** <2000JOC164>. The mechanism involves oxidative addition of aryl halide to the $\text{Pd}(0)$ catalyst followed by a ligand exchange between the halide of Ar-Pd(II)-X and the boryl anion **124** (generated by the reaction of Et_3N with catecholborane), and subsequent reductive elimination of aryl boronate **126** to regenerate the $\text{Pd}(0)$ catalyst (Scheme 19).

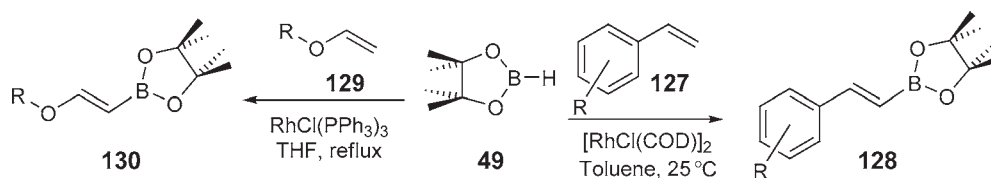
6.15.8.3.3 Dehydrogenative borylation

The reaction of pinacolborane with styrenes **127** in the presence of bis(chloro-1,5-cyclooctadienylrhodium) at room temperature provides styrenyl pinacol boronate **128** <1999TL2585, 2002BCJ825>. While hydroboration of alkenes is the predominant reaction with phosphine-containing rhodium catalysts such as Wilkinson's catalyst and $\text{Rh}(\text{PPh}_3)_2\text{COCl}$, dehydrogenative borylation dominates over hydroboration in the presence of phosphine-free

rhodium catalysts. Dehydrogenative borylation of vinyl ethers **129** in the presence of Wilkinson's catalyst provides vinyloxy boronates **130** <2000CC51> (Scheme 20).

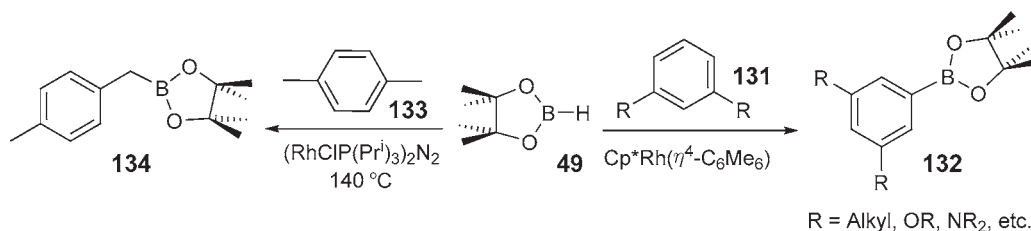


Scheme 19



Scheme 20

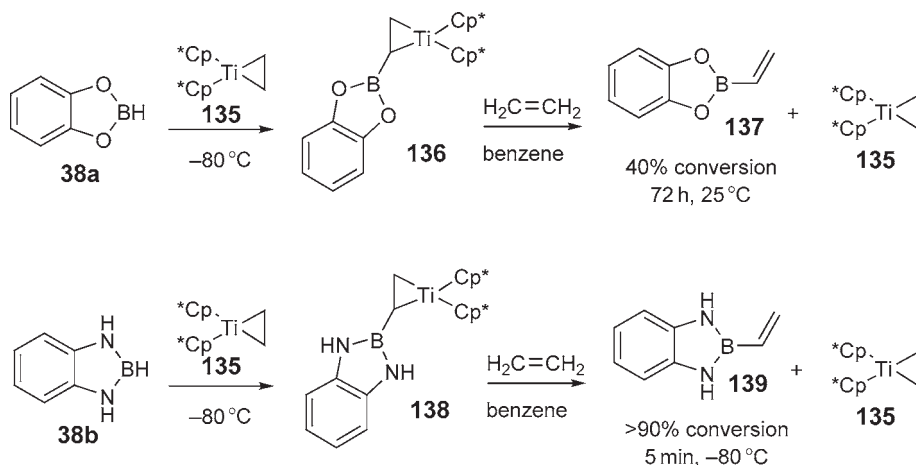
Arenes **131** react with pinacolborane in the presence of rhodium and iridium catalysts such as $\text{Cp}^*\text{Rh}(\eta^4\text{-C}_6\text{Me}_6)$ <2000JA12868, 2001OL2831>, CpIrPMe_3 <1999JA7696>, and $[\text{RhCIP}(\text{Pr}^i)_3]\text{N}_2$ <2001AGE2168> to afford aryl boronates **132**. Toluene and other methyl-substituted arenes **133** undergo dehydrogenative borylation with pinacolborane in the presence of $(\text{RhCIP}(\text{Pr}^i)_3)_2\text{N}_2$ and furnish benzyl boronates **134** via benzylic C–H activation (Scheme 21) <2001AGE2168>.



Scheme 21

Smith and co-workers reported the dehydrogenative borylation of ethylene with catecholborane in the presence of decamethyltitanocene Cp_2^*Ti catalyst to produce *B*-vinyl catechol boronate **137**. Reaction of Cp_2^*Ti with ethylene leads to the formation of metallacyclopropane species **135** that undergoes reaction with catecholborane **38a** to

produce the titanacyclopropyl boronate ester complex **136**. Mechanistic studies revealed initial oxidative insertion of B–H bond across titanacyclopropane, followed by β -hydride elimination to produce the titanocenyl vinyl boronate ester complex **137** with concomitant removal of H_2 . The boronate ester complex further reacts with ethylene to yield *B*-vinyl catechol boronate ester **137** albeit in low conversion rate. However, >90% borylation of ethylene was achieved at -80°C by substituting catecholborane with *o*-phenylene diaminoborane **38b** (Scheme 22) <1995JA6615, 1997JA2743>.

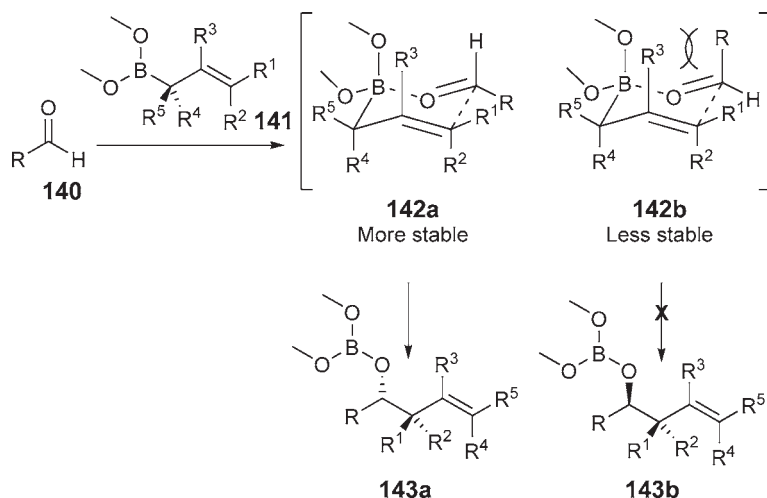


Scheme 22

6.15.8.4 Reactions of B–C: Stereoselective Allylation/Alkylation

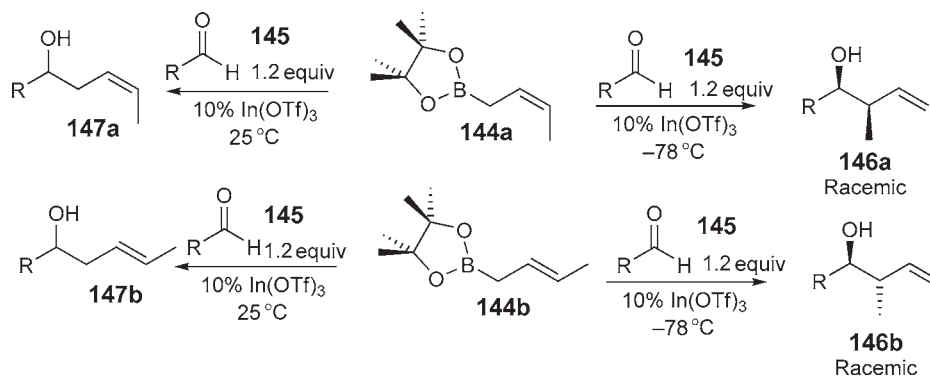
6.15.8.4.1 Racemic allyl boronates

Allylboration constitutes an important C–C bond-forming reaction in organic chemistry. Reaction of ‘allyl’ boranes with carbonyl compounds is far superior to many other ‘allyl’ metalations because of the excellent stereocontrol observed with boron due to a rigid six-membered transition state **142a** and **142b**. There are five different positions available for substitution on the ‘allyl’ borane, thereby making this reaction highly versatile in terms of obtaining a wide variety of complex products (Scheme 23).



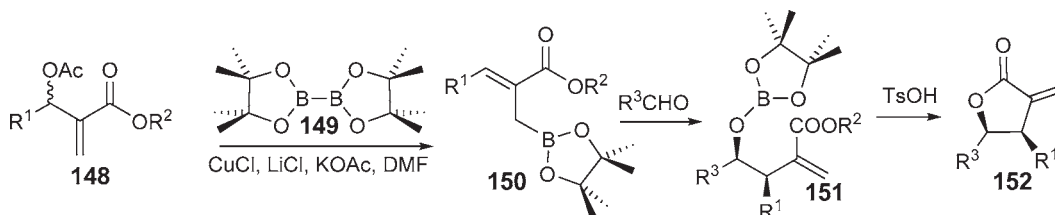
Scheme 23

B-Allylpinacol boronate is one of the stable achiral allylboranes and it reacts with a wide variety of aldehydes. The allyl boronates react slowly with aldehydes compared with allylboranes; however, the reactivity could be improved by the addition of Lewis acids <2005CC1988>. It is interesting to note that the reaction of aldehydes **145** with (*Z*)- and (*E*)-crotyl pinacol boronates **144a** and **144b** in the presence of $\text{In}(\text{OTf})_3$ as the catalyst leads to the formation of two different products depending upon the reaction temperature. At -78°C , the allylation furnishes the usual γ -adduct **146a** and **146b**, while warming the reaction to room temperature results in the α -adduct **147a** and **147b** (Scheme 24) <2005CC1988>.



Scheme 24

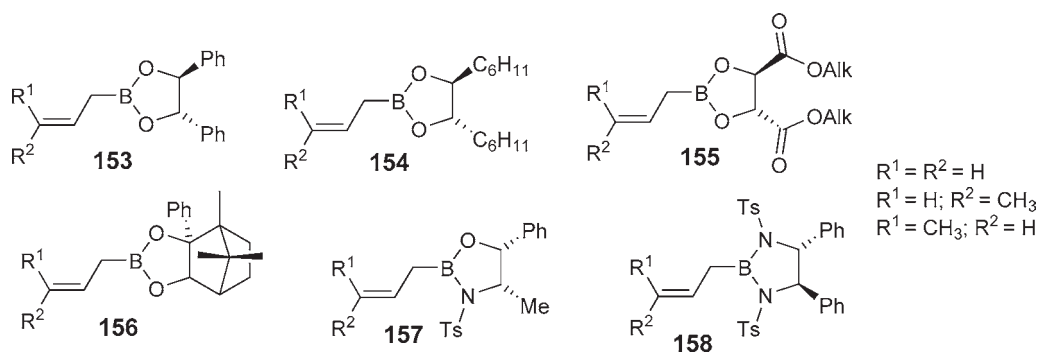
Recently, highly functionalized allyl boronates such as **150** were synthesized from allylic acetates **148** and pinacolatodiboron **149**. These boronates were employed for the allylation of aldehydes, furnishing the borate esters **151** which undergo lactonization to furnish the α -methylene- γ -butyrolactones in high yield and selectivity. The strength of Lewis acids as well as the substituents on the aromatic aldehydes have a profound influence on the stereochemical outcome of the reaction (Scheme 25) <2004OL481>.



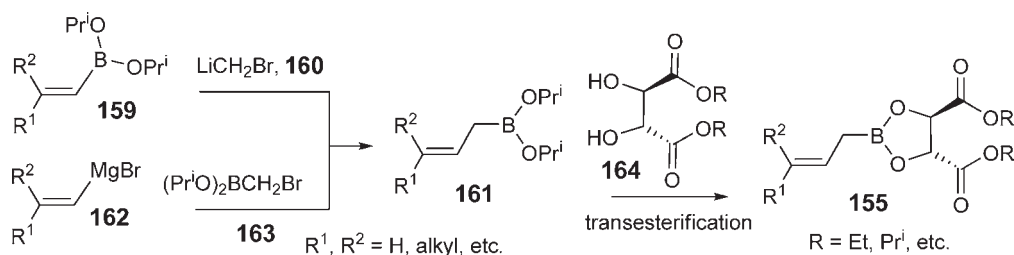
Scheme 25

6.15.8.4.2 Chiral allyl boronates

Allylboranes/boronates derived from several chiral auxiliaries have been prepared for the enantio- and diastereoselective formation of homoallylic alcohols and amines. Hoffmann, Brown, Yamamoto, Roush, and others have made significant contributions in the area of asymmetric 'allyl' boration. Hoffmann and co-workers pioneered the first asymmetric allylboration utilizing a camphor-derived auxiliary. They studied various allyl- and crotylboration reactions using this auxiliary for both single and double diastereoselective asymmetric synthesis. Yamamoto and co-workers introduced tartrate esters as chiral auxiliaries for propargylboration and allenylboration of aldehydes to produce allenyl and homopropargylic alcohols with very high ee. They showed that the ee's of the alcohols depend on the alkyl group of the tartrate ester: ethyl and isopropyl tartrates lead to lower ee's, while cyclododecyl and 2,4-dimethylpentyl tartrates lead to higher ee's. Roush extended the use of isopropyl tartrate as a chiral auxiliary for allyl and crotylboration. Tartramido allyl boronates proved to be better in allylboration than tartrate esters in terms of the selectivity. Several other 'allyl'-borating agents based on chiral boronates derived from chiral 1,2-diols **153–156**, oxazaborolane **157**, diazaborolane **158**, etc., have also been developed.

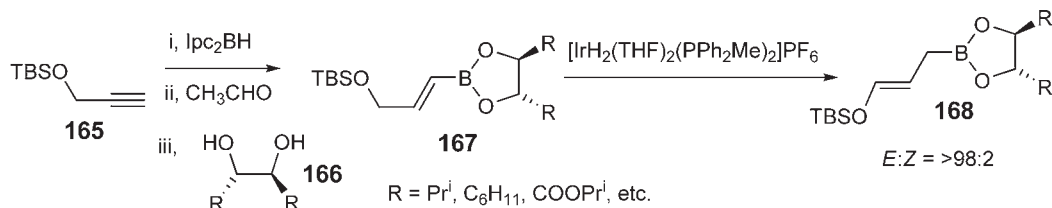


Typical protocols for the preparation of chiral allyl boronates involve Matteson homologation of vinyl boronates **159** with halomethyl lithium **160** or the vinylation of halomethyl boronate **163** with vinyl Grignard **162** followed by transesterification with dialkyl tartrate **164** (Scheme 26) <1996JOC100>.



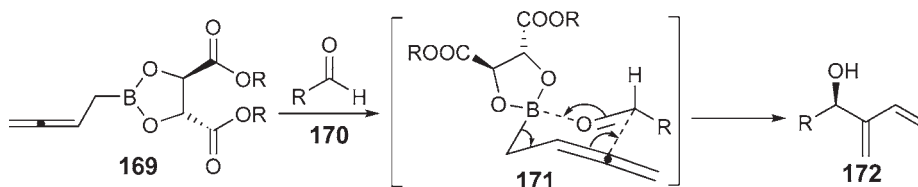
Scheme 26

Another alternative preparation of the allyl boronates involves iridium-catalyzed isomerization of *B*-vinyl boronates. Hydroboration of silylpropargyl ether **165** with Ipc₂BH followed by treatment with acetaldehyde generates the *B*-vinyl diethoxyboronate, that upon transacetalization with the chiral diol **166** furnishes the requisite chiral boronate. The positional isomerization of vinyl boronate to allyl boronate was realized by treatment of boronate **167** with [Ir(COD)(PPh₂Me)₂]⁺PF₆[−] under hydrogen atmosphere (Scheme 27) <1999JOC296>. The reaction proceeds with high conversion rate to afford allyl boronate **168** in >98:2 (*E*):(*Z*) ratio.



Scheme 27

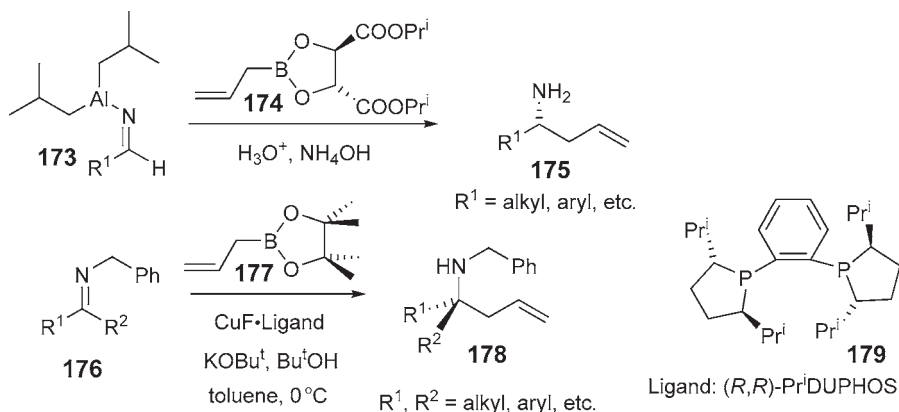
Brown and co-workers developed a novel homoallenyl boronate reagent **169** based on diisopropyl tartrate for the stereoselective homoallenylation of aldehydes **170**. The reagent **169** was prepared via homologation of the corresponding allenyl boronate or the alkylation of halomethyl boronate with allenyl Grignard similar to those reported in Scheme 26. The allyl boronate **169** upon reaction with aldehydes furnished the dienyl alcohols **172** with high ee (Scheme 28) <1996JOC100>.



Scheme 28

6.15.8.4.3 Allylboration of imines

Chiral addition of allyl metals to imines is one of the useful approaches toward the synthesis of homoallylic amines. These amines can be readily converted to a variety of biologically important molecules such as α -, β -, and γ -amino acids. Itsuno and co-workers utilized the allylborane **174** derived from diisopropyl tartrate and α -pinene for the enantioselective allylboration of imines. The corresponding *N*-aluminoimines **173** are readily available from the nitriles via partial reduction using diisobutylaluminium hydride (DIBAL-H) <1999JOM103>. Recently, *N*-benzylimines **176** have also been utilized for the asymmetric allylboration with allylpinacol boronate **177** in the presence of chiral phosphines as the chiral auxiliaries to obtain homoallylic *N*-benzylamines **178** in high yield and selectivity (Scheme 29) <2006JA7687>.



Scheme 29

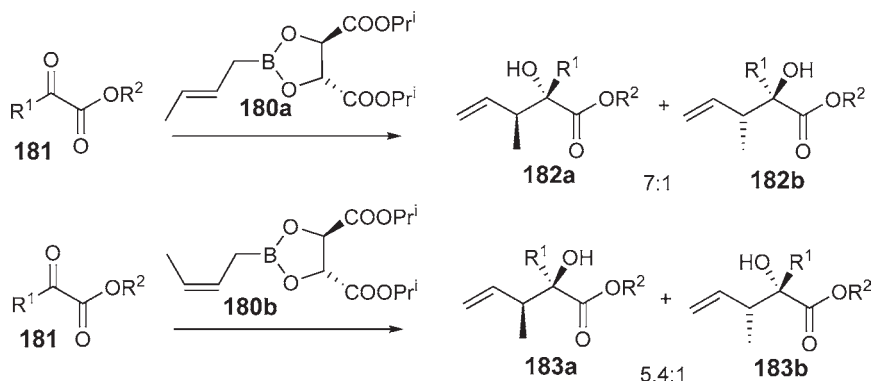
6.15.8.4.4 Allylboration of α -ketoesters

Crotylation of aldehydes with crotyl dialkylboranes and crotyl boronate esters are very well-developed reactions for the stereoselective formation of various substituted homoallylic alcohols, and all the four possible diastereomers could be synthesized based on the choice of (*Z*)- or (*E*)-crotyl reagent as well the antipodes of the chiral auxiliary used. Similarly, the crotylation of α -ketoesters **181** with (*E*)- and (*Z*)-*B*-crotyl boronate reagents **180a** and **180b** also furnished the *anti* (**182a**, **182b**) and *syn* (**183a**, **183b**) β -methyl- α -hydroxy esters respectively in good yield and diastereoselectivity (Scheme 30) <2004TL8285>.

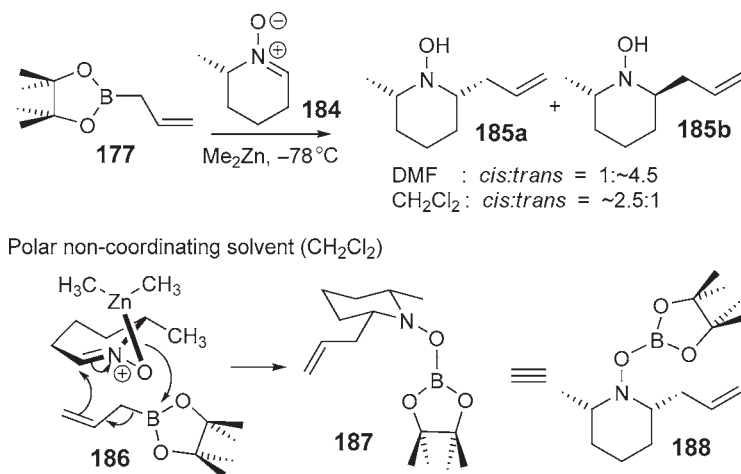
6.15.8.4.5 Allylboration of vinylnitrones

Allyl boronates **177** undergo stereoselective addition to chiral vinyl nitrones **184** in the presence of dialkylzinc as catalytic promoter. For example, 2-methyl tetrahydropyridine *N*-oxide **184** undergoes facile addition with allylpinacol boronate to yield the allylhydroxylamines **185a** and **185b** stereoselectively. The geometry of the two substituents on the six-membered ring depends on the nature of the solvent. In polar protic solvents, such as dimethylformamide (DMF), the *trans*-diastereomer was obtained as the major isomer due to attack of the allyl group from the least hindered face of the alkene. In polar noncoordinating solvents, such as CH_2Cl_2 , the dimethylzinc coordinates to nitron oxygen on the face opposite to the methyl group as depicted in **186**. Consequently, the allyl nucleophile

approaches the face opposite to that of dimethylzinc resulting in a *cis*-selective allylation of the vinyl nitronone providing the borate **188** in high diastereoselectivity (Scheme 31) <2006TA1074>.



Scheme 30



Scheme 31

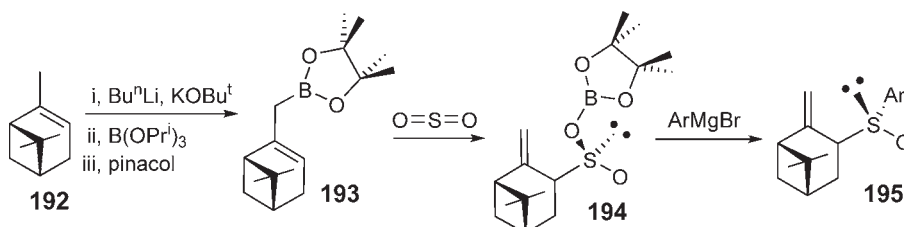
6.15.8.4.6 Bora-ene reaction of SO_2 and allyl boronates

Vogel and co-workers observed the reaction of allyl boronates **177** with sulfur dioxide to yield the mixed anhydride of sulfinic and boric acid **190**, which further reacts with Grignard reagents furnishing alkyl sulfoxides **191** in high yield. The mechanism involves the initial coordination of sulfur dioxide to allyl boronate to furnish **189**, which further undergoes bora-ene rearrangement to yield the mixed anhydride **190** (Scheme 32) <2006TL2783>.



Scheme 32

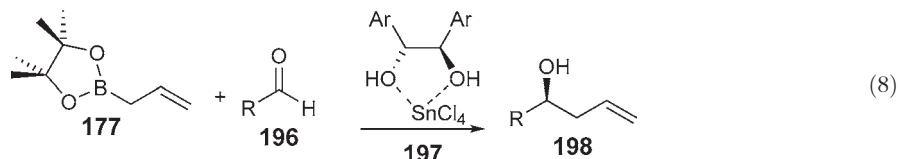
To determine the diastereoselectivity of the above bora-ene reaction, boronate **193** derived from α -pinene was synthesized. Reaction of α -pinene **192** with Schlosser's base ($\text{Bu}^n\text{Li} + \text{KO}^t\text{Bu}$) furnishes the allyl carbanion, which upon treatment with triisopropyl borate and subsequent transesterification with pinacol yields α -pinanyl pinacol boronate **193**. Bora-ene reaction with this allyl boronate and SO_2 at -78°C in CH_2Cl_2 yields the mixed anhydride **194** as a 2.3:1 mixture of diastereomers upon removal of excess SO_2 . Treatment of this mixture of anhydrides with aryl Grignard led to the formation of two diastereomers of aryl sulfoxides **195** in 3.2:1 ratio (**Scheme 33**) <2006TL2783>.



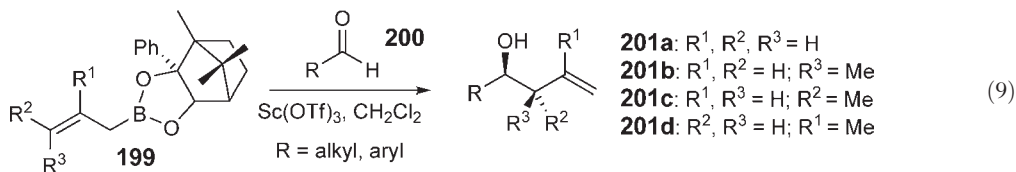
Scheme 33

6.15.8.4.7 Lewis acid-assisted allylboration of aldehydes

Allyl boronates react very slowly with carbonyl compounds as compared to the corresponding allyldialkylboranes, due to the presence of two oxygen atoms on boron which diminish the Lewis acidity of boron. However, the activity of the allyl boronates can be enhanced by the addition of Lewis acid catalysts. There have been two complementary approaches described for the stereoselective allylation with allyl boronates, one involving the use of chiral Lewis acid, and the other involving chiral allyl boronates in conjunction with achiral Lewis acid catalyst. Several chiral C_2 -symmetric-based 1,2-diols **197** have been employed in combination with SnCl_4 as a Lewis acid and excellent level of enantioselectivity has been observed for the allylation to furnish homoallylic alcohols **198** with high ee (**Equation 8**) <2006AGE2426>.



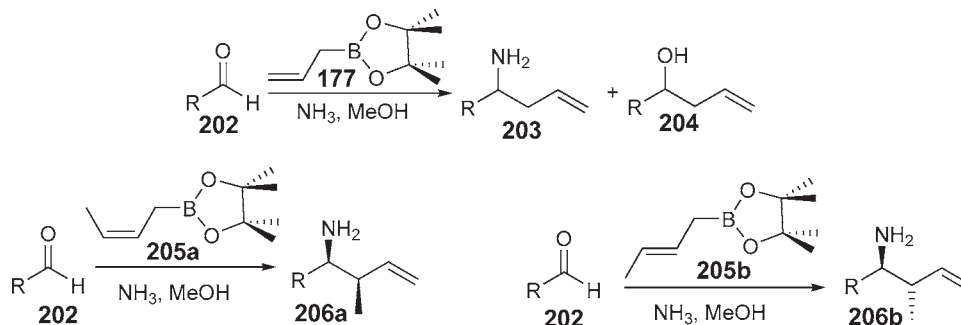
Alternatively, the allylboration of aldehydes **200** with chiral allyl boronates **199a–d** (conveniently prepared from camphorquinone in four steps) also provided the optically active homoallylic alcohols **201a–d** with high ee in the presence of achiral Lewis acid catalysts. These boronates are relatively unreactive with aldehydes at low temperatures in the absence of Lewis acid catalyst. However, they furnish low to moderate ee for the allylation at higher temperatures. Hall and co-workers were able to increase the reactivity of the allyl boronates at low temperatures by the addition of strong Lewis acids such as $\text{Sc}(\text{OTf})_3$ and obtained the homoallylic alcohols with high ee at low temperatures (**Equation 9**) <2003JA10160>.



6.15.8.4.8 Transfer aminoallylation

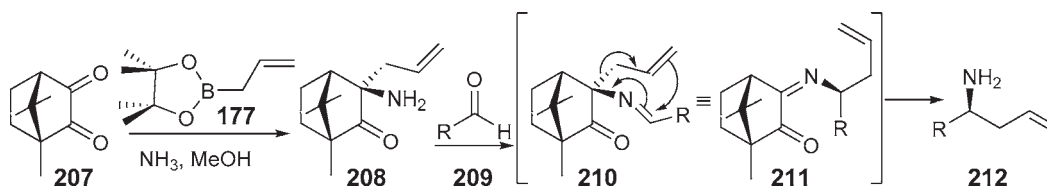
The conventional procedure for the synthesis of homoallylic amines involves the allylboration of imines (generated *in situ* from the partial reduction of expensive and toxic nitriles). Recently, a practical and operationally simple protocol has been developed for the stereoselective formation of homoallylic amines starting directly from the

aldehydes. Allylic boronates **177** react with aldehydes **202** in alcoholic ammonia yielding the homoallylic amines **203** in high yield and de. The authors observed high levels of diastereoselectivity for the (*Z*)- and (*E*)-aminocrotylation of aldehydes as well providing the *syn*- **206a** and *anti*- **206b** amines with high ee and de (**Scheme 34**) <2004JA7182>.



Scheme 34

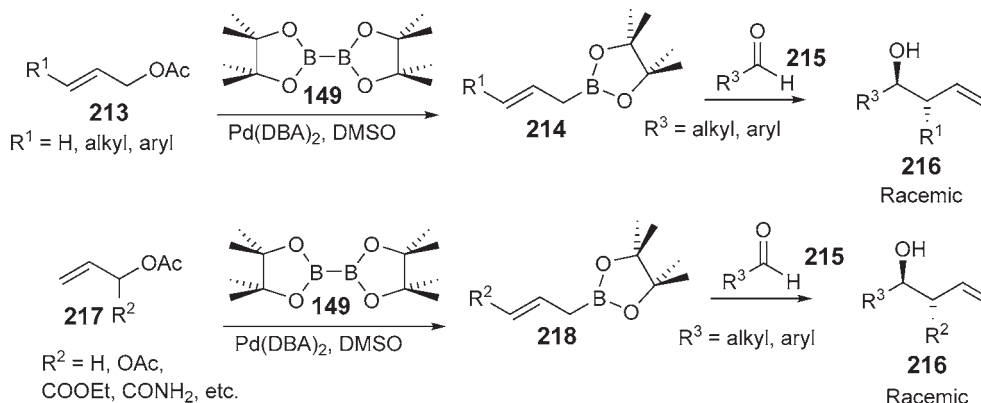
An asymmetric version of aminoallylation has been developed via a ‘transfer aminoallylation’ protocol. This methodology involves the initial aminoallylation of camphorquinone **207** with *B*-allylpinacol boronate **177** in alcoholic ammonia, furnishing the α -aminoketone **208** stereoselectively, which upon treatment with an aldehyde **209** and achiral allyl boronate **177** leads to the *in situ* formation of chiral imine **210** followed by allylation to yield the homoallylic amines **212** (**Scheme 35**) <2006JA11038>. Excellent levels of enantio- and diastereo control were observed for the allylation of a wide array of aldehyde substrates.



Scheme 35

6.15.8.4.9 Palladium-catalyzed allylation

A regio- and stereoselective formation of homoallylic alcohols and amines has been realized by the reaction of easily available allylic acetates **213** and **217** with bispinacolatodiboron **149** in the presence of palladium catalysts followed by the addition of aldehydes/imines (**Scheme 36**) <2005EJO2539>. The mechanism involves the formation of an η^3 -allyl-Pd complex, which inserts between B–B bond, and subsequent reductive elimination to yield the allyl

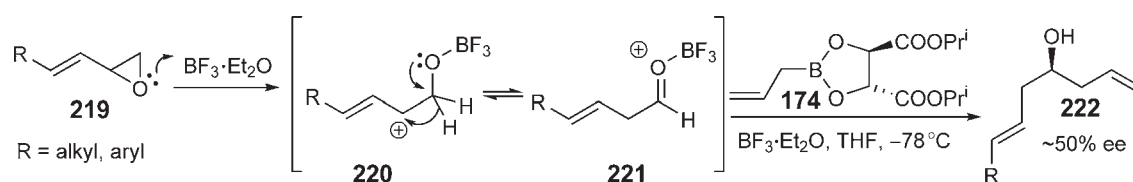


Scheme 36

boronates **214** with high (*E*)-selectivity (>98%). By employing chiral boronates derived from tartrates and α -pinene, moderate chiral induction has been achieved (up to 53% ee) for the corresponding alcohols **216**. The one-pot palladium-catalyzed allylation is operationally simple, and is of immense synthetic significance because of diverse functional group tolerance (esters, carbonates, amides, and nitriles remain unreactive under these conditions).

6.15.8.4.10 Lewis acid-catalyzed allylation of 2-vinylloxiranes

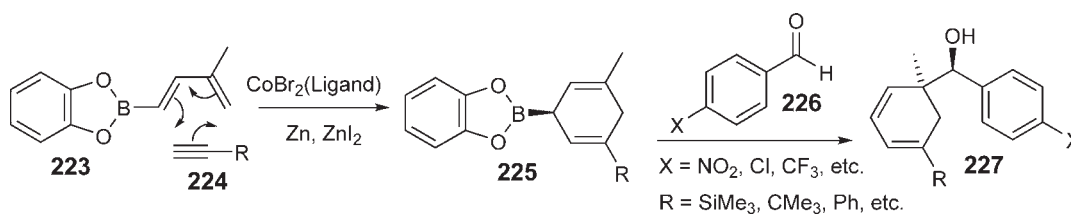
β,γ -Unsaturated aldehydes are poor substrates for allylation because of their inherent instability toward alkene isomerization; accordingly, very few reports describe the allylation of these substrates. However, Lautens *et al.* were able to overcome this problem via an indirect approach by the use of 2-vinylloxiranes **219** as surrogates for the above-mentioned aldehydes. The *in situ* formation of these otherwise unstable aldehydes is achieved via the Lewis acid treatment of vinylloxiranes to furnish aldehydes **221** which further undergo allylation with chiral allyl boronates **174** in moderate ee (Scheme 37) <2002OL83>. The chiral induction could be further enhanced by the use of allylboranes derived from α -pinene.



Scheme 37

6.15.8.5 Reactions of B–C: Diels–Alder Reactions

1-Borono-1,3-butadienes **223** have been utilized for stereoselective cobalt-catalyzed Diels–Alder cycloaddition to terminal alkynes **224**. Chiral diphosphine ligands on cobalt, such as norphos, lead to highly enantioselective [4+2] cycloaddition generating the cyclohexadienyl boronate derivative **225** in good yield (Scheme 38) <2006OL3287>. As a further application of this methodology, the boronates **225** have been utilized for the allylation of aromatic aldehydes **226** so as to obtain chiral homoallylic alcohols **227** with high ee.

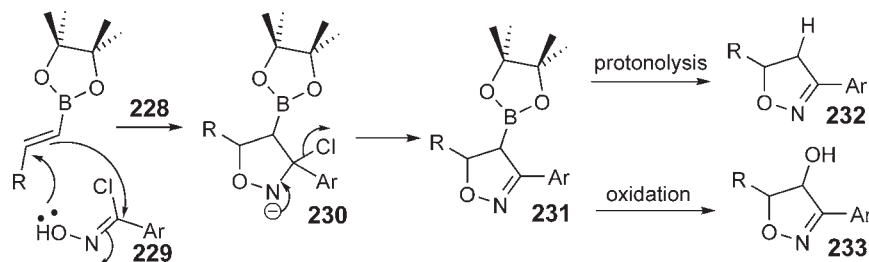


Scheme 38

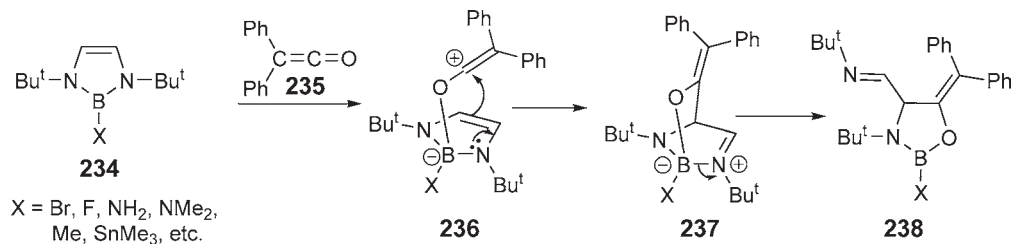
6.15.8.6 Reactions of B–C: Cycloadditions

Vinyl boronates **228** undergo 1,3-dipolar cycloaddition with aryl hydroximinoyl chloride **229** to furnish the imine-oxide **231**. The boronate moiety is highly labile under the reaction conditions and it undergoes protonolysis to yield isoxazolines **232**. Alternatively, the boronates could be oxidized with hydroperoxides or sodium percarbonate to furnish the 4-hydroxyisoxazolines **233** in good yield (Scheme 39) <2000T965>.

The reaction of diphenylketene with 1,3,2-diazaboroles **234** in hexane at -20°C leads to the formation of 1,3,2-oxazaborolidines **238** in 64–70% yield. The reaction proceeds via the coordination of the ketene oxygen to boron **236** followed by a [2+3] cycloaddition yielding the bicyclic intermediate **237**. Fission of B–N bond leads to the product formation as yellow to colorless crystals (Scheme 40) <2000OM5791>.



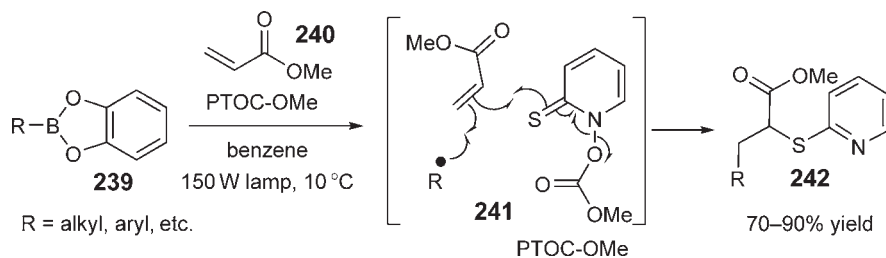
Scheme 39



Scheme 40

6.15.8.7 Reactions of B–C: Radical Conjugate Additions

Ollivier and Renaud [<1999CEJ1468>](#) reported the addition of organoboronates **239** to enones and enals in the presence of radical initiators such as O_2 to furnish 1,4-addition products in high yield. The alkyl radicals generated from the boronate esters undergo 1,4-addition with the enals or enones. However, this reaction fails with α,β -unsaturated esters as a consequence of an inefficient propagation step resulting from the reaction between the radical adducts and boronate ester. Use of a better radical chain-transfer agent, such as Barton carbonate PTOC-OMe ((methoxy)(pyridine-2-thione-*N*-oxy)carbonyl) **241**, provides a clean conjugate addition to α,β -unsaturated esters and sulfones **240** yielding the corresponding Michael addition products **242** (Scheme 41) [<2000AGE925, 2003JOC5769>](#).



Scheme 41

Vinyl boronates **244** undergo radical addition to α,β -unsaturated ketones **245** in the presence of a rhodium catalyst and (*S*)-BINAP to yield the 1,4-addition product **246** in high ee and yield [<1998TL8479>](#). Under the reaction conditions, the boronates undergo hydrolysis to provide the corresponding boronic acids, which further undergo conjugate addition with the enone (Scheme 42).

6.15.8.8 Reactions of B–X

B-Bromoboronates **247** undergo a wide variety of reactions because of the inherent reactivity. The reduction of bromoborane to boron hydrides **248** can be effectively carried out in the presence of hydride reducing agents such as

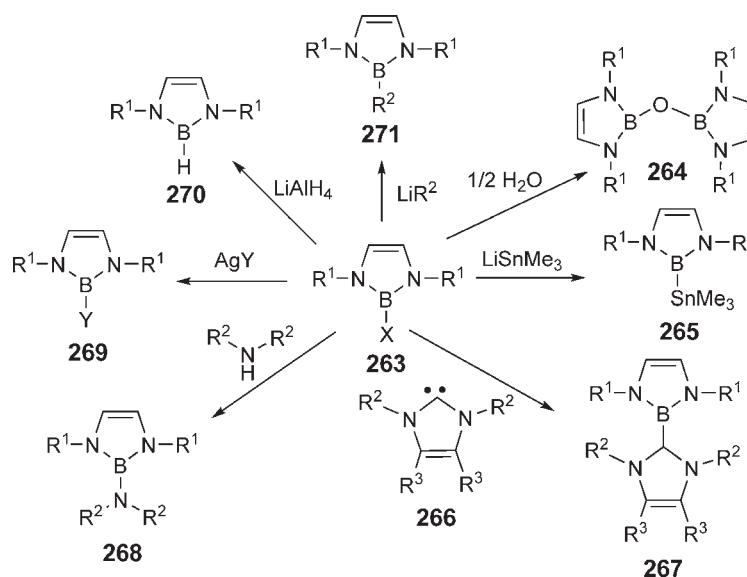


The reaction scheme illustrates the synthesis of various boron and silicon compounds from a central boronate ester (247). The central compound, 247, is a cyclic boronate ester with two R groups on the boron atom and two R groups on the carbon atoms of the ring. The reactions are as follows:

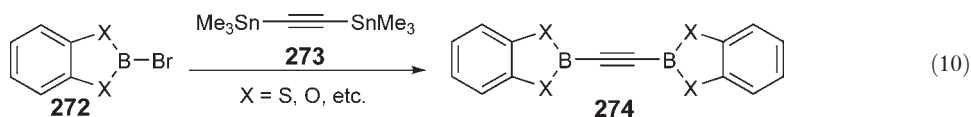
- 247** reacts with Ph_3GeLi to form **256**, a cyclic boronate ester with a GePh_3 group.
- 247** reacts with Me_3SiNCS to form **251**, a cyclic boronate ester with a B-N=C=S group.
- 247** reacts with RMgBr to form **249**, a cyclic boronate ester with a B-R group.
- 247** reacts with LiAlH_4 or SiMe_3H to form **248**, a cyclic boronate ester with a B-H group.
- 247** reacts with $\text{LiM}(\text{Cp})_2$ to form **257**, a cyclic boronate ester with a $\text{LiM}(\text{Cp})_2$ group.
- 247** reacts with L_nM to form **260**, a cyclic boronate ester with a L_nM group.
- 247** reacts with $\text{Ar-Si(Ar)}_2\text{-Si(Ar)}_2\text{-Ar}$ to form **261**, a cyclic boronate ester with a Si-Si bridge.
- 247** reacts with $\text{Ar-Si(Ar)}_2\text{-Cl}$ to form **262**, a cyclic boronate ester with a $\text{B-Si(Ar)}_2\text{-Cl}$ group.
- 247** reacts with $\text{C}_6\text{H}_5\text{M}$ to form **252**, a cyclic boronate ester with a $\text{C}_6\text{H}_5\text{M}$ group.
- 247** reacts with $\text{C}_6\text{H}_5\text{B(OR)}_2$ to form **253** and **254**, cyclic boronate esters with a $\text{C}_6\text{H}_5\text{B(OR)}_2$ group.
- 247** reacts with $\text{C}_6\text{H}_5\text{B(OR)}_2$ to form **258**, a cyclic boronate ester with a $\text{C}_6\text{H}_5\text{B(OR)}_2$ group.
- 247** reacts with $\text{C}_6\text{H}_5\text{B(OR)}_2$ to form **259**, a cyclic boronate ester with a $\text{C}_6\text{H}_5\text{B(OR)}_2$ group.

Scheme 43

1,3,2-Dioxo-, oxathia-, and dithiaboroles undergo efficient transmetalation with alkynyl stannanes, furnishing the *B*-alkynyl boroles. Thus the reaction of bis(trimethylstannyl) acetylene **273** with 2 equiv of bromoboranes **272** in toluene at room temperature furnishes air-sensitive boroles **274** as colorless solids in good yield (Equation 10) <2004EJ14223>.

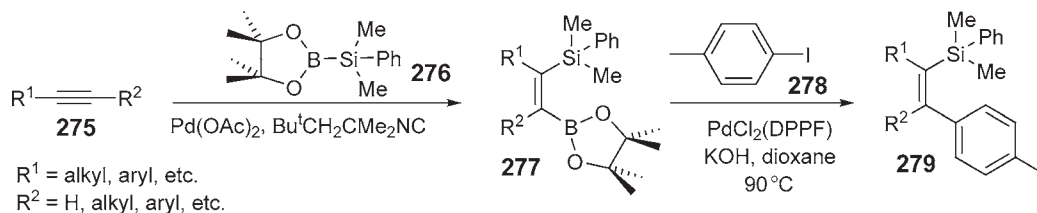


Scheme 44



6.15.8.9 Reactions of B-Si

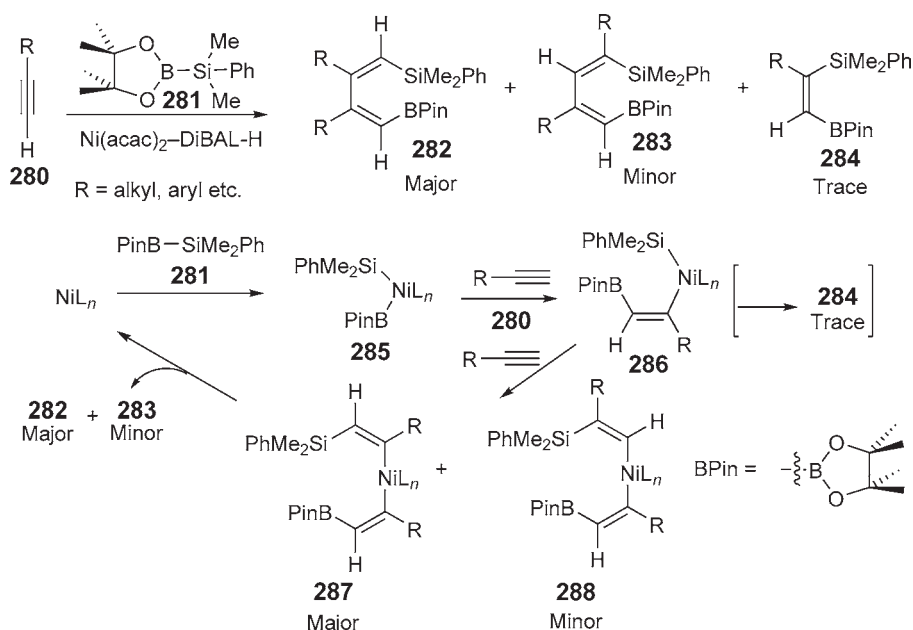
Addition of the Si-B bond in dimethylphenylsilyl pinacol boronate **276** across triple bonds in the presence of palladium alkylisocyanide complex leads to the regio- and stereoselective formation of (*Z*)-1-boryl-2-silylalkenes. Silaboration takes place due to the ability of palladium isocyanide complex to undergo oxidative insertion to B-Si bond. The mild reaction conditions facilitate product formation for a wide variety of substrates such as alkyl, aryl-substituted terminal, and internal alkynes **275**. The corresponding product vinyl boronates **277** undergo palladium-mediated cross-coupling under Suzuki-Miyaura conditions to afford 1-aryl-2-silyl alkenes **279** (Scheme 45) <1996CC2777>. The corresponding silaboration of alkenes with *B*-silylpinacol boronates is catalyzed by the use of $\text{Pt}(\text{CH}_2=\text{CH}_2)(\text{PPh}_3)_2$ instead of palladium-isonitrile complex <1997AGE2516>.



Scheme 45

Suginome *et al.* discovered that the use of $\text{Ni}(\text{acac})_2$ and DIBAL-H as a reductant results in the double insertion of alkynes **280** across the B-Si bond in silaborane **281** to afford silaborated butadienes **282-284** (acac = acetylacetonate). NMR experiments revealed the stereoselective formation of head-to-head dimerization product **282** as the

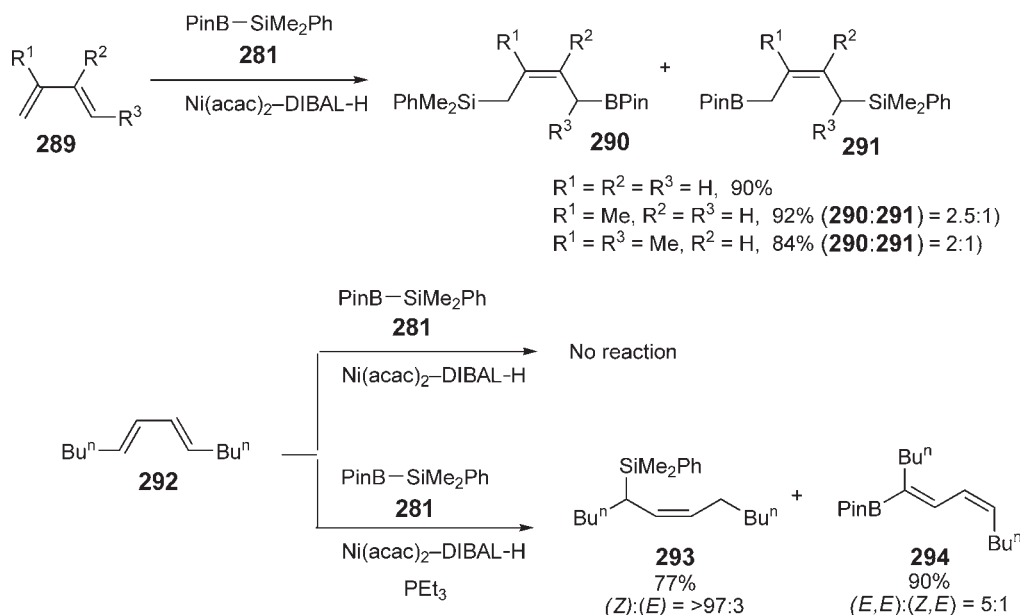
major isomer, and head-to-tail dimerized product **283** as the minor isomer. Monomeric silaborated product **284** was obtained only in trace quantities (Scheme 46). The mechanism for the dimerization involves the initial oxidative addition of *B*-(dimethylphenylsilyl)pinacolborane to the nickel catalyst to generate the complex **285**. Coordination of Ni with the alkyne followed by *cis*-insertion of terminal alkyne into the B–Ni bond generates the vinyl boronate species **286**. This insertion is highly regioselective, leading to the exclusive Ni–C bond formation at the internal alkynyl carbon due to the steric effects (much similar to hydroboration, wherein the boron atom always attaches to the least sterically crowded carbon). This terminal vinyl boronate–nickel complex **286** further undergoes regioselective insertion of second alkyne across the Si–Ni bond with moderate preference for the Ni–C bond formation at the internal alkynyl carbon generating a mixture of vinyl silanes **287** and **288**, which eventually produce the dimerized silaboranes **282** and **283** as major and minor products, respectively, upon reductive elimination (Scheme 46) <1998OM5233>.



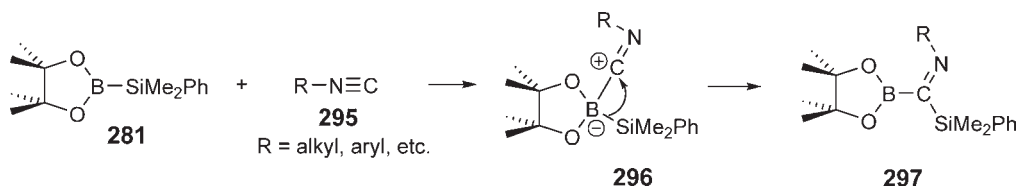
Scheme 46

The Ni(acac)₂ catalyst system also promotes the 1,4-addition of Si–B bond to 1,3-butadienes **289** furnishing 4-boryl-1-silyl-2-alkenes **290** and **291** as predominantly (*Z*)-diastereomer (>99%) <1999OL1567>. Replacing the nickel catalyst system with Pt(CH₂=CH₂)(PPh₃)₂ complex leads to formation of the corresponding conjugate silaborated adduct **290** as a 1:1 mixture of (*Z*)- and (*E*)-isomers <1998JA4248>. 2-Methyl- and 1,3-dimethyl-substituted 1,3-butadienes stereoselectively undergo B–Si addition furnishing the (*Z*)- silaboranes **290** and **291** as ~2:1 regiomic mixtures. However, 1,1-, and 1,4-disubstituted butadienes fail to undergo B–Si insertion under these conditions. Addition of phosphine ligand leads to the complete consumption of starting diene **292**, but instead of the expected 4-boryl-1-silyl-2-alkenes, two products were obtained and were characterized as allylsilane **293** and dienyl boronate **294**, respectively (Scheme 47) <2003JOM43, 2006OL2929>.

In contrast to the silaborations of carbon–carbon multiple bonds that require the use of transition metal catalysts, insertion of isonitriles across B–Si bonds proceeds thermally without the use of any catalysts. *B*-dimethylphenylsilyl pinacol boronate **281** reacts with alkyl or aryl isonitriles **295**, via ‘ate’ complex **296** formation, followed by silyl migration to the α-carbon atom generating the 1-boryl-1-silyliminomethanes **297** in moderate to good yields. The product imines were crystallized as BH₃ adducts and analyzed by X-ray crystallography to reveal the (*E*)-geometry of the borane coordinated to imine moiety in which the alkyl and silyl groups were observed to be *trans* to each other (Scheme 48) <2000OM719>.



Scheme 47

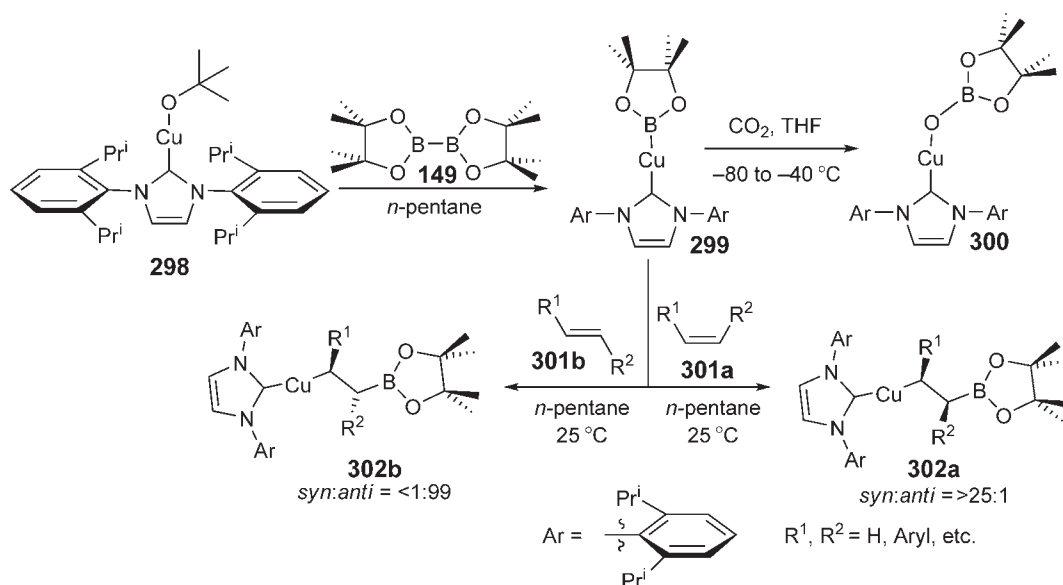


Scheme 48

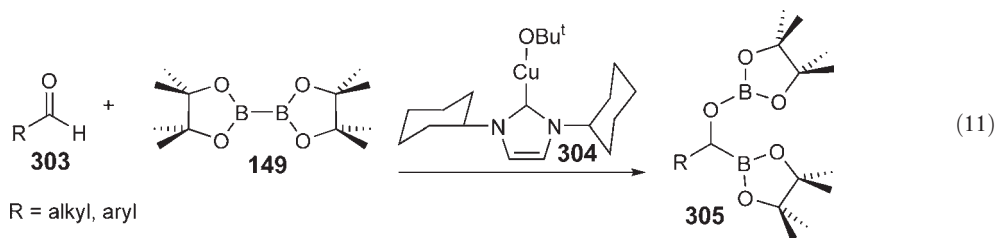
6.15.8.10 Reactions of B–Cu

Recently, ‘boryl’ cuprates have gained prominence because of the relative stability of the ensuing species as compared to the corresponding boryl metallates (B–Li, B–Na, etc.). Moreover, boryl copper offers the possibility of a soft cation which eventually facilitates nucleophilic substitution and addition reactions. The boryl cuprates can be readily generated via the reaction of inorganic copper salts with pinacolatodiboron. The reaction of *N,N*-diaryl dihydroimidazolyl copper *tert*-butoxide **298** with bispinacolato diboron **149** in pentane provides the boryl cuprate **299**, which readily undergoes oxidation with carbon dioxide yielding the copperborate **300** <2005JA17196>. The boryl cuprate **299** also undergoes addition to vinyl arenes yielding the 1-borono-2-cupryl species **302a** and **302b**. The addition proceeds with high *syn*-diastereoselectivity; hence *cis*-stilbene **301a** furnishes *syn*-adduct **302a** in >25:1 ratio while *trans*-stilbene **301b** provides the *anti*-adduct **302b** as a single diastereomer (Scheme 49) <2006OM2405>.

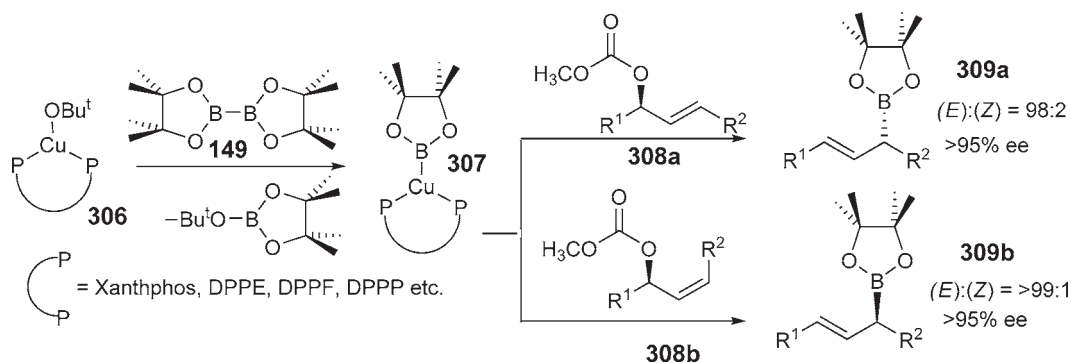
The copper *tert*-butoxide salts **304** have also been utilized for the diboration of aldehydes **303**. The insertion of carbonyl group of aldehyde between the metal and boron leads to the formation of metal–carbon σ -bond, which further undergoes transmetallation with another equivalent of diboron reagent to generate a C–B bond. An imidazolylcopper catalyst efficiently catalyzes the diboration of aldehydes yielding synthetically useful masked α -hydroxyalkyl anion equivalents **305** in high yield (Equation 11) <2006JA11036>.



Scheme 49



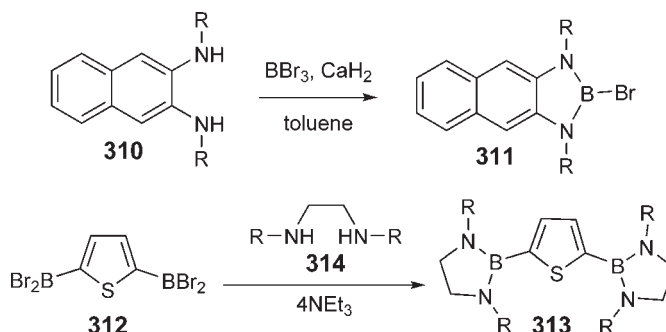
Copper *tert*-butoxide reacts with pinacolatodiboron **149** in the presence of bis-phosphines, such as xanthphos, bis(diphenylphosphino)ethane (DPPE), DPPF, 1,3-bis(diphenylphosphino)propane (dppp), etc., yielding the bisphosphinocopper boronate **307** in high yield. The resulting boryl copper species have been utilized for the nucleophilic S_N2' displacement of allylic carbonates **308a** and **308b** yielding the allylic boronates **309a** and **309b** with allylic rearrangement. The reaction is highly diastereoselective affording the (*E*)-alkene as the major isomer (Scheme 50) <2005JA16034>.



Scheme 50

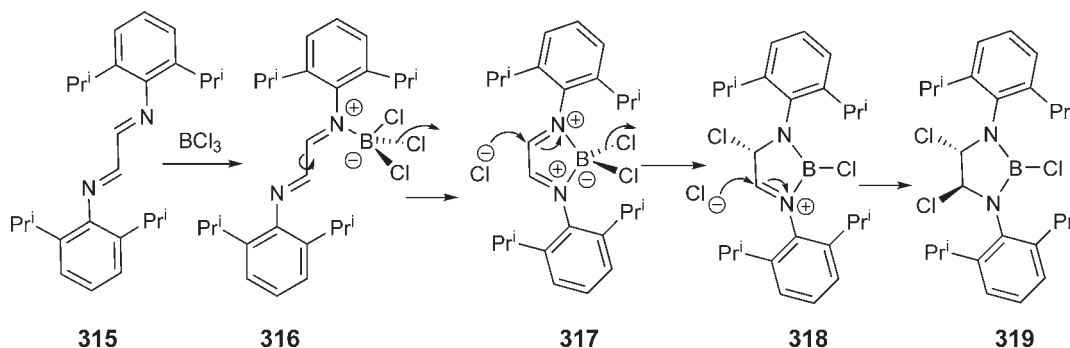
6.15.9 Ring Syntheses from Acyclic Compounds Classified by Number of Ring Atoms Contributed by Each Compound

The typical preparation of the cyclic boroles from acyclic starting materials usually involves acid base chemistry or transacetalization protocols. 1,3,2-Diazaborolidines, such as **311** and **313**, are readily available via the reaction of the corresponding amines **310** and **314** with boron tribromide (BBr_3) and boron halide **312** (Scheme 51) <2006JCD3777>.



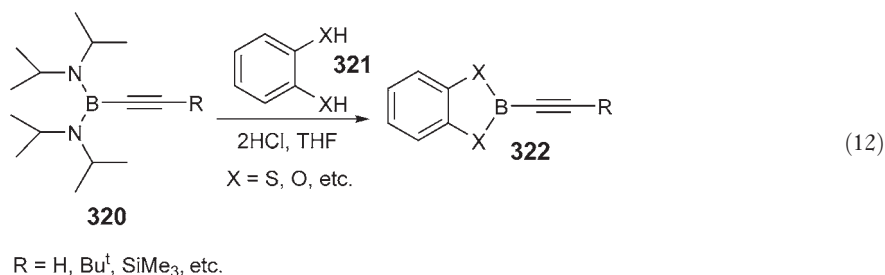
Scheme 51

1,2-Ethylene diimines such as *N,N'*-bis(2,6-diisopropylphenyl)-1,4-azadiene **315** undergo a unique double chloroboration reaction with boron trichlorides furnishing the trichlorodiazaborolidine **319** stereoselectively. The product formation is explained by the initial coordination of BCl_3 to the imine followed by elimination of chloride to yield intermediate **317**, which further eliminates another chloride to yield intermediate **318**. Further addition of chloride to the second imine generates the final product **319** as an orange solid (Scheme 52) <2001CC1136>.

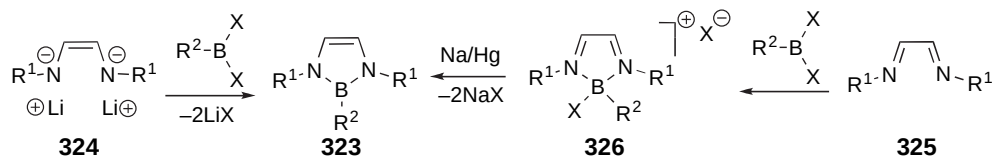


Scheme 52

1,3,2-Dioxa-, 1,3,2-dithia-, and 1,3,2-oxathiaborolanes **322** can be readily prepared by reaction of bis(diisopropyl-amino)borylacetylenes **320** with the appropriate diol, dithiol, or hydroxythiol (**321**: $\text{X} = \text{O}, \text{S}$) in the presence of 2 equiv of HCl (Equation 12) <2004EJI4223>.



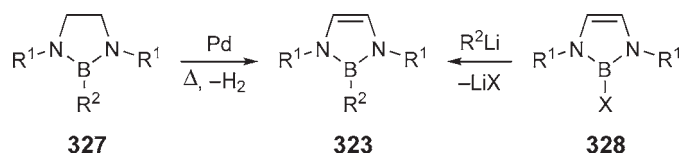
One of the prominent synthetic protocols for the preparation of diazaborolines **323** involves the reaction of lithiated diamides **324** with boron halides and subsequent elimination of lithium halide salt. Another protocol involves synthesis via cyclocondensation of 1,2-diimines **325** with alkylboron halides to yield the diazaborolium salts **326** that undergo reduction with sodium amalgam yielding the diazaborolines **323** in high yield (Scheme 53) <2005EJI4715>.



Scheme 53

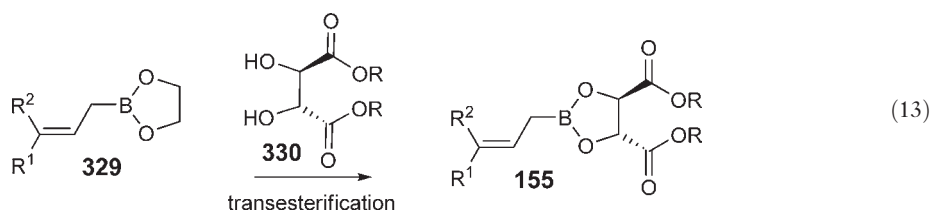
6.15.10 Ring Syntheses by Transformations of Another Ring

The reaction of saturated diazaborolidines **327** with palladium at very high temperature leads to dehydrogenation yielding the diazaborolines **323** albeit in low yields <2005EJI4715>. Another synthetic protocol involves the addition of alkyl lithium species to the corresponding *B*-bromodiazaborolines **328** to yield the *B*-alkyldiazaborolines **324** in high yield (Scheme 54).



Scheme 54

Another common synthesis of cyclic boron compounds involves transesterification. For example, the chiral allyl boronates **155** can be synthesized via the reaction of dioxaborolane **329** with dialkyl tartrate **330** in high yield. The transacetalization affords an attractive alternative to the formation of these chiral boronates, which are otherwise difficult to prepare (Equation 13).

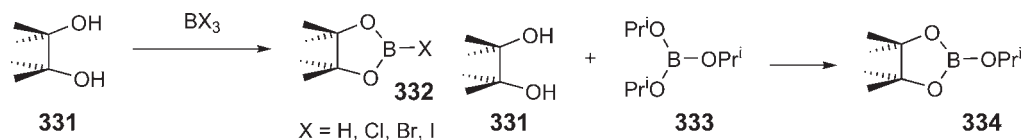


6.15.11 Syntheses of Particular Classes of Compounds and Critical Comparison of the Various Routes Available

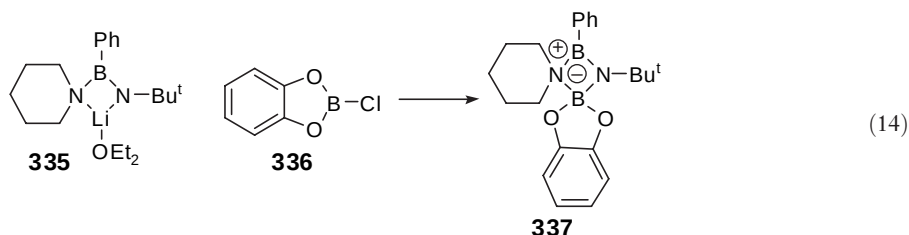
6.15.11.1 Ring Systems Containing Boron and Two Oxygen Atoms

Important examples of this type of compounds include pinacolborane, catecholborane, etc. These compounds are readily available by the reaction of pinacol **331** or catechol with either borane or boron halides. Transesterification also provides an attractive alternative for the synthesis of these compounds (Scheme 55).

Certain diaminodioxaborole salts **337** could be easily prepared by the reaction of *B*-chlorocatecholborane **336** with the corresponding lithium amide **335** (Equation 14) <2004EJI3629>.

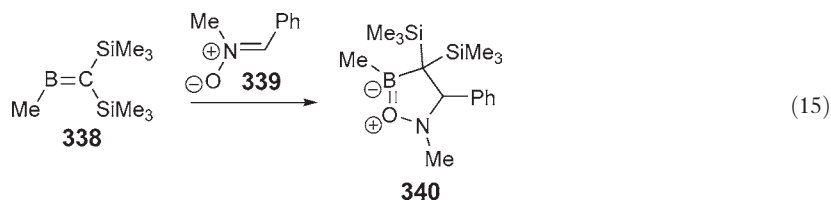


Scheme 55



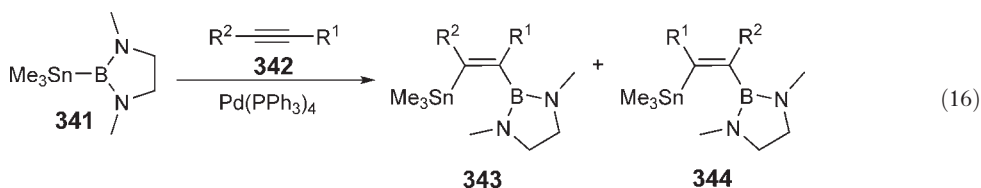
6.15.11.2 Ring Systems Containing Boron, Oxygen, and Nitrogen Atoms

Apart from the conventional transesterification and acid base reaction protocols mentioned above, oxazaborolidines could also be synthesized by a facile [3+2] cycloaddition of the *N*-oxide **339** with *B*-methyl methyldene borane **338** (Equation 15) <2004ZFA508>.

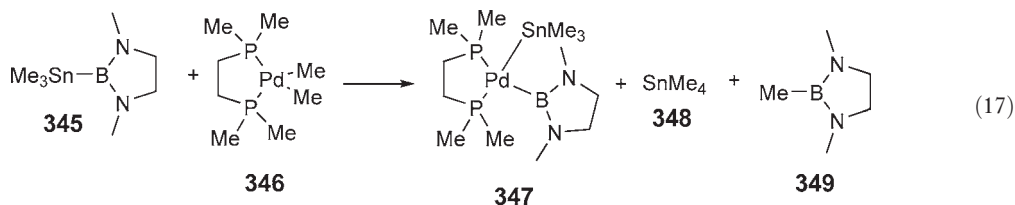


6.15.11.3 Ring Systems Containing Boron and Two Nitrogen Atoms

Similar to dioxa- and oxazaborolanes, diazaborolanes can also be synthesized via transesterification protocols. Tanaka and co-workers discovered that reaction of borylstannanes **341** with alkynes **342** in the presence of catalysts such as $Pd(PPh_3)_4$ and $Pd(DBA)_2$ yields the (*Z*)-alkenes **343** and **344** regioselectively (Equation 16) <1996OM5450>.

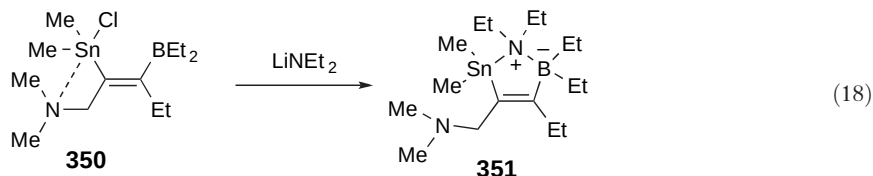


To determine the mechanism of the above reaction, a modified palladium catalyst, namely $Me_2Pd(DMPE)$ **346** (DMPE = 1,2-bis(dimethylphosphino)ethane), was reacted with stannylborane **345** and it was observed that the catalysis is triggered by the oxidative insertion of the B–Sn bond across the palladium atom, which was evident by the formation of $SnMe_4$ as well as *B*-methyldiazaborolidine **349** along with the expected palladium insertion product **347** (Equation 17) <1996OM5450>.

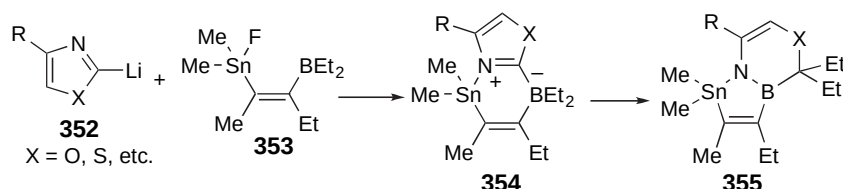


6.15.11.4 Ring Systems Containing Boron and Other Heteroatoms

The hypervalent tin compound **350** reacts with the strong base lithium diethylamide leading to the elimination of chloride and subsequent coordination between B–N–Sn to form azoniastannaboratole derivative **351** (Equation 18) <2003JOM188>. The starting materials (*cis*-borylstannanes **350**) can be obtained by the organoboration of alkynylstannanes stereoselectively.

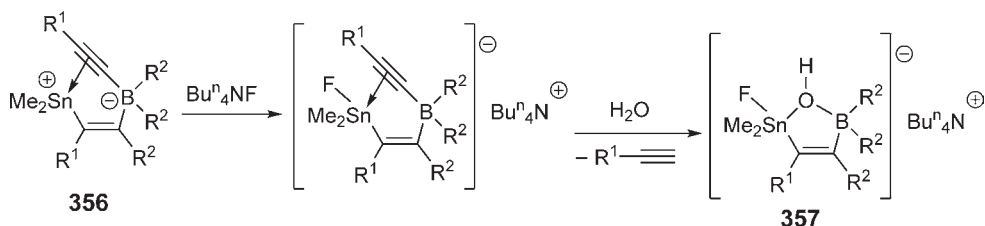


Another significant method for the synthesis of azoniastannaboratoles involves the reaction of lithiated azoles **352** with vinylstannaboranes **353** at low temperature. The intermediate **354** thus obtained upon warming to room temperature undergoes final rearrangement to yield the required product **355** in high yield and stereoselectivity (Scheme 56) <1995JOM197>.



Scheme 56

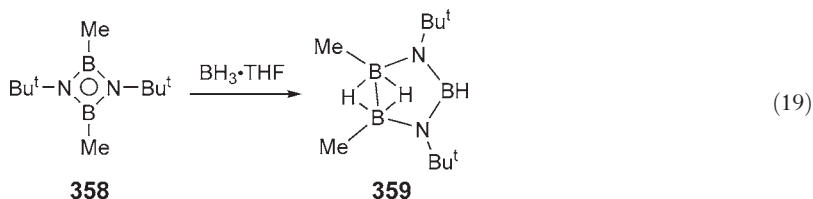
The oxoniastannaboratole derivatives **357** are synthesized by the reaction of zwitterionic η^2 -(alkynylborate)alkenyl stannane derivatives **356** with tetrabutylammonium fluoride (TBAF) followed by water. The stannanes **356** react readily with TBAF even at -65°C yielding the Sn–F compounds, which then react with water with concomitant elimination of alkyne to yield the stannaboratole **357** in high yield (Scheme 57) <1999JOM93>.



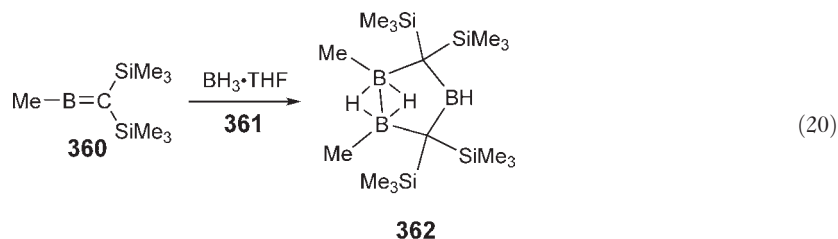
Scheme 57

6.15.11.5 Ring Systems Containing Boron and Multiple Heteroatoms

The diazatriborole **359** can be obtained by the reaction of BH_3 with diazadiboretane **358** (Equation 19). The final product **359** has a binding of two boryl ends via two B–H–B three-center, two-electron bridged bonds.

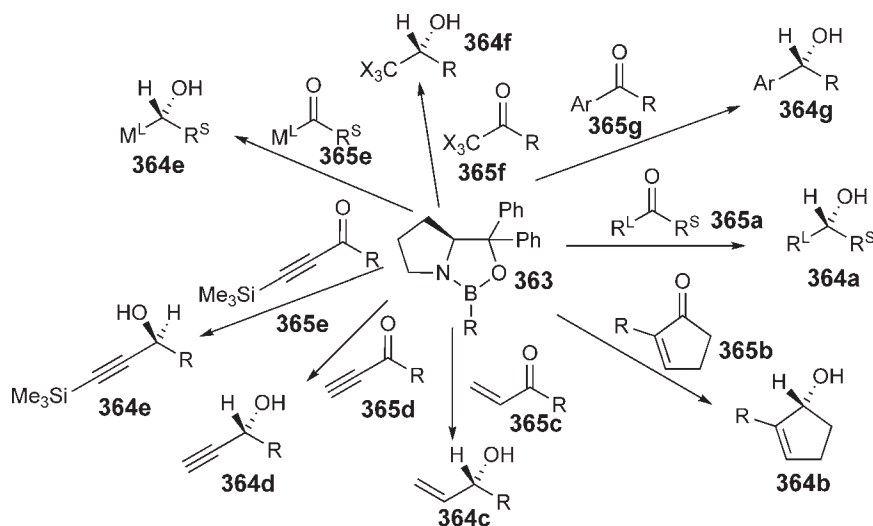


Alkylidene borane **360** undergoes reaction with $\text{BH}_3 \cdot \text{THF}$ **361** to yield a dimerized cycloaddition product **362**. BH_3 hydroborates the $\text{B}=\text{C}$ bond in two molecules of methyldiene borane **360**. The regioselectivity of hydroboration is governed by the electronic factors which facilitate the attack of boron (from BH_3) on the two terminal carbon atoms, thus generating the $\text{B}-\text{C}-\text{B}-\text{C}$ chain. The final product is obtained by the binding of two boryl ends via two $\text{B}-\text{H}-\text{B}$ three-center, two-electron bridged bonds (Equation 20) <2004ZFA508>.



6.15.12 Important Compounds and Applications

Asymmetric reduction has been an extensively studied area of research for the past few decades. Several chirally modified reducing agents derived from LiAlH_4 , NaBH_4 , BH_3 , and AlH_3 have been developed and successfully utilized for chiral reduction. Compounds such as CBS catalyst (an 1,3,2-oxazaborolidine derivative) have gained prominence owing to their widespread commercial applications especially in the stereoselective reduction of ketones and imines to the corresponding alcohols and amines. The reaction of chiral tertiary aminoalcohols with borane furnishes oxazaborolidines with concomitant elimination of 2 equiv of hydrogen. Corey, Bakshi, and Shibata developed the diphenylprolinol-based oxazaborolidine catalyst (CBS catalyst) for the stereoselective reduction of a wide variety of ketones. The mechanism of reduction with the *B*-alkyl 1,3,2-oxazaborolidine involves the coordination of the ketone oxygen with the boron followed by hydride delivery from an additional borane added as a co-reductant. Alkyl, aryl, aralkyl, vinyl, acetylenic, and a wide variety of organometallic ketones (**365a–f**) undergo facile reduction with the CBS catalyst **363** furnishing the corresponding alcohols (**364a–g**) with high ee. A wide variety of functional groups are tolerant under these conditions (Scheme 58) <1998AGE1986>.



Scheme 58

6.15.13 Further Developments

6.15.13.1 Theoretical Methods

The density functional calculations of the electronic, and molecular structures of σ -bonded manganese complexes of catechol and pinacolborane were investigated at the DFT B3LYP and BP86 levels to understand the structures, bonding, and energetics of the interactions and were found to be in excellent correlation with the experimental values <2007JOM1997>.

Recently, density functional calculations were performed to determine the nature and stereochemistry of the olefin insertion into the Cu–B bond of (NHC)Cu boryl complexes (NHC = *N*-heterocyclic carbene). The theoretical calculations confirm that the mechanism of insertion involves a nucleophilic attack of the boryl ligand on the coordinated olefin. Furthermore, the hyperconjugation of Cu–C (σ -bond) with the empty *p* orbital in boron was found to be responsible for the small Cu–C–B bond angles, which was also experimentally confirmed by the X-ray diffraction studies of these boryl–copper complexes <2007OM2824>.

6.15.13.2 Thermodynamic Aspects

Lavigne and coworkers have recently reported the self-assembly of poly(dioxaborole)s **366** as blue-emissive materials (Figure 5) <2006JA16466>.

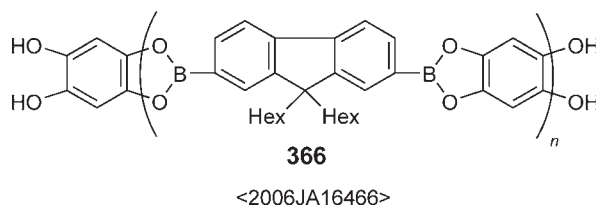


Figure 5

6.15.13.3 Reactivity of Fully Conjugated Rings

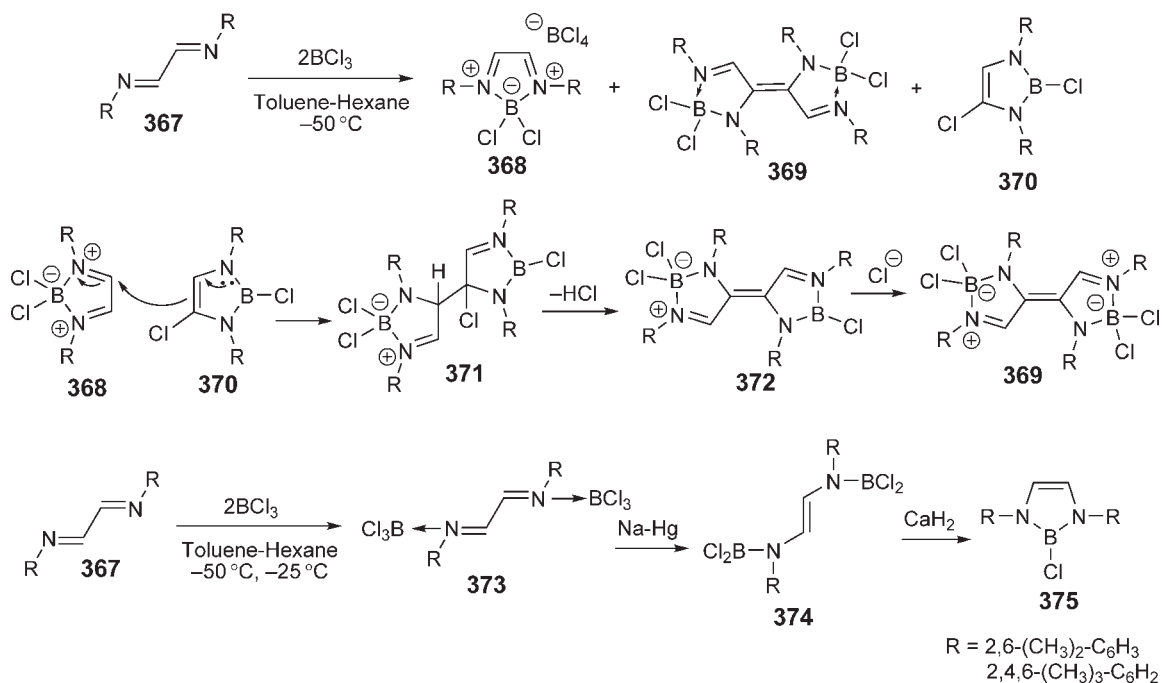
Weber and coworkers reported the synthesis of novel substituted borazoles. The reaction of boron trichloride with 1,2-diimines **367** provide a mixture of products. The formation of dimeric borazole **369** was explained based on a nucleophilic attack of the chloroborane **370** on the 'ate' complex **368** followed by dehydrohalogenation. Alternatively, a controlled addition of BCl₃ to the diimine **367** results in a clean formation of the imine–borane complex **373** that upon reduction with sodium amalgam and calcium hydride provided the chloroborazole **375** (Scheme 59) <2006EJI5048>.

6.15.13.4 Reactions of B–X

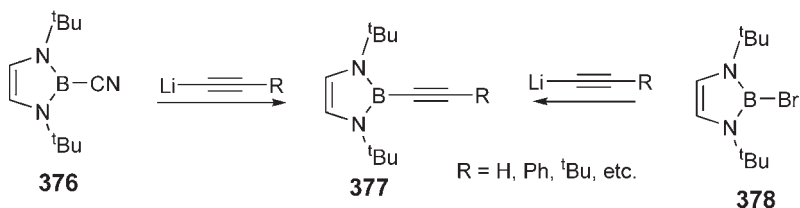
Weber and coworkers have reported the synthesis of several borylacetylides **377** based on the reactions of boron nitriles **376** or halides **378** with the corresponding acetylides (Scheme 60) <2007ZFA563>.

6.15.13.5 Reactions of B–Si

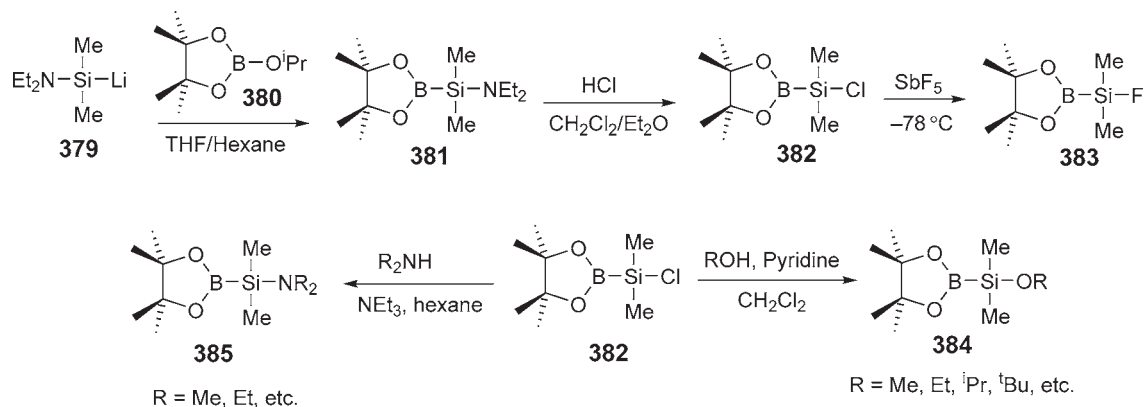
Recently silylboronates functionalized on silicon were reported by Suginome and coworkers via the reaction of silyl lithium **379** with borate ester **380** to yield the borosilamide **381**. Further transformations on the amine with HCl furnish the chlorosilane **382**, and reaction of SbF₅ with **382** provide the fluorosilane **383**. The chlorosilanes **382** also react with alcohols or amines to provide the alkoxy or amine substituted silylboronates **384** and **385** respectively (Scheme 61) <2007OM1291>.



Scheme 59



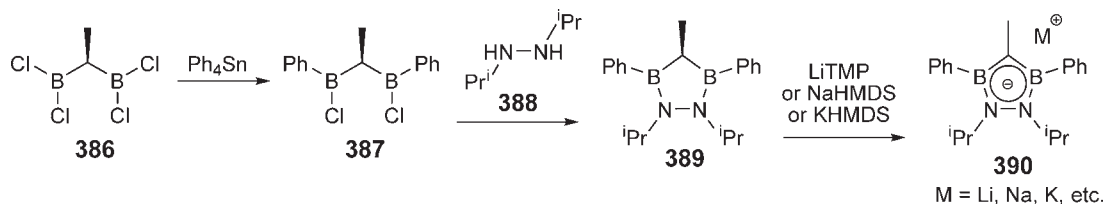
Scheme 60



Scheme 61

6.15.13.6 Ring Systems Containing Boron and Multiple Heteroatoms

Roesler and coworkers have reported the synthesis of substituted diaza-diborolyls **390** as novel cyclopentadienyl derivatives containing one carbon atom in the ring skeleton. The reaction of **386** with SnPh_4 followed by addition of hydrazine **388** yields the diazadiborolane **389** that upon proton abstraction provides an aromatic diazadiborolyl **390** (Scheme 62) <2007OM1750>.



Scheme 62

References

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6.16

Three or Four Heteroatoms including at least One Silicon

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6.16.1 Five-Membered Rings Containing Tetravalent Silicon Atoms	656
6.16.1.1 Introduction	656
6.16.1.2 Theoretical Methods	658
6.16.1.2.1 Structure and spectroscopic properties	658
6.16.1.2.2 Thermodynamic properties and reactivity	658
6.16.1.3 Experimental Structural Methods	658
6.16.1.3.1 X-Ray and gas-phase electron diffraction	658
6.16.1.3.2 NMR and EPR spectroscopy	661
6.16.1.3.3 Mass spectrometry	663
6.16.1.3.4 UV spectroscopy	663
6.16.1.3.5 IR and Raman spectroscopy	663
6.16.1.3.6 Electron spectroscopy	664
6.16.1.3.7 Electrochemical properties	664
6.16.1.4 Thermodynamic Aspects	664
6.16.1.5 Reactivity of Fully Conjugated Rings	664
6.16.1.6 Reactivity of Nonconjugated Rings	664
6.16.1.6.1 Isomers of aromatic compounds	664
6.16.1.6.2 Dihydro compounds	664
6.16.1.6.3 Tetrahydro compounds	664
6.16.1.7 Reactivity of Substituents Attached to Ring Carbon Atoms	665
6.16.1.8 Reactivity of Substituents Attached to Ring Heteroatoms	665
6.16.1.9 Ring Synthesis Classified by Number of Ring Atoms in Each Component	665
6.16.1.9.1 Formation of one bond between two heteroatoms	665
6.16.1.9.2 Formation of one bond adjacent to one heteroatom	666
6.16.1.9.3 Formation of two bonds: Four-atom fragments and silicon	666
6.16.1.9.4 Formation of two bonds: Four-atom fragments and nitrogen	667
6.16.1.9.5 Formation of two bonds: Four-atom fragments and C, O, S, Se, P, or metal	667
6.16.1.9.6 Formation of two bonds: [3+2] Atom fragments by cycloaddition	667
6.16.1.9.7 Formation of two bonds: [3+2] Atom fragments by other processes	668
6.16.1.10 Ring Synthesis by Transformation of Other Heterocycles	669
6.16.1.10.1 Insertion	669
6.16.1.10.2 Elimination and extrusion	670
6.16.1.10.3 Rearrangements and other transformations	670
6.16.1.11 Survey of Ring Synthesis	670
6.16.1.12 Important Compounds and Applications	671
6.16.2 Five-Membered Rings Containing Divalent Silicon Atoms	671
6.16.2.1 Theoretical Methods	671
6.16.2.1.1 Structure and spectroscopic properties	671
6.16.2.1.2 Thermodynamic stability, the question of aromaticity and reactivity	671

6.16.2.2 Experimental Structural Methods	672
6.16.2.2.1 X-Ray and gas-phase electron diffraction methods	672
6.16.2.2.2 NMR and EPR spectroscopy	672
6.16.2.2.3 UV spectroscopy	674
6.16.2.2.4 IR and Raman spectroscopy	674
6.16.2.2.5 Mass spectrometry	674
6.16.2.2.6 Electron spectroscopy	674
6.16.2.2.7 Electrochemical properties	674
6.16.2.3 Thermodynamic Aspects	675
6.16.2.4 Reactivity	675
6.16.2.4.1 Thermal and photochemical monomolecular reactions	676
6.16.2.4.2 Electrophilic attack at ring silicon	676
6.16.2.4.3 Electrophilic attack at ring nitrogen	680
6.16.2.4.4 Nucleophilic attack at ring silicon	680
6.16.2.4.5 Reactions involving radicals and reducing agents	680
6.16.2.4.6 Reactions with cyclic transition states	684
6.16.2.4.7 Reactions of substituents	688
6.16.2.5 Synthesis	688
6.16.2.5.1 Synthesis by reduction of compounds with tetravalent silicon atoms	688
6.16.2.6 Possible Applications	689
References	689

This chapter is a sequel to Section 4.24.1.2 in Chapter 4.24 of CHEC-II(1996) <1996CHEC-II(4)829> and it covers the chemistry of five-membered heterocyclic silicon-containing compounds with three or four heteroatoms. The silaheterocycles that have been described in the chemical literature from 1996 until July 2006 and which are covered by this chapter are summarized in [Figure 1](#). The reader will miss in this chapter cyclic silicon compounds in which the ring is formed by a dative bond to silicon, thus leading to penta- or hexa-coordination at silicon. Similarly, metal complexes with chelating ligands including silicon but donor groups acting either as *n*-donors or having hapticity larger than 1 are not included here. The number of silicon-containing heterocyclic compounds increased significantly during the last 10 years and this development is for a good part due to the substantial progress in the chemistry of low-coordinated organosilicon compounds, which opens new synthetic approaches toward heterocyclic compounds. The most influential development in the area of silicon-containing heterocycles is the discovery of stable *N*-heterocyclic silylenes by Denk and West <1994JA2691> and their benzoannelated analogues by the Gehrhus/Lappert group <1995CC1931> (ring systems **a**, X=N, **c**, and **g**, X=N). The physical properties and the chemistry related to these divalent silicon compounds are clearly different from those of regular cyclic compounds with tetravalent silicon atoms; therefore, a division of this chapter into two sections is appropriate. [Section 6.16.1](#) deals exclusively with silicon in the tetravalent state, while [Section 6.16.2](#) describes the chemistry of *N*-heterocyclic silylenes with dicoordinated silicon atoms.

6.16.1 Five-Membered Rings Containing Tetravalent Silicon Atoms

6.16.1.1 Introduction

The types of five-membered silaheterocycles dealt with in this survey are shown in [Figure 1](#). Many of these ring systems can be found in CHEC-II(1996) <1996CHEC-II(4)829>. However, new aspects of their chemistry are presented here. The most intriguing novel ring system included in this chapter is the germadisilole **i** from which a cyclopentadienyl analogue was prepared opening a completely new area in silaheterocyclic chemistry.

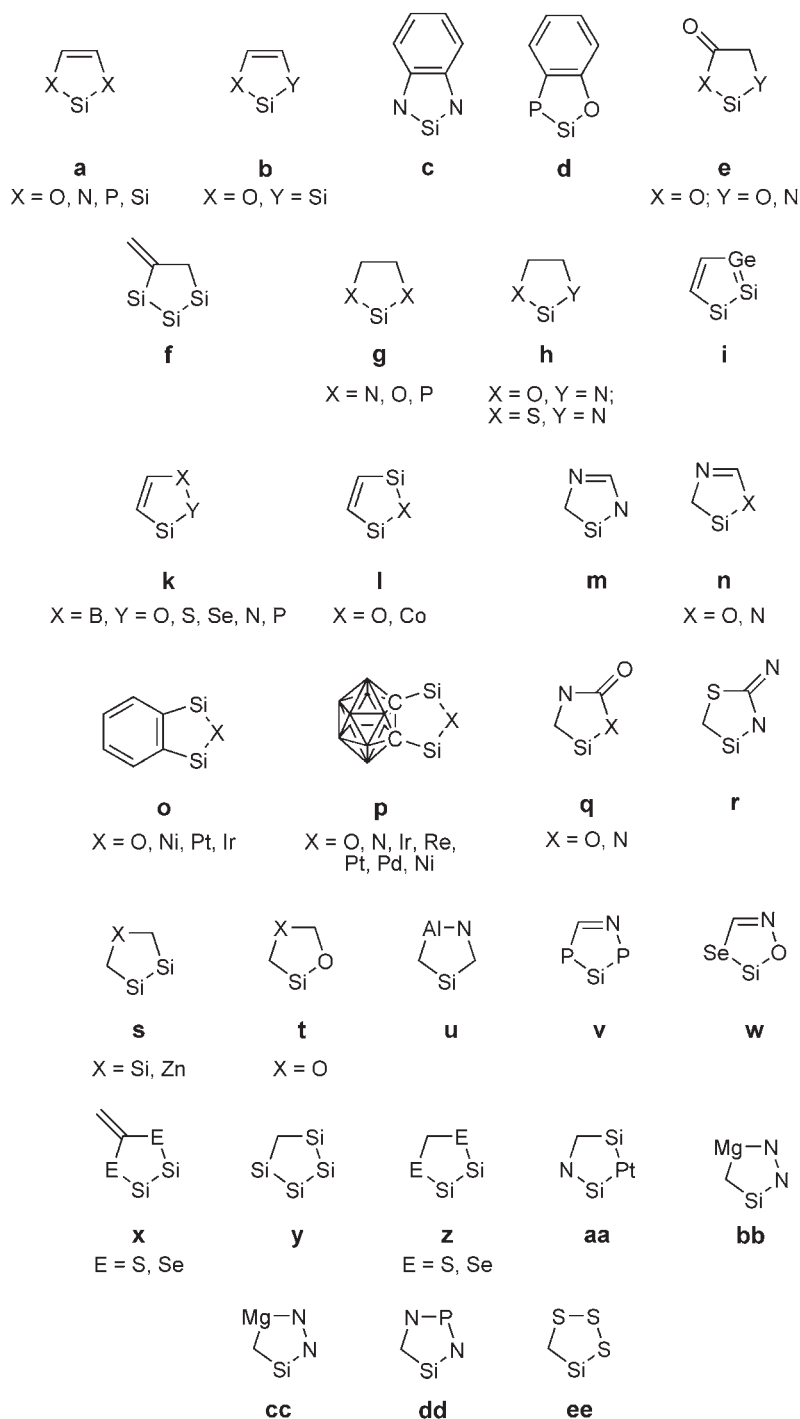
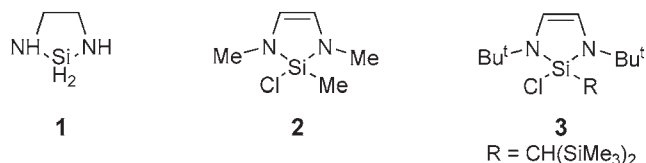


Figure 1 Silicon-containing five-membered heterocycles with three or four heteroatoms.

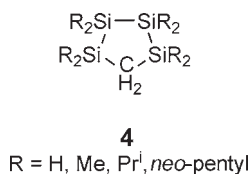
6.16.1.2 Theoretical Methods

6.16.1.2.1 Structure and spectroscopic properties

The structure of 1,3-diaza-2-silacyclopentane **1** was optimized using the MP2/6-31G(d) level of theory. A twist structure of C_2 molecular symmetry with all ring hydrogen atoms in an eclipsed conformation was found to be the most stable conformer. This structure was found to be more stable than the corresponding staggered structure by 7.1 kJ mol^{-1} . The C_s symmetric envelope conformation of molecule **1** was predicted not to be a minimum on the potential energy surface but a higher-order saddle point <2004IC3537>. Density functional computation at the B3LYP/6-31+G(d,p) level for 1,3-diaza-2-silacyclopentene **2** and its radical cation $2^{+\cdot}$, as models for the more bulky substituted silacyclopentenenes **3** and $3^{+\cdot}$, reveals structurally closely resembling molecular structures which indicates the suitability of this theoretical model chemistry for the prediction of the molecular structure of these types of compounds <2005CL486>.



Geometry optimizations at the B3LYP/6-31G(d) level of theory for the tetrasilacyclopentanes **4** ($\text{R} = \text{H}$ or Pr^i) predict molecular structures which are, in the case of $\text{R} = \text{Pr}^i$, close to experimental values. For example, the difference between computed and experimentally observed Si-Si and Si-C bond lengths does not exceed 3–4 pm <2003OM4721>.



6.16.1.2.2 Thermodynamic properties and reactivity

The ring strain in tetrasilacyclopentanes **4** was calculated using homodesmotic model reactions. At the highly accurate ONIUM/G2MS:MP2/6-31G(d) level of theory, the ring strain was computed to be relatively small (18.8 kJ mol^{-1} for $\text{R} = \text{H}$) and for the bulky Pr^i -substituent even smaller strain energies are predicted (14.2 kJ mol^{-1}) <2003OM4721>. Estimated ring strains computed for the same molecules at the PM3 level agree surprisingly well with these data <2002EJI1772>.

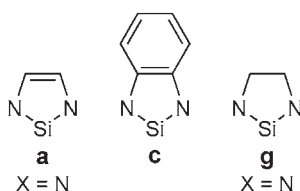
6.16.1.3 Experimental Structural Methods

6.16.1.3.1 X-Ray and gas-phase electron diffraction

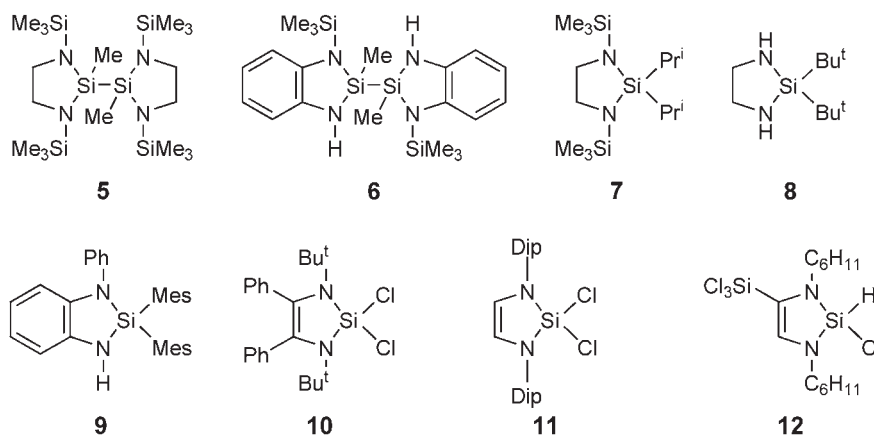
In connection with the thorough study of the chemistry of stable cyclic diaminosilylenes, a series of compounds which feature either a 1,3-diaza-2-silacyclopentene (**a**, $\text{X} = \text{N}$), its benzo[*b*]condensated variation (**c**), or the saturated 1,3-diaza-2-silacyclopentane ring (**g**, $\text{X} = \text{N}$) (see Figure 1), all three with tetracoordinated silicon atoms, were crystallized and their molecular structure was investigated. The diazasilacyclopentene rings were found to be nearly planar with normal $\text{C}=\text{C}$ double bond, $\text{C}-\text{N}$ and $\text{N}-\text{Si}$ distances. Similarly, regular $\text{C}-\text{C}$, $\text{C}-\text{N}$, and $\text{N}-\text{Si}$ bond lengths are encountered in diazasilacyclopentanes. The five-membered rings in these molecules are, however, twisted. Representative structural data can be found in Table 1 and further examples can be found in the literature <1996JOM211, 1998JA12714, 2000CJC1526, 2002JA4186, 2005JA14730, 2005JCD2945, 2006OM3802>.

Table 1 Structural data of five-membered heterocycles **a** (X = N), **c**, **g** (X = N) derived from X-ray structure analysis and gas-phase electron diffraction

Compound	Si–N (pm)	N–C (pm)	C–C (pm)	$\alpha(\text{NSiN})$	Reference
5 ^a	173.3–174.8	149–151		95.4–95.6°	1997H(44)177
6 ^a	174.6–177.0	139–144	141–144	92.6–93.7°	1997H(44)177
7 ^a	173.7–173.9	148.8	151.1	96.2°	2002ZNB99
8 ^b	172.4	146.6	154.5	93.0°	2004IC3537
9 ^a	173.1–174.9			90.8°	1999EJI1755
10 ^a	169.7, 170.4	143.6, 144.0	138.4	91.17°	1998ZFA295
11 ^a	170.1, 170.3	141.6	132.8	94.3°	1998ZFA295
12 ^a	170.8, 172.2	142.7, 138.4	135.5	93.36°	1998ZFA295
3 ^a	172.8; 172.9	141.5, 141.2	132.0		2005CL486
3 ^{++a,c}	178.2; 178.0	133.6, 133.3	137.2		2005CL486

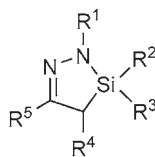
^aSolid-state X-ray diffraction.^bGas-phase electron diffraction.^cRadical cation counteranion: tetrakis(pentafluorophenyl)borate.

A gas-phase electron diffraction study revealed that 2,2-di-*t*-butyl-1,3-diaza-2-silacyclopentane **8** exists at 305 K as a mixture (76:24, $\Delta G = 2.9 \text{ kJ mol}^{-1}$) of two conformers, both possessing a twist conformation with C_2 molecular symmetry. In the prevailing conformer the NH bonds stagger the adjacent CH_2 group, and in the minor form the N–H bonds eclipse the CH_2 groups <2004IC3537>.

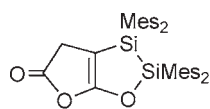
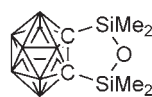
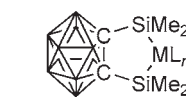
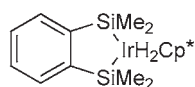
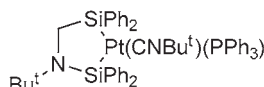
Dip : 2,6-di-Prⁱ-phenyl

Comparison of the molecular structures of 1,3-diazasilacyclopentene **3** and its radical cation **3**⁺⁺ in $[\text{B}(\text{C}_6\text{F}_5)_4]^-$ salt (**Table 1**) was used to examine the electronic nature of the diazasilacyclopentene cycle. Comparison of the data indicates the antibonding nature of the highest occupied molecular orbital (HOMO) in neutral **3** <2005CL486>.

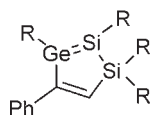
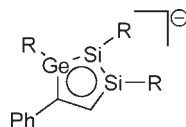
The molecular structures of several substituted 1,2-diaza-3-silacyclopentenes **13** have been reported. The X-ray structure analysis of all investigated compounds reveals an envelope conformation with the silicon positioned out of the plane of the nitrogen and carbon atoms. The most important geometrical parameters of the five-membered heterocycle are: $d(\text{Si–C}) = 187.4\text{--}190.6 \text{ pm}$, $d(\text{C–C}) = 152.0\text{--}152.8 \text{ pm}$, $d(\text{C=N}) = 128.0\text{--}129.5 \text{ pm}$, $d(\text{N–N}) = 140.8\text{--}142.4 \text{ pm}$, $d(\text{N–Si}) = 173.4\text{--}177.2 \text{ pm}$; angle (NSiC) = $90.6\text{--}92.1^\circ$ <2006ZFA1097>.

**13**

An oxadisilole cycle was characterized crystallographically as part of the bicyclic molecule **14**. The most important structural parameters of this silaheterocycle are: $d(\text{Si-Si}) = 255.8 \text{ pm}$, $d(\text{Si-O}) = 172.5 \text{ pm}$, $d(\text{Si-C}) = 194.7 \text{ pm}$, $d(\text{C=C}) = 132.7 \text{ pm}$, $d(\text{C-O}) = 132.3 \text{ pm}$; angle $(\text{OSiSi}) = 89.4^\circ$ <2001OM2451>. The molecular structure of the cyclic disiloxane **15** obtained by X-ray diffraction shows the expected bonding pattern with relatively long C-C (169.1 pm) and C-Si (191.4 pm) separations while the Si-O bond length is normal (164.2 pm) <1999IC486>. Similar structures were reported for metallacycles **16** and **17**. The C-Si bonds are even longer (193.8–195 pm) while the Si-M distances are normal (Si-Re bonds in structure **16** are 247.7 and 247.5 pm; and Si-Pt distances in metallacycle **17** are 236.2 and 235.4 pm) <2004OM135, 2004OM490>. Closely related structurally are the cyclic disilyl metal complexes **18** and **19**. For both compounds regular silicon metal bond lengths have been reported: ($d(\text{IrSi})$ in complex **18** = 235.9, 235.5 pm and $d(\text{PtSi})$ in metallacycle **19** = 235.7, 233.3 pm) <2004OM135, 2004OM4771>.

**14****15****16** $\text{ML}_n = \text{ReH}_5(\text{PPh}_3)_2$
17 $\text{ML}_n = \text{Pt}(\text{PPh}_3)_2$ **18****19**

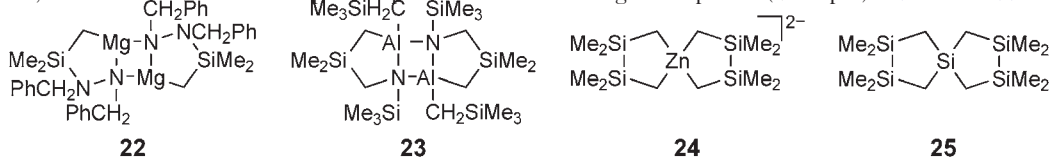
The reported molecular structure of 3-germa-1,2-disilole **20** shows a planar five-membered ring but no indication of conjugation between the $\text{C}=\text{C}$ and the $\text{Ge}=\text{Si}$ double bond was found. The following bond lengths in the five-membered ring were reported: $d(\text{Si-Si}) = 236.4 \text{ pm}$, $d(\text{Si-Ge}) = 225.0 \text{ pm}$, $d(\text{Ge-C}) = 197.2 \text{ pm}$, $d(\text{C=C}) = 134.3 \text{ pm}$, $d(\text{Si-C}) = 188.8 \text{ pm}$ <2000JA12604, 2001JOM41, 2004OM2822>. In contrast, the molecular structure of the related anion 1,2-disila-3-germacyclopentadienide **21** in its $\text{Li}(\text{THF})$ (THF – tetrahydrofuran) salt reveals the structural consequences of a delocalized 6π -electron system ($d(\text{Si-Si}) = 224.0 \text{ pm}$, $d(\text{Si-Ge}) = 232.2 \text{ pm}$, $d(\text{Ge-C}) = 193.0 \text{ pm}$, $d(\text{C-C}) = 140.2 \text{ pm}$, $d(\text{Si-C}) = 182.7 \text{ pm}$) <2005JA13143>. The Li^+ cation is bonded in a nearly η^5 fashion to all atoms of the five-membered ring.

**20****21**

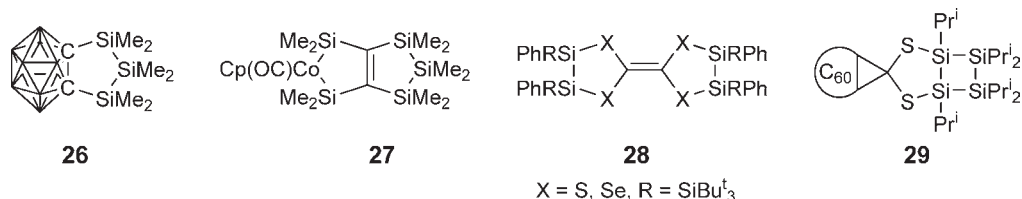
$\text{R} = \text{Bu}^t_2\text{MeSi}$

The molecular structure of the cyclic magnesium hydrazide **22** reveals its dimeric nature: two five-membered rings are connected via two Mg-N dative bonds <2002EJ1495>. A closely related molecular structure was found for compound **23**. The reported bonding parameters for the 1-sila-3-aluma-4-aza cyclopentane ring in compound **23** indicate that the innercyclic Si-C bonds are significantly different due to the unsymmetrical electron distribution in the five-membered ring ($\text{Si-CH}_2(\text{N}) = 191 \text{ pm}$, $\text{Si-CH}_2(\text{Al}) = 184.9 \text{ pm}$) <2000ZFA2284>. Similar spirocyclic molecular structures were reported for the zincate dianion **24** and the neutral carbosilane **25** <1996OM2833, 2000OM4223>. The Si-Si and the Si-C bond lengths in the five-membered zinca-cycle in dianion **24** are close to normal (234.5 pm (Si-Si) and 184.8, 185.4 pm (Si-C)). The Zn-C atom distances in the five-membered ring are long and differ significantly from each other (220.5 and 213.9 pm) <1996OM2833>. All Si-C bond lengths in the spirocyclodisilane **25** fall in a very narrow range (187.6–189.1 pm), which is slightly longer than the mean Si-C bond

distance, and for the Si–Si bond in spirocompound **25** a normal length is reported (235.4 pm) <2000OM4223>.



The molecular structure of the cyclic trisilane **26** reveals a nearly planar five-membered ring with bond parameters similar to those of analogous compounds ($d(\text{Si}–\text{Si}) = 234.1, 233.6$ pm; $d(\text{Si}–\text{C}) = 191.7, 193.0$ pm; $d(\text{C}–\text{C}) = 172.7$ pm) <2004OM490>. The prominent feature of the trisilacyclopentene unit in compound **27** is a relatively acute SiSiSi bond angle of 92° which is combined with a relatively long C=C double bond of $d(\text{C}–\text{C}) = 137$ pm. The Si–Si and Si–C bonds in compound **27** are normal ($d(\text{Si}–\text{Si}) = 233.9, 234.6$ pm), and for the Si–Co linkage bond lengths of $d(\text{Si}–\text{Co}) = 227.8$ and 229.1 pm are reported <1996OM3606>. The five-membered rings in the tetrathiafulvalene analogue **28**, $\text{X} = \text{S}$, adopt a half-chair conformation, the Si–Si bond lengths (241.7 pm) are longer, and the Si–S distances (216.9 pm) are larger than the regular bond lengths <2002CEJ2730>. Similarly, the dithiadisilolane ring in the C_{60} cycloadduct **29** possesses a half-chair structure and relatively long Si–S bond lengths (218.5 pm), while the central Si–Si bond length is normal (235.8 pm) <2005AGE7567>. The molecular structure of tetrasilacyclopentane **4** ($\text{R} = \text{Pr}^i$) was studied by X-ray crystallography. The five-membered ring was found to adopt an envelope conformation. The bond lengths of Si–Si (239.3 pm) and Si–C (188.8 pm) in the Si_4C cycle are within the normal ranges <2002EJI1772>.

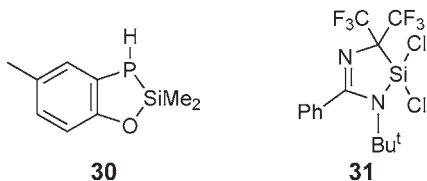


6.16.1.3.2 NMR and EPR spectroscopy

6.16.1.3.2(i) NMR spectroscopy

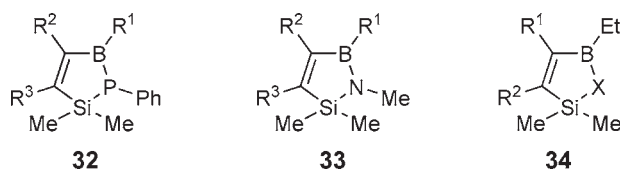
^{29}Si NMR (NMR – nuclear magnetic resonance) data for five-membered rings are of special interest, since the ^{29}Si NMR resonance of the ring silicon atom is usually significantly shifted to lower field compared to similarly substituted acyclic compounds. A great wealth of ^{29}Si NMR spectroscopic information on five-membered silaheterocycles of the general types **a**, $\text{X} = \text{N}$, **c** and **g**, $\text{X} = \text{N}$ with tetracoordinated silicon atoms (see Figure 1) has been gathered in connection with the study of the chemistry of stable cyclic diaminosilylenes. For example, for the respective dichlorosilyl compounds ^{29}Si NMR chemical shifts of about $-40, -24$ and -17 ppm have been reported for heterocycles of type **a**, $\text{X} = \text{N}$, **c** and **g**, $\text{X} = \text{N}$, respectively <1996JOM211, 1998JA12714, 2002ZNB99>. Additional ^{29}Si NMR data including varying substitution pattern at the five-membered ring can be found in the following references: <1997IC1758, 1996JOM211, 1998JA12714, 1998ZFA295, 1999HAC605, 2000CJC1526, 2002JA4186, 2002JA7920, 2002OM1319, 2002ZNB99, 2004OM1180, 2005JA14730, 2005JCD2945, 2006OM3802>.

The silicon atom in oxaphosphasilole **30** is characterized by a resonance at $\delta^{29}\text{Si} = 44.1$ ppm. The coupling constant in compound **30** between silicon and phosphorus is $^1J(\text{SiP}) = 18.3$ Hz ($\delta^{31}\text{P} = 175$ ppm) <1997HAC383>. For oxadisilole **14** resonances at $\delta^{29}\text{Si} = -22.3$ and 20.9 ppm were detected <2001OM2451>. The dichloro-substituted 1,4-diaza-2-silacyclopentene **31** is characterized by $\delta^{29}\text{Si} = -18.4$ ppm <1995JA5160>, and for substituted 1,2-diaza-3-silacyclopentenes **13** ^{29}Si NMR resonances are in the range between 30 ppm (for 2,2-dialkyl substituted compounds) and -14 ppm (for 2-fluoro-2-amino-substituted heterocycles) <2006ZFA1097>.

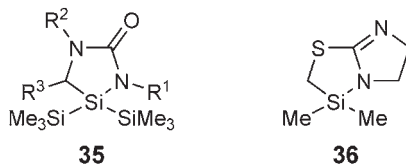


The unsaturated silicon atoms in 3-germa-1,2-disilole **20** and the silole anion **21** give rise to highly deshielded signals in their ^{29}Si NMR spectra ($\delta^{29}\text{Si} = 124.2$ ppm **20** and $\delta^{29}\text{Si} = 54.4$ and 69.1 ppm (anion **21**, Li^+ salt in toluene- d_8). The tetracoordinated silicon atom in disilole **20** shows a resonance at $\delta^{29}\text{Si} = -45.6$ ppm <2000JA12604, 2001JOM41, 2004OM2822, 2005JA13143>. Interestingly, the ^{29}Si NMR chemical shift reported for the Li^+ salt of anion **21** strongly depends on the solvent, for example, in THF the silicon atoms are more deshielded ($\delta^{29}\text{Si} = 97.4, 104.9$ ppm (in THF- d_8)). This is probably due to a more localized structure induced by a different coordination of the lithium gegenion to the silole anion in THF. The different chemical environment for the Li atom is indicated by the different ^7Li NMR chemical shifts found for the salt $\text{Li}^+\text{21}$ in THF and in toluene ($\delta^7\text{Li} = -5.4$ ppm (toluene- d_8); $\delta^7\text{Li} = -0.6$ (THF- d_8)) <2005JA13143>.

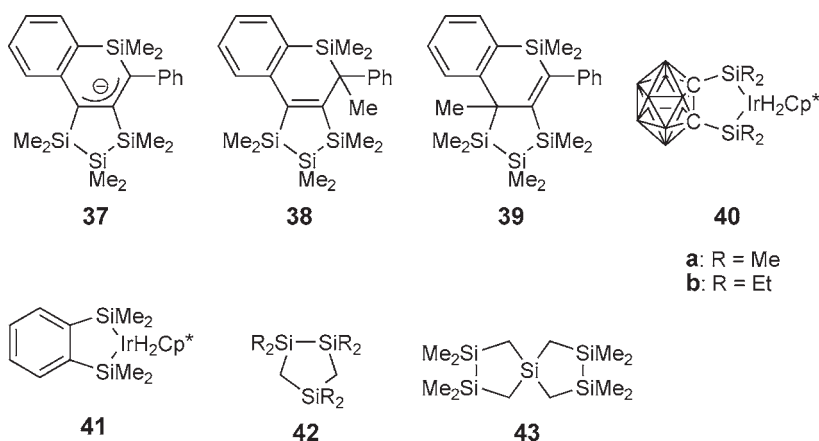
Complete NMR characterizations of 2,5-dihydro-1,2,5-phosphasilaboroles derivatives **32** and dihydro-1,2,5-azasilaboroles **33** including ^{29}Si , ^{31}P , ^{13}C NMR chemical shifts and coupling constants were reported. The ^{29}Si NMR chemical shifts for silaboroles **32**, **33** were found in the range of 11–18 ppm **32** and 12–14 ppm **33**. Complexation with $\text{M}(\text{CO})_3$ ($\text{M} = \text{Fe}, \text{Ru}$) fragments results in a low field shift of $\delta^{29}\text{Si}$ by 30 ppm **32** and 10 ppm **33** <1996MRC625, 2000MRC520, 2002MRC406>. ^{29}Si NMR chemical resonances for silaboroles **34** ($\text{X} = \text{O}, \text{S}, \text{Se}$) are found in a small range ($\delta^{29}\text{Si} = 23$ –27 ppm), while the positions of the ^{11}B signals are highly sensitive to the nature of the chalcogen atom ($\delta^{11}\text{B} = 51$ ppm ($\text{X} = \text{O}$), 74 ppm ($\text{X} = \text{S}$), 81 ppm ($\text{X} = \text{Se}$)) <2002MRC406>.



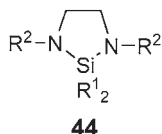
The ring silicon atoms of 1-sila-2,4-diaza-3-oxocyclopentanes **35** give rise to signals in the ^{29}Si NMR at -9 to -10 ppm <2003OM1314>, and the related heterocycle **36** is characterized by $\delta^{29}\text{Si} = 14.0$ ppm <2003RJO1507>.



^{29}Si NMR chemical shift data were reported for the cyclic trisilanes **37**–**39**. Clear assignment is only possible for the central silicon ($\delta^{29}\text{Si} = -48.9$ ppm (**37**), -57.6 ppm (**38**), -50.9 ppm (**39**)) <1996OM3480>. This data is similar to that found for the silicon atoms in 1,2,3-trisilane **26** ($\delta^{29}\text{Si} = -42.2$ ppm (central Si), -0.7 ppm (terminal Si)) and for those in the trisilacyclopentene moiety of compound **27** ($\delta^{29}\text{Si} = -49.4$ ppm (central Si), -11.3 ppm (terminal Si)). Characteristic for the Si–Co linkage in compound **27** is the strongly deshielded resonance of the silicon atoms attached to the Co atom ($\delta^{29}\text{Si} = 57.5$ ppm) <2004OM490, 1996OM3606>. A smaller deshielding effect on the silicon atom was found for the iridadisilacyclopentenes **40** and **41** ($\delta^{29}\text{Si} = 30.1$ ppm (**40b**), 14.0 ppm (**40a**), 1.1 ppm (**41**)) <2004OM135>. The 1,2,4-trisilacyclopentane **42** ($\text{R} = \text{Me}$) is characterized by ^{29}Si NMR resonances at -12.9 ppm for the silicon atoms of the disilane unit and 9.5 ppm for the isolated silicon atom <2002OM503>, which is in agreement with ^{29}Si NMR data reported for the spirocompound **43** ($\delta^{29}\text{Si} = -13.6, 17.4$ ppm) <2000OM4223>. In the case of tetrasilacyclopentane **4** a substantial effect of the alkyl substituent on the ^{29}Si NMR chemical shift was detected. That is, for $\text{R} = \text{Pr}^i$ $\delta^{29}\text{Si} = 1.9$ ppm ($\text{Si}^{1/4}$) and -18.6 ppm ($\text{Si}^{2/3}$) was reported, while for $\text{R} = \text{neo-pentyl}$ a marked high field shift was detected ($\delta^{29}\text{Si} = -8.7$ ppm ($\text{Si}^{1/4}$) and -39.9 ppm ($\text{Si}^{2/3}$)) <2002EJI1772>.



^{15}N NMR data have been reported for 1,3,2-diazasilacyclopentanes **44**: $\delta^{15}\text{N} = -372.4$ ppm ($^1\text{J}(\text{NH}) = 75.9$ Hz) ($\text{R}^2 = \text{H}$, $\text{R}^1 = \text{Bu}^t$, **8**) <2004OM1180>, -356.4 ppm ($\text{R}^2 = \text{Pr}^i$, H , $\text{R}^1 = \text{H}$, SiH_3), -348.9 ppm ($\text{R}^2 = \text{Bu}^t$, $\text{R}^1 = \text{H}$, SiH_3) (all data vs CH_3NO_2) <1997IC1758>.

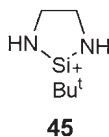


6.16.1.3.2(ii) EPR spectroscopy

Oxidation of diazasilacyclopentene **3** with Ag^+ gives the corresponding radical cation **3** $^{+\cdot}$ with the following characteristic parameter: $g = 2.0029$, $a(\text{N}) = 0.451$ mT, $a(\text{H}) = 0.729$ mT <2005CL486>.

6.16.1.3.3 Mass spectrometry

Detailed mass spectrometry data (EI, 50 eV) were recorded for 1,3-diaza-2-silacyclopentane **8**. The molecular ion peak has only small intensities (5%) and for the base peak, the mass of the stabilized silylium ion **45** is detected <2004IC3537>. Similar results were obtained for other diazasilacyclopentanes <2004OM1180>.



6.16.1.3.4 UV spectroscopy

The following ultraviolet (UV) data in hexane have been reported for the 3-germa-1,2-disilole **20** and for the related anion **21**: for disilole **20** $\lambda_{\text{max}} (\epsilon) = 243$ nm (37330), 307 nm (6570), 472 nm (5540); for anion **21** $\lambda_{\text{max}} (\epsilon) = 375$ nm (4050), 474 nm (4020) <2005JA13143>. The bathochromic shift of the high-energy band suggests the occurrence of cyclic conjugation in the anion **21**. The UV spectrum of tetrasilacyclopentane **4**, $\text{R} = \text{Me}$, was studied in a comparative investigation of cyclic tetrasilanes. The following data in hexane were reported for compound **4**, $\text{R} = \text{Me}$: $\lambda_{\text{max}} (\epsilon) = 211$ nm (8500), 235 nm (3700), 258 nm (300) <1997PCA4579>. Comparison of tetrasilacyclopentanes **4** with larger groups at the silicon atoms revealed no significant influence of the bulkiness of the substituents on the position of the long wave UV absorption: for compound **4** ($\text{R} = \text{Pr}^i$), $\lambda_{\text{max}} (\epsilon) = 261$ nm (1100); for compound **4** ($\text{R} = \text{neo-pentyl}$), $\lambda_{\text{max}} (\epsilon) = 233$ nm (6550), 254 nm (1500) <2002EJ11772>.

6.16.1.3.5 IR and Raman spectroscopy

No systematic studies on vibrational spectroscopy of five-membered heterocycles with three or more heteroatoms and at least one tetracoordinated silicon atom were reported.

6.16.1.3.6 Electron spectroscopy

Tetrasilacyclopentane **4**, R = Me, was studied by He(I) photoelectron spectroscopy. The following peak energies were reported for compound **4**, R = Me: E (eV) = 7.62, 8.39, 9.44, 9.68, 10.3 <1997PCA4579, 2002PCA2369>. These experimental data correlate well with molecular orbital (MO) energies obtained at the MP2/TZ level of theory <2002PCA2369>.

6.16.1.3.7 Electrochemical properties

The electrochemical oxidation of tetrasilacyclopentanes **4** was found to be irreversible, indicating the instability of the generated radical cations. The oxidation potential versus saturated calomel electrode (SCE) was reported to be as follows: for compound **4** (R = Prⁱ), 1.17 V (CH₃CN), 1.43 V (CH₂Cl₂); and for compound **4** (R = *neo*-pentyl), 1.02 V (CH₃CN), 1.20 V (CH₂Cl₂) <2002EJ11772>.

6.16.1.4 Thermodynamic Aspects

No systematic experimental studies on thermodynamic properties of five-membered heterocycles with three or more heteroatoms and at least one tetracoordinated silicon atom were reported. The aromaticity of the fully conjugated germadisiloleanion **21**, a heavy congener of the cyclopentadienyl anion, was deduced mainly from its NMR spectroscopic and structural parameters <2005JA13143>.

6.16.1.5 Reactivity of Fully Conjugated Rings

The germadisiloleanion **21** is the only fully conjugated cyclic compound that is included in this chapter <2005JA13143>. No report on its reactivity has been published so far.

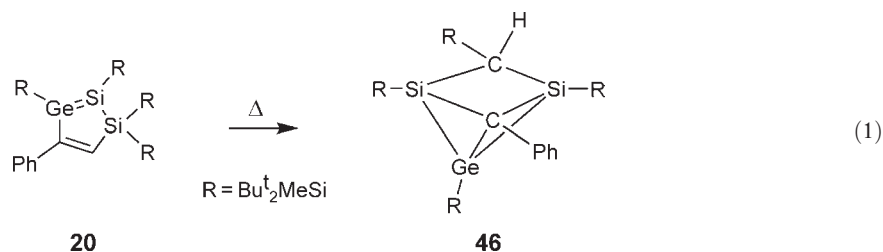
6.16.1.6 Reactivity of Nonconjugated Rings

6.16.1.6.1 Isomers of aromatic compounds

No isomer of an aromatic five-membered ring compound is dealt with in this chapter.

6.16.1.6.2 Dihydro compounds

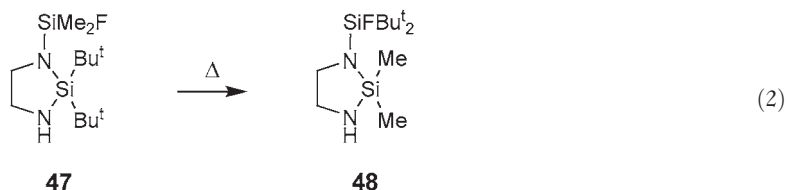
The 3-germa-1,2-disilole **20** upon heating undergoes an unprecedented rearrangement to give the cage molecule **46** with a tricyclo[2.1.0.0^{2,5}]pentane skeleton (Equation 1) <2002JA9962, 2004OM2822>.



The reactivity of disilole **20** is dominated by the Ge=Si double bond. In the reactions of disilole **20** with alkynes, with carbonyl groups or with oxygen the products of formal [2+2] cycloaddition involving the GeSi bond were observed. No [4+2] cycloaddition products, usually predominant in silole chemistry, were found <2000JA12604, 2001JOM41, 2004OM2822>. Reduction of disilole **20** with C₈K in THF gives the anion **21** in 23% isolated yield. Structural and computational data indicate that the electrons in 3-germa-1,2-disilasiloleanion **21** are delocalized <2005JA13143>. The reaction of 2,2-dihalo-1,3,2-diazasilacyclopentenes with strong reducing agents to give stable compounds with divalent silicon atoms is treated in detail in Section 6.16.2.

6.16.1.6.3 Tetrahydro compounds

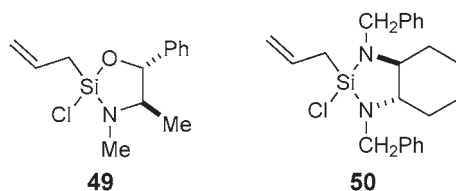
During distillation (129°C, 20 mbar), the *N*-silylsubstituted 1,3-diaza-2-silacyclopentane **47** rearranges in part to the 1,3-diaza-2-silacyclopentane **48** in which the inner and exocyclic silyl groups have changed their positions (Equation 2) <2004OM1180>.



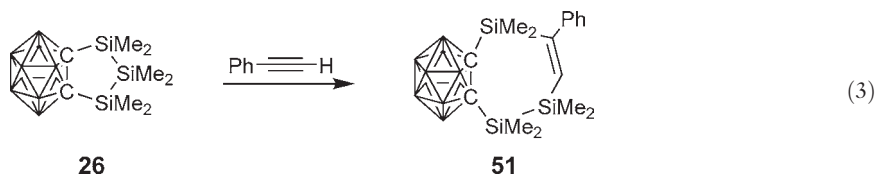
Reduction of 2-chloro-1,3-diaza-2-silacyclopentanes with lithium metal in THF gives the corresponding lithium compound which was shown to be configurationally stable by NMR spectroscopy up to temperatures of 333 K in THF or 388 K in diglyme <2002OM1319>. Reaction of the lithium compound with electrophiles can be used to functionalize the silaheterocycle at the silicon atom <2002OM1319>.

Substitution reactions at the silicon atom of 2,2-dichloro-1,3,2-diazasilacyclopentanes with nucleophiles such as amide and methoxide were reported to proceed in high yields <2002ZNB99>.

The Lewis acidity of chiral allyl-silacyclopentanes such as silaoxazolidine **49** or silazolidine **50** has been recently used to transfer an allyl group to aldehydes, ketones, acylhydrazones, and carbinamines to afford the corresponding alcohols or amines in high yields and with excellent enantiomeric excess <2002JA7920, 2003AGE946, 2003JA9596, 2004JA5686, 2005AGE938>.



An interesting reaction of disilane is the transition metal-catalyzed insertion of unsaturated hydrocarbons. The palladium-mediated reaction of cyclotrisilane **26** with phenylacetylene to afford the seven-membered carbosilane **51** (Equation 3) indicates that this general reaction scheme is also applicable to strained cyclic trisilanes <2004OM490>.



6.16.1.7 Reactivity of Substituents Attached to Ring Carbon Atoms

No unique or characteristic reactivity of the substituents attached to a carbon atom of the heterocycles has been reported.

6.16.1.8 Reactivity of Substituents Attached to Ring Heteroatoms

No unique or characteristic reactivity of the substituents attached to a heteroatom of the heterocycles has been reported.

6.16.1.9 Ring Synthesis Classified by Number of Ring Atoms in Each Component

6.16.1.9.1 Formation of one bond between two heteroatoms

Tetrasilapentanes **4**, R = Prⁱ or *neo*-pentyl, were synthesized by reductive coupling of the linear 1,5-dichloro-1,2,4,5-tetrasilapentane with lithium biphenyl in 77–87% yields <2002EJI1772>.

6.16.1.9.2 Formation of one bond adjacent to one heteroatom

There were no reports in the literature between 1996 and 2006 on new syntheses of five-membered heterocycles containing three or more heteroatoms and at least one silicon atom that employ this particular synthetic methodology.

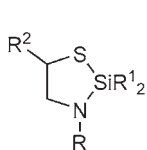
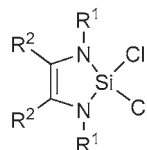
6.16.1.9.3 Formation of two bonds: Four-atom fragments and silicon

An established synthesis of 1,3,2-diazasilacyclopentanes and benzo[*b*]annelated 1,3,2-diazasilacyclopentenes is the reaction of 1,2-diamines with geminal silyl dichlorides in the presence of bases such as triethylamine or DABCO <1997H(44)177, 1997IC1758, 1999HAC605, 2002OM1319, 2002ZNB99, 2002JA7920, 2003AGE946, 2006OM3802>. Examples of more complex heterocycles obtained by this methodology are bis(2-silaimidazolidine) **5** and bis(2-silaimidazoline) **6** which can be prepared by the reaction of 1,2-dimethyl-1,1,2,2-tetrachlorodisilane with the corresponding diamines in the presence of triethylamine in 38% and 61% yield, respectively <1997H(44)177>. Alternatively, dilithiated diamines can be used, as shown for example for the synthesis of trisilane **52** <1999HAC605>. The use of lithiated amines is obligatory when silyl fluorides are starting materials <2002ZNB99, 2004OM1180>.

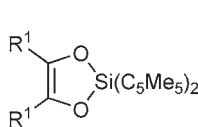
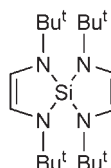
**52**

R = *neo*-pentyl

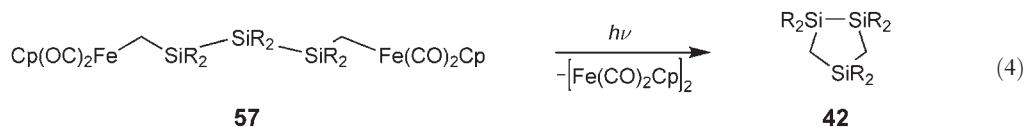
This general scheme can be extended and was successfully applied for the syntheses of other heterocycles as for example for the chiral silaoxazolidine **49** <2002JA7920>, silathiazolidines **53** <2004AOM291> and to benzoxaphosphasilole **30** <1997HAC383>. Silathiazolidines **53** were also prepared by transamination reactions starting from geminal silyldiamines <1999AOM583>. The metathesis reaction of dilithiated 1,4-diaza-1,3-butadienes with dichlorosilanes is frequently used for the synthesis of 1,4-diaza-2-silacyclopentenes <1987CB795, 1998JA12714>. For diimines for which this reduction is not applicable the Benkeser reaction provides a possible alternative <1971ACR94>. That is, the reaction of trichlorosilane with *tert*-amines provides the trichlorosilyl anion SiCl_3^- , which acts in certain cases as a dichlorosilylene synthon. Thus, [4+1] cycloadditions of 1,3-diazabutadienes or 1,4-diazabutadienes in the system $\text{HSiCl}_3/\text{NR}_3$ lead to dichloro-substituted diazasilacyclopentene derivatives such as **31** and **54** <1995JA5160, 1998ZFA295>. 4*H*-1,2-Diaza-3-siloles **13** are prepared by reaction of the corresponding dilithio compound with silicon di-, tri-, or tetrahalides <2006ZFA1097>.

**53****54**

Reaction of stable or transient silylenes with 1,4-diaza- or 1,4-dioxabutadienes proceeds via a formal [1+4] addition to give the corresponding diazasilacyclopentenes or dioxasilacyclopentenes, such as **55** or **56** <1996PAC785, 1996OM1930, 1997OM4861, 1997CC1374, 1998OM1378, 1998JA12714, 2000ACR704>.

**55****56**

Photolysis of the acyclic trisilane **57** produces 1,2,4-trisilacyclopentanes **42** in moderate yields (67–79%) (Equation 4). Marker experiments suggest that the reaction proceeds via a bimetallic silylene bridged dimer, which collapses to give the cyclic carbosilane <2002OM503>.



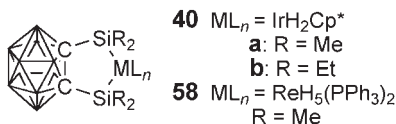
6.16.1.9.4 Formation of two bonds: Four-atom fragments and nitrogen

There have been no reports in the literature between 1996 and 2006 on the synthesis of five-membered heterocycles containing three or more heteroatoms and at least one silicon atom that use this particular synthetic methodology.

6.16.1.9.5 Formation of two bonds: Four-atom fragments and C, O, S, Se, P, or metal

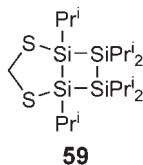
The cyclic magnesium hydrazide **22** was prepared in moderate yield (40%) by the treatment of di-*n*-butyl magnesium with *N,N*-dibenzyl-*N'*-trimethylsilylhydrazine in hexane <2002EJI1495>. A Wurtz-type coupling reaction of zinc dichloride and 1,4-dichloro-2,3-disila-2,2,3,3-tetramethylbutane affords the spirocyclic zincate **24** in 70% yield <1996OM2833>. Similarly, a low-yield synthesis of tetrasilacyclopentane **4** (R = Me) was reported by the coupling of the corresponding 1,4-dichlorotetrasilane and dibromomethane under Wurtz conditions <1997PCA4579>.

In the reaction between bis(silyl)-*o*-carboranes and (Cp^{*}IrCl₂)₂ or ReH₇(PPh₃)₂ metalation occurs at both Si–H sites, giving rise to the complexes Cp^{*}IrH₂[η¹:η¹-(SiR₂)₂C₂B₁₀H₁₀-Si^{*i*},Si^{*i'*}] **40** or (Ph₃P)₂ReH₅-(SiMe₂)₂C₂B₁₀H₁₀-Si^{*i*},Si^{*i'*} **58**, in which the metal center forms part of a five-membered metallacycle (M–Si–C–C–Si) (M = Ir, Re) <2004OM135>. Treatment of 1,2-dimethylsilylbenzene with (Cp^{*}IrCl₂)₂ likewise affords the 1,3-disila-irida-cyclopentene **18**. The metallacycles **18**, **40**, **58** were isolated in yields which varied from 29% to 68% <2004OM135>.

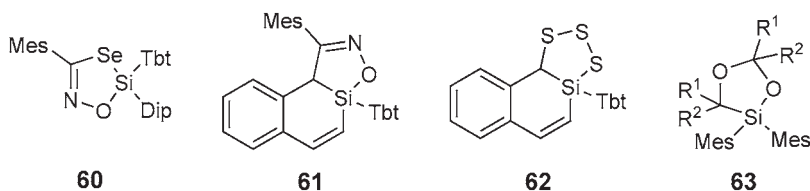


6.16.1.9.6 Formation of two bonds: [3+2] Atom fragments by cycloaddition

[3+2] Cycloaddition reactions of transient or isolable disilenes with heterocumulenes such as CX₂ (X = S, Se) produce heterocyclic carbenes, for example, carbene **59**, which has a disilane backbone. These carbenes are only transient species and were not isolated but were either trapped with C₆₀, or dimerization of the carbenes occurred to give the tetrathiafulvalene or tetraselenafulvalene analogues **28** <2002CEJ2730, 2005AGE7567>.

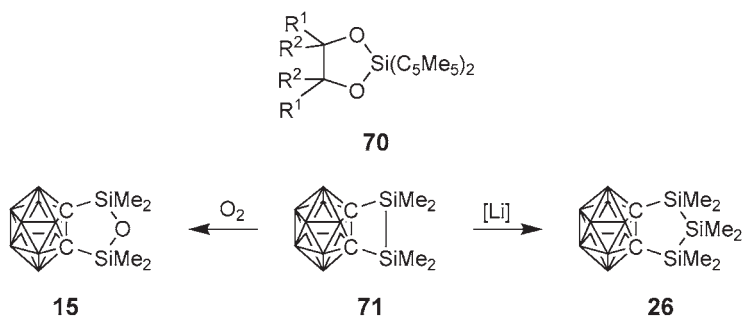
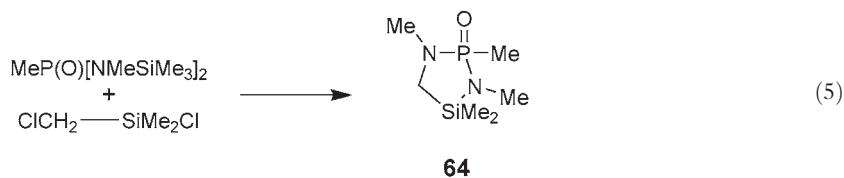


Formal cycloaddition reactions between silicon compounds which have Si=X multiple bonds and 1,3-dipolar molecules yield five-membered silaheterocycles. That is, a formal [3+2] cycloaddition between mesitronitrile oxide and a kinetically stabilized silaneselone or 2-silanaphthalene affords the heterocyclic compounds **60** and **61** in 69% and 77% yield, respectively (Tbt = 2,4,6-tris[bis(trimethylsilyl)methylphenyl]; Dip = 2,6-diisopropylphenyl) <2002CL34, 1999JA11336>. The reaction of 2-silanaphthalene with excess sulfur provides access to the cyclic trisulfide **62** in low yields (20%) <1999JA11336>. Surprisingly, the reaction of a disilene with maleic anhydride gives oxadisilole **14** in high yields <2001OM2451>. Photochemically generated dimesitylsilylene reacts with carbonyl compounds to give silacarbonyl ylides, Mes₂Si⁺-CR¹R²-O[−], which undergo a facile [3+2] dipolar cycloaddition with a second equivalent of the carbonyl compound to give 1-sila-2,4-dioxacyclopentanes **63** in moderate to good yields <1999CC1857>.

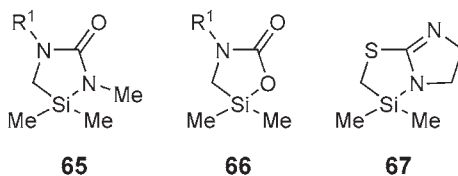


6.16.1.9.7 Formation of two bonds: [3+2] Atom fragments by other processes

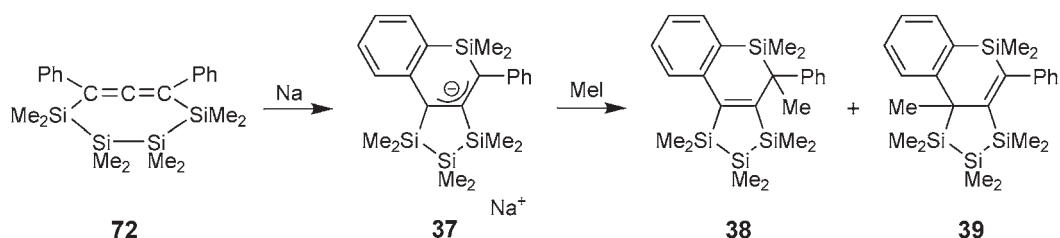
The cyclic phosphine oxide **64** was prepared in moderate yields (72%) according to Equation (5) from chloro(chloromethyl)dimethylsilane <2001RJC327>. A similar procedure using bis-silylated ureas as reactants resulted in the formation of the corresponding 1-sila-2,4-diaza-3-oxocyclopentanes **65** <2004RJC1051>, and the reaction with silylated carbamates afforded substituted 1-sila-4-aza-2-oxa-3-oxocyclopentanes **66** <2001RJC2025>. Finally, the thiasilole **67** was obtained by the reaction of bis-silylated 2-imidazolidinethione with chloro(chloromethyl)dimethylsilane <2003RJO1507>.



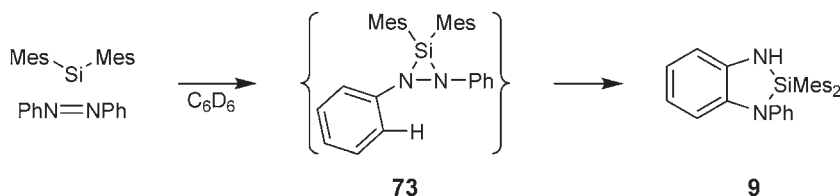
Scheme 1



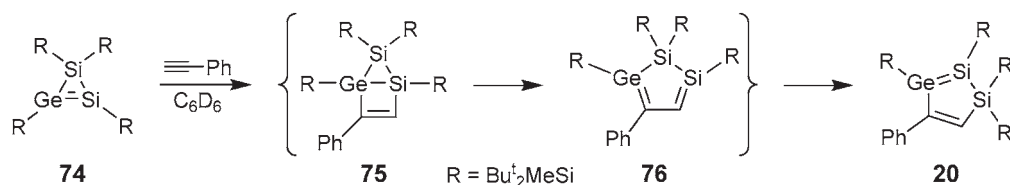
A different synthetic approach to 1-sila-2,4-diaza-3-oxocyclopentanes utilized the reaction of silenes **68** with ureas and afforded the heterocycles **69** in moderate yields (50–65%) (Equation 6). It was proposed that the reaction proceeds in two steps with the ring-forming process being the nucleophilic attack of the nitrogen atom at the carbon center <2003OM1314>.



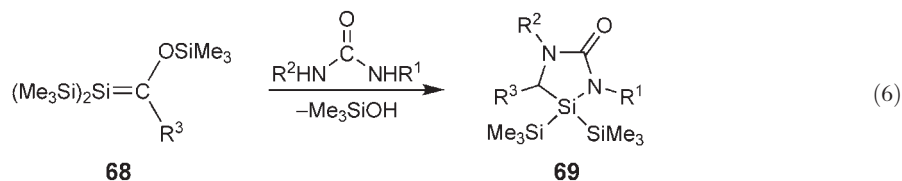
Scheme 2



Scheme 3



Scheme 4



Spirocompound **43** was prepared in low yields (20%) by salt metathesis reaction of tetrakis(lithiomethyl)silane with 1,2-dichloro-1,1,2,2-tetramethyl disilane <2000OM4223>.

6.16.1.10 Ring Synthesis by Transformation of Other Heterocycles

6.16.1.10.1 Insertion

The insertion reaction of stable diaminosilylenes into four-membered rings is treated in Section 6.16.2.4.6(ii). Treatment of nucleophilic silylenes with ketones affords oxasiliranes which are reactive against a second equivalent of the ketone and as final products dioxasilolanes, for example, **70**, are isolated <1996OM1930, 2003JCD236>. Exposure of 1,2-disilacyclobutane **71** to air gives the cyclic siloxane **15** in 40% isolated yield <1999IC486>. On the

other hand, the reaction with catalytic amounts of lithium metal produces the trisilane **26** in 48% yield (see [Scheme 1](#)). Also the formation of the platinacycle **17** from the reaction of a linear *o*-dicarbadodecacarborane-substituted disilane with $\text{Pt}(\text{PPh}_3)_3$ is thought to proceed via the disilacyclobutane **71** [<2004OM490>](#).

6.16.1.10.2 Elimination and extrusion

There have been no reports in the literature between 1996 and 2006 on the synthesis of five-membered heterocycles containing three or more heteroatoms and at least one silicon atom that employ this particular synthetic methodology.

6.16.1.10.3 Rearrangements and other transformations

Reduction of the cyclic allene **72** by sodium metal affords the polycyclic allyl anion **37**, which was crystallized and characterized. Reaction with methyl iodide resulted in the formation of the methylated compounds **38** and **39** ([Scheme 2](#)) [<1996OM3480>](#).

Dimesitylsilylene reacts with azobenzene to give benzo[*b*]fused 1,3,2-diazasilacyclopentene **9**, however, only in 36% yield. The reaction probably proceeds in several steps ([Scheme 3](#)). A [2+1] cycloaddition yields a transient silaazirane **73** which then undergoes a rearrangement with ring enlargement to give the benzocondensated heterocycle **9** [<1999EJI1755>](#).

The [2+2] cycloaddition of germadisilacyclopentene **74** with phenylacetylene affords the 3-germa-1,2-disilole **20** in 42% yield. As intermediates in this reaction sequence, the 'house' **75** and the isomeric silole **76** were discussed ([Scheme 4](#)) [<2000JA12604, 2001JOM41>](#).

Cobalt(I)-mediated ring contraction of a permethylated pentasilacycloheptyne gives the bicyclooctene **27** derivative in isolated yields of about 72% [<1996OM3606>](#).

6.16.1.11 Survey of Ring Synthesis

The most widely used and most common synthetic approaches to five-membered silaheterocycles are polar reactions, for example, salt metathesis reactions or reductive coupling reactions. These transformations involve, in most cases, the use of geminal or vicinal silyldichlorides (or more general, α,ω -dichlorides) as reactants. These starting materials are very often commercially available, or reliable synthetic protocols for their high-yield synthesis are available. These reactions give satisfactory yields for the syntheses of saturated compounds (see, e.g., [<1996JOM211, 2002JA7920, 2003AGE946>](#)). However, the synthesis of unsaturated silaheterocycles is very often severely hampered by low yields (see, however, [<1998JA12714>](#)). This might be tolerated in cases where starting materials are cheap and easily accessible. In this respect the use of low-valent organosilicon compounds might open new synthetic avenues to silaheterocycles. Silylenes and compounds featuring multiple-bonded silicon atoms such as silenes, disilenes, silaimines, and even disilynes are now available either as stable compounds or as easily accessible reactive intermediates. Their chemistry and in particular their cycloaddition chemistry is still at its infancy, although in many cases the principal reactivity has been demonstrated and novel silaheterocyclic compounds have been generated. In the previous sections of this survey the results of several of these studies can be found (see, e.g., [<1999CC1857,](#)

Table 2 Experimental and calculated geometries of *N*-heterocyclic silylenes using different methods (bond lengths in pm, bond angles in degrees)

Compound	R	Method	<i>r</i> (SiN)	<i>R</i> (CN)	<i>R</i> (CC)	α (NSiN)	Reference
77	H	MP2/6-31G(d)	177.4	138.5	136.4	84.6	1996JA2023
	Bu ^t	B3LYP/6-31G(d)	179.1	138.8	135.6	87.3	2004OM5689
	Bu ^t	X-ray	175.0	140.0	135.0	175.0	2004OM5689
	Bu ^t	Electron diffraction	175.3	140.0	134.7	90.5	1994JA2691
78	H	MP2/6-31G(d)	174.0	146.7	152.9	88.5	1996JA2023
	Bu ^t	B3LYP/6-31G(d)	175.7	150.0	152.9	90.9	2004OM5689
	Bu ^t	X-ray	171.9	148.9	152.1	92.0	2005OM3346
79	H	MP2/6-31G(d)	176.8	138.9	141.2	85.8	1998CEJ541
	<i>Neo</i> -pentyl	X-ray	174.7/175.2	138.0/138.5	141.7	88.2	1995CC1931
80	H	MP2/6-31G(d)	177.7/176.6	138.1/138.5	141.4	86.2	1998CEJ541
86	<i>Neo</i> -pentyl	X-ray	174.2/174.0	139.5/139.6	140.6	89.0	2005ZFA1383

1999JA11336, 2000JA12604, 2001JOM41, 2002CL34, 2003OM1314>). Clearly, the use in low-coordinated organo-silicon compounds in organic transformations is severely underexploited and there is obviously a high potential in the use of these compounds in heterocyclic chemistry.

6.16.1.12 Important Compounds and Applications

A diminution in the toxicity and increase in radioprotective efficacy were shown for substituted silathiazolidine derivatives compared with the organic analogues in *in vivo* experiments <1999AOM583, 2004AOM291>. A potentially important synthetic method is the allyl-transfer reaction based on the 'strain-release Lewis acidity' <1990OM3015> of five-membered silaheterocycles such as compounds **49** and **50**, which has been developed recently by Leighon and co-workers <2002JA7920, 2003AGE946, 2003JA9596, 2004JA5686, 2005AGE938>.

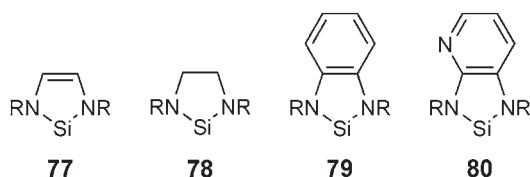
6.16.2 Five-Membered Rings Containing Divalent Silicon Atoms

The landmark papers on the synthesis of stable *N*-heterocyclic silylenes of the 1,3,2(λ^2)-diazasilacyclopentene and -pentane type from the Denk/West and the Gehrhus/Lappert group in 1994/95 <1994JA2691, 1995CC1931> were included in CHEC-II(1996) <1996CHEC-II(4)829>. The following years, however, witnessed a vivid exploration of the properties and of the chemistry of this novel type of organosilicon compounds. The chemistry of these silaheterocycles is clearly dominated by the unique properties of the divalent silicon atom and must be distinguished from that of the compounds treated in Section 6.16.1.

6.16.2.1 Theoretical Methods

6.16.2.1.1 Structure and spectroscopic properties

The molecular structures of *N*-heterocyclic silylenes **77**–**80** having different substituents at the ring nitrogen atoms were computed at several levels of sophistication (see Table 2). The theoretical results obtained using different methods are not only very similar but also close to the experimental results.



The HOMO computed for the unsaturated silylene **77** ($R = \text{Bu}^t$) is essentially a combination of p-type orbitals of all five ring atoms <2004OM5689> and is of similar shape as that predicted for silylene **79** ($R = \text{H}$) <1996JCD1475>. In contrast, the HOMO obtained for the saturated cyclic silylene **78** ($R = \text{Bu}^t$) reveals heteroallylic NSiN conjugation. The predicted vertical ionization energies for compounds **77** ($R = \text{Bu}^t$) (6.98 eV), **78** ($R = \text{Bu}^t$) (7.30 eV), and **79** ($R = \text{H}$) (7.43 eV) are close to the values obtained experimentally <2004OM5689, 1996JCD1475>. The calculated isotropic ^{29}Si NMR chemical shifts for compounds **77**–**79** ($R = \text{H}$) are close to the experimental values obtained for the *t*-butyl (**77**, **78**) or *neo*-pentyl-substituted **79** compounds. The theoretical analysis reveals, for all three silylenes, a highly anisotropic NMR chemical shift tensor with the most deshielded component δ_{11} in the plane spanned by the NSiN group and perpendicular to the vector of the silicon lone pair (e.g., for compound **77** ($R = \text{H}$): $\delta_{11} = 278$ ppm, $\delta_{22} = -40$ ppm, $\delta_{33} = -46$ ppm; chemical shift anisotropy (CSA) = 320.8 ppm) <1998JA1639>. The high anisotropy and the orientation of the ^{29}Si NMR chemical shift tensor is typical for silylenes <2003JOM251>.

6.16.2.1.2 Thermodynamic stability, the question of aromaticity and reactivity

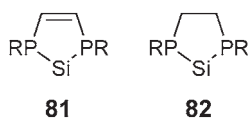
Thermodynamic, structural, and magnetic criteria, the properties of the charge distributions, and low-energy ionization processes show consistently that cyclic electron delocalization does indeed occur in the C=C unsaturated imidazol-2-ylidene system **77**, in particular, with respect to the corresponding C–C saturated imidazolin-2-ylidenes **78**. However, the conclusion regarding the degree of conjugation and aromaticity depends on the criteria used, being quite small according to the 'atoms-in-molecules' charge analysis but more significant according to the energetic and the magnetic

properties <1996JA2023, 1996JA2039>. The semi-quantitative nucleus-independent chemical shift (NICS) estimate for aromatic delocalization suggests, for structures **77** and **79**, a ring current that is half of that of benzene <1998JA1639>. Computations of the enthalpy of isodesmic reactions for silylenes **77** and **78** ($R = \text{Bu}^t$) indicate that the unsaturated silylene **77** is more stable than the saturated analogue **78** by 52.7 kJ mol^{-1} <2003JOM112>.

The stability of bis(amino)silylenes against dimerization to disilenes is related to the singlet-triplet splitting energy, $\Delta E_{S \rightarrow T}$. Qualitatively, large $\Delta E_{S \rightarrow T}$ energies indicate stability toward dimerization to the $\text{Si}=\text{Si}$ bonded dimer. This is in line with high $\Delta E_{S \rightarrow T}$ values predicted for compounds **77** and **78** ($248\text{--}273 \text{ kJ mol}^{-1}$ (**77**, $R = \text{H}$, depending on the level of theory) and $315.6 \text{ kJ mol}^{-1}$ (**78**, $R = \text{H}$)), which are significantly larger than computed for the nonstabilized silylenes such as SiH_2 (84.0 kJ mol^{-1}) <2003JOM112, 1999IC4819>.

The unusual tetramerization reaction of the saturated silylene **78** ($R = \text{Bu}^t$) was studied computationally for **78** ($R = \text{Me}$) with density functional methods. In agreement with the experiment, it was found that the barrier for insertion of the silylene into the Si-N bond is small (45 kJ mol^{-1}) and the free energy difference (ΔG) between the silylene **78** ($R = \text{Me}$) and the insertion product is small at ambient temperature ($\Delta G(298 \text{ K}) = 2.1 \text{ kJ mol}^{-1}$), thus accounting for the observed monomer/tetramer equilibrium <1999JA9479>.

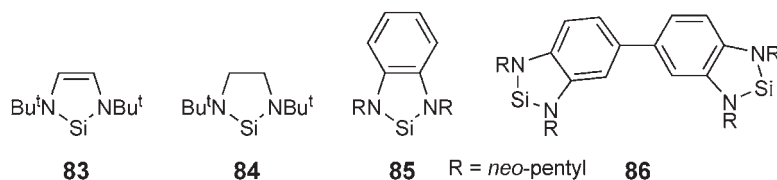
A theoretical analysis identifies the phospho analogues **81** and **82** of diamino-silylenes **77** and **78** as stable molecules and as good candidates for synthesis <2004IC2585>.



6.16.2.2 Experimental Structural Methods

6.16.2.2.1 X-Ray and gas-phase electron diffraction methods

Structures have been determined by gas-phase electron diffraction for compound **83** and by X-ray crystallography for compounds **83–86** <1994JA2691, 2004OM5689, 2005OM3346, 1995CC1931, 2005ZFA1383>. Significant molecular parameters of the five-membered rings in these compounds are summarized in Table 2.

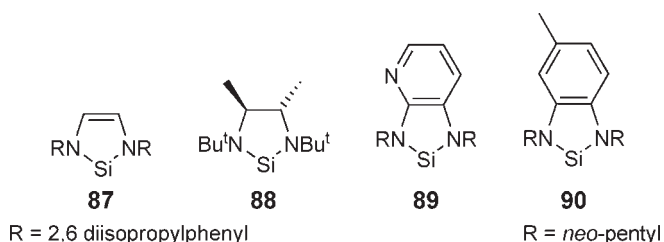


The bond distances and angles within the five-membered rings are quite similar in compounds **83**, **85**, and **86**. The five-membered rings of the diazacyclopentenenes **83**, **85**, **86** are planar, but the diazasilacyclopentane ring in silylene **84** is necessarily puckered. The NC distances within the ring are shorter in unsaturated *N*-heterocyclic silylenes than in the saturated silylene **84**. The Si-N bond lengths are similar to normal Si-N single bond distances, which are about $172\text{--}174 \text{ pm}$. The two $\text{Si}(\text{NR})_2\text{C}_6\text{H}_3$ units in bis-silylene **86** are twisted by 30.3° <2001JOM209, 2005ZFA1383>.

6.16.2.2.2 NMR and EPR spectroscopy

6.16.2.2.2(i) NMR spectroscopy

For silylenes the ^{29}Si NMR chemical shifts are highly characteristic since the divalent silicon nucleus in silylenes is strongly deshielded compared to tetravalent silicon atoms. The following values have been obtained in aromatic solvents: $\delta^{29}\text{Si} = 75 \text{ ppm}$ (**87**, <1998ZFA295>), 78 ppm (**83**, <1994JA2691>), 95 ppm (**89**, <1998CEJ541>), 97 ppm (**85**, <1995CC1931>), 97 ppm (**86**, <2001JOM209, 2005ZFA1383>), 98 ppm (**90**, <1996JOM211>), 120 ppm (**84**, <1999JA9479>), 123 ppm (**88**, <2006OM3802>).



The chemical shift values for compounds **83–85** in solution differ only insignificantly from $\delta^{29}\text{Si}$ obtained by solid-state NMR: $\delta^{29}\text{Si}$ = 75 ppm **83**, 93 ppm **85**, 115 ppm **84** <1998JA1639>. The ^{29}Si NMR chemical shift tensors measured for compounds **83–85** are highly anisotropic and reveal one dominant deshielded contribution (e.g., for compound **83**, δ_{11} = 284.9 ppm, δ_{22} = –16.1 ppm, δ_{33} = –43.3 ppm) <1998JA1639>. The $\delta^{29}\text{Si}$ reported for silylenes **83–90** differ however markedly from that detected for silylene **91** ($\delta^{29}\text{Si}$ = 567 ppm) <1999JA9722, 1999CL263>, which lacks the electronic stabilization by the two nitrogen atoms. Even when compared to $\delta^{29}\text{Si}$ of the closely related acyclic bis(amino)silylene **92** ($\delta^{29}\text{Si}$ = 224 ppm) <2003JA8114>, the high field shift of the ^{29}Si resonance detected for the cyclic bis(amino)silylenes **83–90** is significant. The shielding of the divalent silicon atom in the cyclic bis(amino)silylenes was rationalized by a more favorable π -conjugation of the formally empty Si(3p) orbital with the nitrogen lone pairs in the planar cyclic molecules **83–90** compared to the nonplanar acyclic bis(amino)silylene **92** <2003JA8114, 2003JOM251>. ^{15}N NMR chemical shift (vs CH_3NO_2) were reported for the silaimidazolidines **83** ($\delta^{15}\text{N}$ = –170 ppm) and **85** ($\delta^{15}\text{N}$ = –225 ppm). The ^1H NMR chemical shift data obtained for the vinylic protons in the silaimidazolidines **83** and **87** ($\delta^1\text{H}(=\text{CH})$ = 6.75 ppm <1994JA2691>, R = 2,6-isopropyl-phenyl $\delta^1\text{H}(=\text{CH})$ = 6.43 <1998ZFA295>) have been put forward as an indication for an aromatic ring current <2000ACR704>. For compound **83** this resonance is low-field-shifted by 1.02 ppm compared to the reference compound **93** for which no cyclic delocalization is possible.

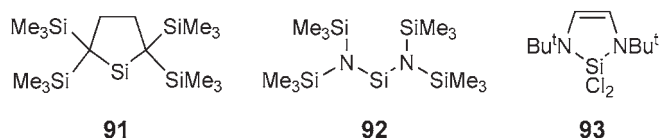


Table 3 Experimental ionization potentials of *N*-heterocyclic silylenes

Compound	1st band	2nd band	3rd band	Reference
83	6.96 eV		8.21 eV	1994JA6641
84	7.54 eV		8.11 eV	1994JCD2405
85	7.32 eV	7.91 eV	8.55 eV	1996JCD1475
89	7.24 eV	8.62 eV	8.98 eV	1998CEJ541

6.16.2.2.2(ii) EPR spectroscopy

Radical cation **83**⁺ obtained by oxidation of 1,3,2(λ^2)-diazasilole **83** was detected by electron paramagnetic resonance (EPR) spectroscopy and its life time in solution was determined to be $t_{1/2}$ = 10 min at 20 °C. The following EPR parameters have been determined for **83**⁺: g = 2.0017, $a(^1\text{H})$ = 8.63 G, $a(^{14}\text{N})$ = 2.83 G <2004JOM4165>. EPR results after electrochemical reduction of silylene **83** suggest the formation of a trimeric radical anion [**83**]₃^{•–} ($h\nu$ to six nitrogen atoms and three silicon atoms (g = 2.0035, $a(^{29}\text{Si})$ = 25.77 G, $a(^{14}\text{N})$ = 1.3 G)) as a short-living intermediate <2004JOM4165>. From the reduction of silylene **85** with sodium, the analogous radical anion [**85**]₃^{•–} (g = 2.0045, $a(^{29}\text{Si})$ = 25.77 G, $a(^{14}\text{N})$ = 4.56 G) was isolated and characterized by crystal structure analysis <2005CC5112>.

6.16.2.2.3 UV spectroscopy

The $S_1 \rightarrow S_0$ transition is responsible for the characteristic UV-Vis band of silylenes in general. This transition is best described by an excitation of an electron from the lone pair at the divalent silicon atom to the empty $3p$ orbital. In the case of the cyclic diaminosilylenes **84**, **85**, **88**, and **89**, this band is strongly blue-shifted compared to other silylenes such as $\text{Me}_2\text{Si:}$ or silylene **91**. The following λ_{max} values for this band are reported: $\lambda_{\text{max}} = 268 \text{ nm}$, 292 nm **84**, 270 nm , 295 nm **88**, 249 nm **85**, 249 nm **89** <1999JA9479, 1996JOM211, 1998CEJ541, 2003JOM251, 2006OM3802>. Additional UV-Vis bands have been reported for the yellow compounds **85** and **89** ($\lambda_{\text{max}} = 344 \text{ nm}$ **85**, 302 nm **89**).

6.16.2.2.4 IR and Raman spectroscopy

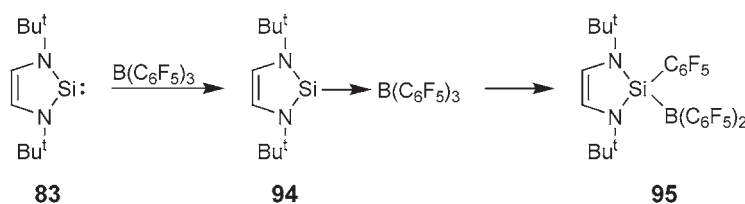
For 1,3,2(λ^2)-diazasilacyclopentene **83**, the following Raman lines at 650 , 991 , 1178 , 1566 , 1573 cm^{-1} were reported in the solid state. The intensive doublet at 1566 and 1573 cm^{-1} was assigned to the ($\text{C}=\text{C}$) stretch vibration. The observed bathochromic shift of this band in the spectra of compound **83** compared to heterocyclic compounds having a tetravalent silicon, for example, **93**, and the significant intensity enhancement of this band indicates cyclic conjugation in molecule **83** <2000JST329, 2004JA4114>.

6.16.2.2.5 Mass spectrometry

Routine MS data are available for 1,3,2(λ^2)-diazasiloles **83**, **85**, **89**, and **90**. Using electron impact methods the positive M^+ ion was detected in 35–64% relative abundance <1994JA2691, 1995CC1931, 1996JOM211, 1998CEJ541>. In the case of the bis-silylene **86** the molecular ion was obtained as the base peak <2005ZFA1383>. Similarly, chemical ionization of compound **87** resulted in the detection of the molecular ion as the most abundant peak <1998ZFA295>.

6.16.2.2.6 Electron spectroscopy

The electronic structures of the 1,3,2(λ^2)-diazasiloles **83–85** and **89** have been probed by He(I) and He(II) photoelectron spectroscopy. The experimental ionization potentials are summarized in Table 3. The molecular orbitals were assigned with the help of quantum mechanical computations for model compounds and in each case the HOMO was found to be a π -type MO of b_1 symmetry. In the case of the benzo[*b*] and pyrido[*b*] fused compounds **85** and **89** also the HOMO-1 is a π -type MO. The next band was assigned to a lone pair-type MO of a_1 symmetry, which is mostly located at the dicoordinated silicon atom. Therefore, the HOMOs of the cyclic silylenes **83** and **84** differ in nature from those of the homologues *N*-heterocyclic carbenes which consist of an essentially a_1 lone pair-type MO at



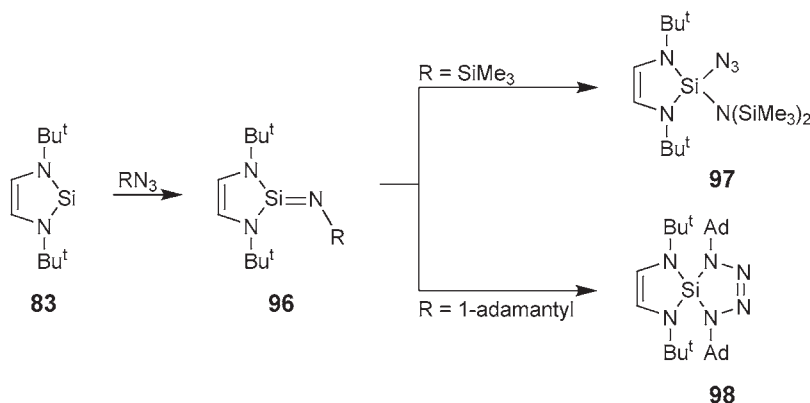
Scheme 5

the dicoordinated carbon atom <1994JA6641, 2004OM5689>.

The analysis of core excitation spectroscopy for the *N*-heterocyclic silylenes **83** and **84** indicates significant π -allyl delocalization over the $\text{N}-\text{Si}(\lambda^2)-\text{N}$ fragment with additional cyclic conjugation in **83** <1998OM2352, 1999OM1862>.

6.16.2.2.7 Electrochemical properties

In cyclic voltammetry experiments, the silaimidazolidine **83** shows an oxidation wave at 0.67 V (vs Ag/AgCl) and a reduction wave at -2.67 V . The C–C saturated analogue **84** displays an oxidation wave at 0.95 V and two reduction waves at -1.75 V and -2.35 V . In both cases the voltammetric waves are all irreversible and the oxidation peaks do

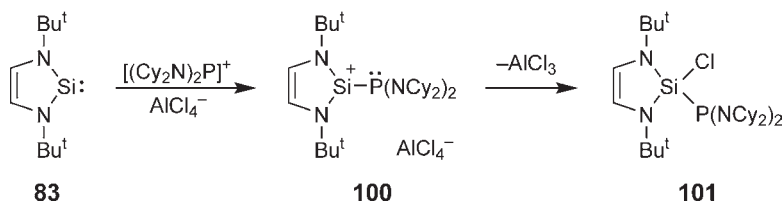


Scheme 6

not correlate with the ionization potentials. This probably indicates the importance of kinetic and surface effects in the experiments [<2001CL68, 2004OM5689>](#).

6.16.2.3 Thermodynamic Aspects

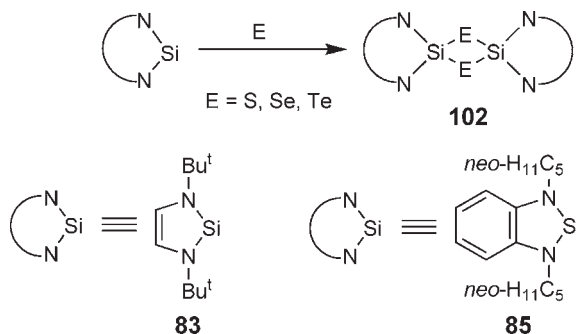
Although there is considerable interest in the potential aromaticity of the 1,3,2(λ^2) diazasiloles and their benzo- or pyrido-fused analogues, such as **83**, **85**, and **89**, there are no experimental studies tackling these problems. All information about stability and aromaticity is derived from computations.



Scheme 7

6.16.2.4 Reactivity

Since the first report on the synthesis of cyclic bisaminosilylenes in 1994, their reactions with various reagents have been studied in much detail. However, the investigations were restricted to stable silylenes **83–85** and nearly nothing



Scheme 8

is known on the reactivity of compounds **86–90**. The reactivity of heterocyclic compounds **83–85** is dominated by the nucleophilicity of the dicoordinated silicon atom. This reactivity overrules any differences between fully conjugated compounds such as **83** and its saturated analogues **84**. Therefore, the reactions of **84** will be discussed along with those of **83** and **85** and deviations from the common reactivity scheme will be noted.

6.16.2.4.1 Thermal and photochemical monomolecular reactions

The most spectacular properties of silylenes such as **83–90** are their thermostability and their stability toward dimerization reactions leading to disilenes.

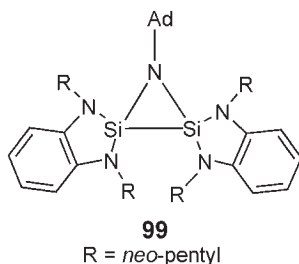
Compounds **83** and **86** decompose only at temperatures above 200 °C and the silylenes **88**, **85**, **89**, and **90** can be distilled in vacuum without decomposition <1994JCD2405, 1994JA2691, 1995CC1931, 1996JOM211, 1998JA12714, 1998CEJ541, 2001JOM209, 2005ZFA1383, 2006OM3802>. The exception is silylene **84** which reacts slowly at room temperature in a reversible reaction to afford a tetramer (see Section 6.16.2.4.2) <1994JCD2405, 1999JA9479, 2000CJC1526>. No photochemical reactivity has been reported for compounds **83–90**.

6.16.2.4.2 Electrophilic attack at ring silicon

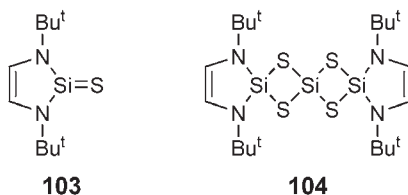
The reaction of 1,3,2(λ^2)-diazasilole **83** with strong Lewis acids such as tris(pentafluorophenyl)borate $B(C_6F_5)_3$ yields a Lewis acid–base adduct **94** which can be isolated at room temperature and which transforms slowly into silylborane **95** (Scheme 5) <1996CC2657>.

Electrophilic attack of nitrenes at the ring silicon atom of 1,3,2(λ^2)-diazasiloles is a method to obtain the corresponding silaimines. Thus, the reaction of silylene **83** with trityl azide in THF affords silaimine **96** ($R = CPh_3$) as a complex with THF <1994JA10813>. In the case of sterically less hindered azides, either the [1,2] addition product of the intermediate silaimine **97** (for $R = SiMe_3$) or the product of a [2+3] cycloaddition **98** (for $R = 1$ -adamantyl) was obtained (Scheme 6) <1994JA10813, 1996PAC785>. An excess of silylene in this reaction leads to the isolation of disilaaziridines as demonstrated for the reaction of silylene **85** with adamantyl azide which gives three-membered ring compound **99** <1998POL999, 2001JOM209>.

The phosphonium cation $[(C_6H_11)_2N]_2P^+$ (Cy = cyclohexyl) adds to the silicon atom in silylene **83** to give the transient cation **100**. The cation **100** is trapped by chloride anion and the chlorosilane **101** was observed as the final product (Scheme 7) <2004CC546>.



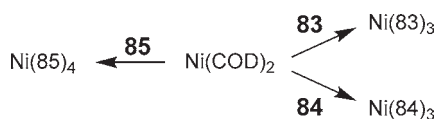
The reaction of silylenes **83** and **85** with the chalcogens S, Se, Te resulted in the formation of the respective four-membered heterocycle **102** (Scheme 8) <1996JOM211, 1998JA12714>. For the reaction of silylene **83** with 1 equiv of sulfur low-temperature NMR studies suggest the formation of silanethione **103** which then dimerizes. Reaction of excess sulfur with silylene **83** results in the formation of compound **104** with simultaneous release of the diimine ligand.



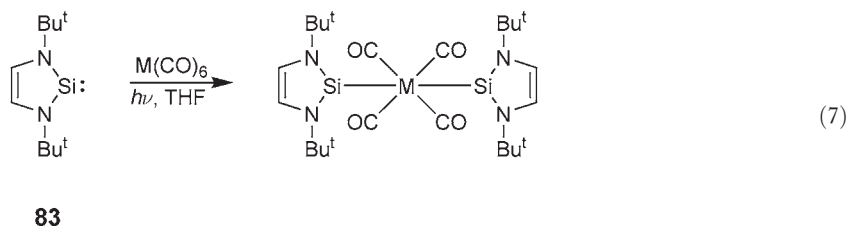
In the reactions with organometallic complexes of f-metals, the reactivity of a pure Lewis base for the 1,3,2(λ^2)-diazasiloles was observed. Thus, silylene **85** reacts with $(Cp)_3Ln$ to give the complexes $(Cp)_3Ln(85)$ ($Ln = Y, Yb$)

<2000CJC1484> and from the reaction of $(\text{Cp}^*)_2\text{Sm}$ with λ^2 -diazasilole **83** the silylene complex $(\text{Cp}^*)_2\text{Sm}(\textbf{83})$ was isolated. It is noteworthy that these complexes are rather labile. Thus, even THF substitutes the silylene ligand in $(\text{Cp}^*)_2\text{Sm}(\textbf{83})$ <2003OM1160>.

Silylenes **83–85** react with a wide variety of metal complexes which have labile ligands giving in substitution reactions the corresponding silylene complexes. For example, group 6 metal carbonyls form with both monocyclic silylenes, **83** and **84**, *trans*-configured bis-silylene complexes $\text{M}(\textbf{83})_2(\text{CO})_4$ and $\text{M}(\textbf{84})_2(\text{CO})_4$ ($\text{M} = \text{Cr}, \text{Mo}, \text{W}$) (e.g., Equation 7) <2001JOM17>. In the case of the bis-silylene complex $\text{Mo}(\textbf{85})_2(\text{CO})_4$, the formation of both geometrical isomers, *cis*- and *trans*- $\text{Mo}(\textbf{85})_2(\text{CO})_4$, was observed <2002JCD484>.

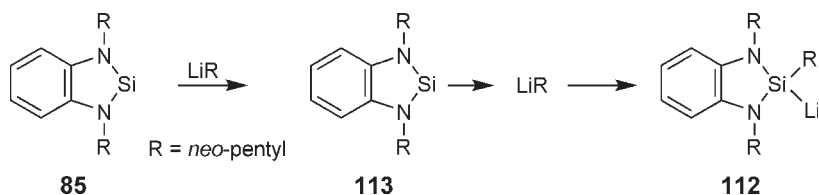


Scheme 9

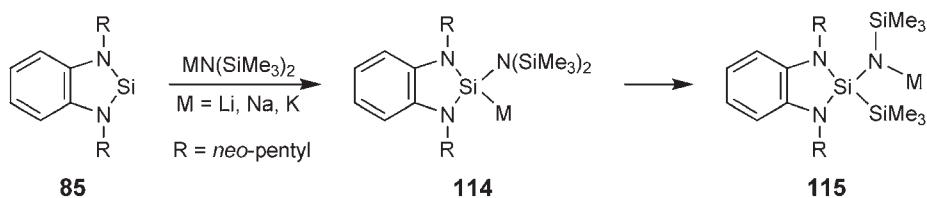


A trigonal molybdenum silylene complex $\text{Cp}_2\text{Mo}(\textbf{83})$ has been synthesized by reacting $\text{Cp}_2\text{MoPEt}_3$ with silylene **83** <1999OM2615>.

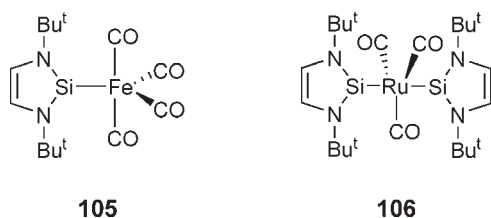
The expected monosilylene complex $\text{Fe}(\text{CO})_4(\textbf{83})$ (i.e., **105**) was isolated in high yields from the reaction of diiron nonacarbonyl with compound **83**, but reaction of $\text{Ru}_3(\text{CO})_{12}$ with silylene **83** gives the bis-silylene complex $\text{Ru}(\text{CO})_3(\textbf{83})_2$ (i.e., **106**) <2001JOM17>.



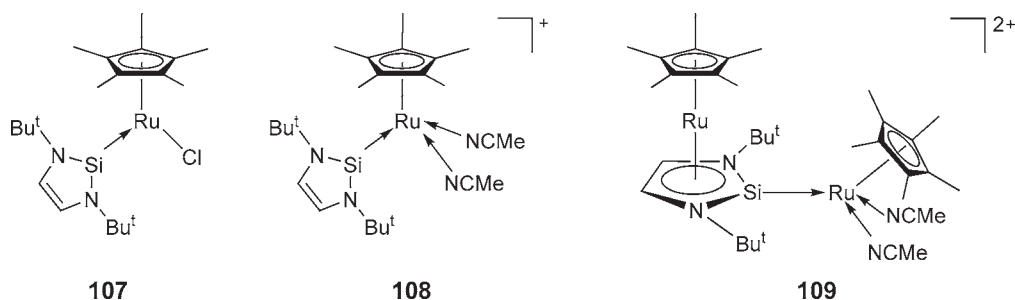
Scheme 10



Scheme 11



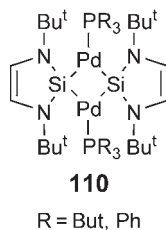
Examples for complexes of silylene **83** with $\text{Ru}(\text{I})$, such as **107** and **108**, are known. Both were synthesized by ligand exchange reactions. Interestingly, cation **108** undergoes upon heating further ligand displacement/dimerization reactions and yields the unusual complex **109**. The dinuclear complex **109** was characterized by NMR spectroscopy. Dication **109** is the first example of a complex in which the 1,3,2(λ^2)diazasilole **83** acts as an η^5 -ligand [\[2000OM4726\]](#).



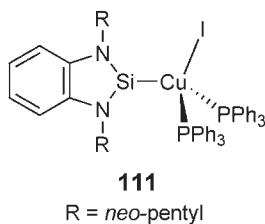
With nickel, silylene complexes of different composition were isolated. Thus, Ni(**83**)₂(CO)₂ was obtained by mixing Ni(CO)₄ with silylene **83** <1994CC33>, and the reaction of excess **83** with Ni(COD)₂ gives the homoleptic trigonal planar 16VE complex Ni(**83**)₃ (COD = cyclooctadiene) <2000OM3263>. While the saturated compound **84** gives the analogous complex Ni(**84**)₃, the sterically less congested benzo[*b*]-1,3,2(λ²)-diazasilole **85** furnishes the tetrahedrally-coordinated complex Ni(**85**)₄ (Scheme 9) <1998OM5599>.

Homoleptic cationic Rh(I) complexes [Rh(**83**)₄]⁺ and [Rh(**84**)₄]⁺ were obtained quantitatively from the reaction of silylenes **83** or **84** with [Rh(COD)₂]⁺ in hexane <2005OM2008>.

Palladium forms with both silylenes **83** and **84** silylene-bridged dinuclear complexes. The dinuclear Pd(0) complex **110** (R = Ph) was found to be active in Suzuki and Stille cross-coupling reactions <2001CC2372, 2002JOM141>. NMR investigations indicate that also homoleptic silylene complexes of Pd(0) such as Pd(**83**)₃, [Pd(**83**)₂]₂, and Pd(**84**)₄ exist; these complexes are, however, very labile <2002JOM141>.



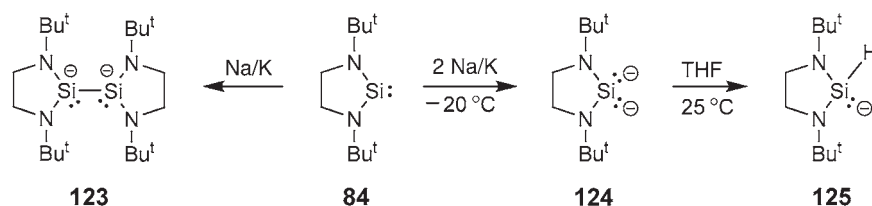
In the case of platinum, the Pt(0) complex Pt(**85**)₃(PPh₃) was isolated from the reaction of Pt(PPh₃)₄ and silylene **85** <2001JOM209, 2003JOM321>. The only characterized complex of coin metals with 1,3,2(λ²)diazasiloles is the tetrahedral Cu(I) complex **111**, which was obtained by phosphine displacement reaction from CuI(PPh₃)₃.



The experimental data demonstrate that in their transition metal chemistry silylenes **83–85** are able to replace carbonyl, tertiary phosphine or alkene ligands from a metal and it suggests that the silylene behaves as a strong σ-donor and a weak π-acceptor. Therefore, it behaves more like the isolobal PR₃ ligand than CO. Differences in reactivity between the two silylenes **83** and **85** are due to the different steric requirements. The sterically more flexible ligand is silylene **85**.

The reaction of benzo[*b*]-1,3-diazasilole **85** with lithium alkyls yields the insertion product **112**. It was suggested that the initial step of this reaction is the formation of the donor–acceptor complex **113** (Scheme 10) <2002JOM272, 2002JOM150>. The tetracoordinated silicon compounds **112** might have synthetic potential as silylene transfer reagents.

Analogous products were obtained from the reaction of silylene **85** with silyl lithium compounds, with alkali metal silylamides and alkali metal alkylamides, and sodium methoxide <2000CC1427, 2004JCD3288, 2005JCD2720, 2005CC5112>. In the case of the reaction with metallated silylamides a thermally initiated rearrangement (**114** → **115**) to give the new silylamide **115** took place (Scheme 11).



Scheme 12

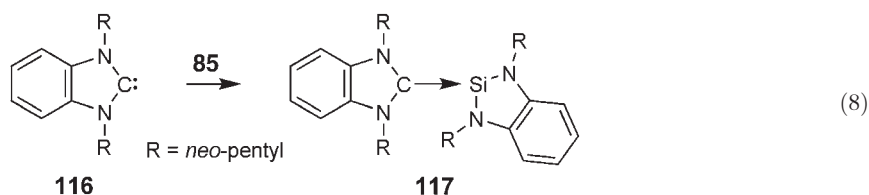
Formal insertion reactions of silylene **85** into M–X bonds, which probably involve electrophilic attack at silicon as the initial step, were reported. Treatment of $[MCl_2(PPh_3)_2]$ ($M = Pd, Pt$) with compound **85** gave the square planar d^8 complexes *trans*- $[M(85)_2(85Cl)_2]$, while with $[NiCl_2(PPh_3)_2]$ reduction of the metal took place and d^{10} complexes $[Ni(85)_n(PPh_3)_{4-n}]$ and $(85Cl)_2$ were produced <2003JOM321>. In a similar manner, the reaction between the metal dihydrides $[Cp_2MH_2]$ $M = Mo, W$ and silylene **83** gave the insertion products $[Cp_2M(H)(83H)]$ <1999OM2615>.

6.16.2.4.3 Electrophilic attack at ring nitrogen

Although the results of photoelectron spectroscopy and quantum mechanical calculations suggest that the HOMO of 1,3,2(λ^2)diazasiloles, such as **83–85**, are π -type MOs with large coefficients at the nitrogen atoms, there are no reports on reactions of bisaminosilylenes **83–85**, which indicate the initial attack of an electrophile at the ring nitrogen atoms.

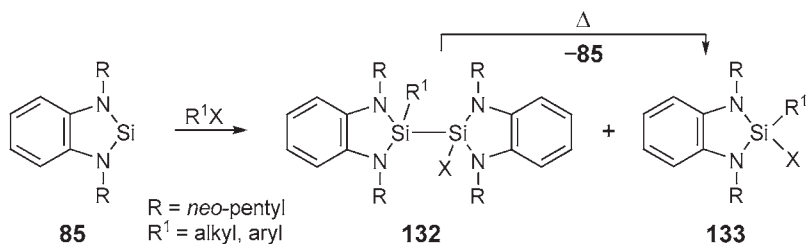
6.16.2.4.4 Nucleophilic attack at ring silicon

Lewis acidity is the predominant reactivity pattern of simple silylenes. In contrast, no donor–acceptor complexes between 1,3,2(λ^2)diazasiloles **83–85** and strong bases such as pyridine and triethylamine were detected (although silylene **85** reacts with pyridine and quinoline in a [2+1] cycloaddition reaction) <1998JA12714, 2000CJC1526, 2004JOM1350>. The oxidative addition of alcohols ROH ($R = \text{alkyl, aryl}$) or water to silylenes **83–85** is probably a reaction which proceeds via an initial nucleophilic attack at silicon; however, neither experimental nor theoretical study on this insertion reaction has been published, and concerted reaction pathways as suggested for the insertion reaction into CH bonds <1999IC4819> cannot be ruled out. Clear experimental evidence for nucleophilic attack at silicon is provided, however, in the reaction of the stable carbene **116** with silylene **85**. The molecular structure of the weakly bonded donor–acceptor complex **117** clearly indicates pyramidalization at the silicon atom and density functional theory (DFT) computations indicate the reverse polarity ($C(+)-Si(-)$) of the exceedingly long C–Si bond in complex **117** (Equation 8) <1999CC755, 2000JCD3094>.

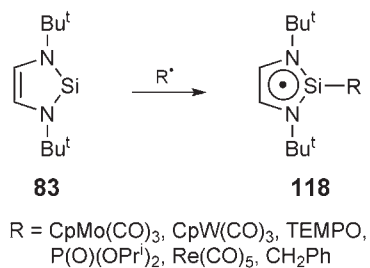


6.16.2.4.5 Reactions involving radicals and reducing agents

The reaction of 1,3,2-diazasilole **83** with several organometallic and organic radical sources has been studied by EPR spectroscopy (Equation 9). They form neutral radical adducts **118** with the unpaired electron delocalized over the five-membered ring. Several of these radicals persist at room temperature for days <2004JA7786>.

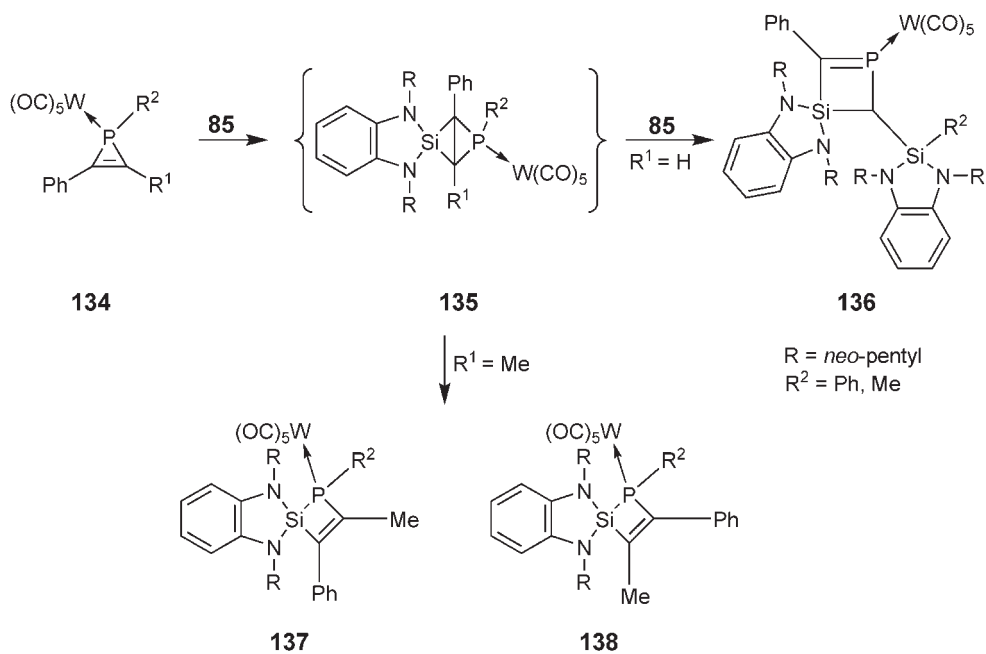


Scheme 13

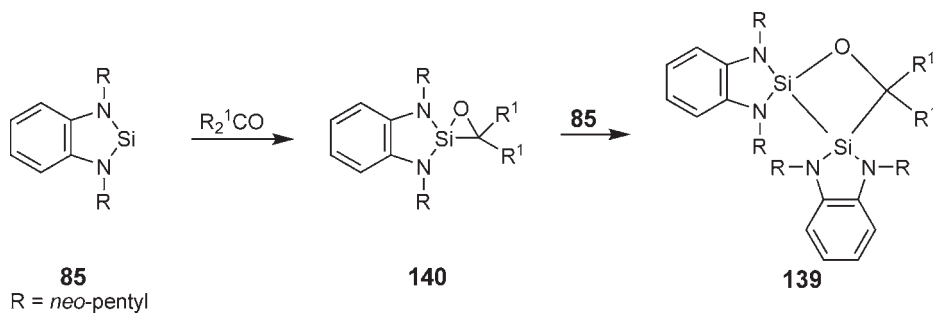


(9)

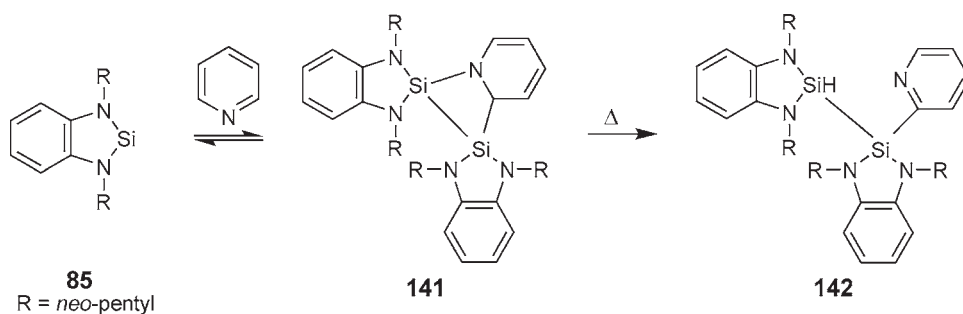
Similar reaction of the saturated silylene **84** with $[\text{CpW(CO)}_3]^+$ gave the adduct **119**, in which delocalization across the five-membered ring cannot occur and the radical is localized at the tungsten atom.



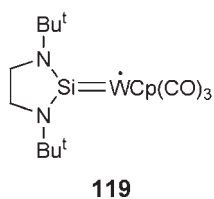
Scheme 14



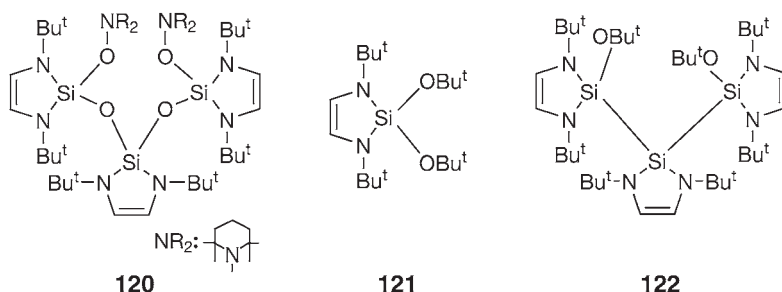
Scheme 15



Scheme 16

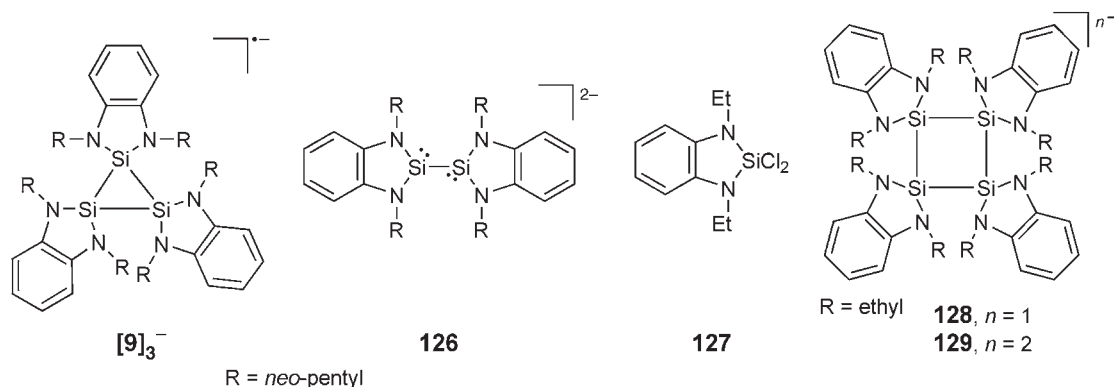


Reaction of compound **83** with 2,2,6,6-tetramethyl-piperidine-1-oxyl (TEMPO) on a preparative scale affords in a multistep reaction trisiloxane **120** as the major product in 80% yield, while with $Bu^tO\cdot$ radical the 1:2 adduct **121** was isolated and, as a by-product, the trisilane **122** in 15% yield <2004OM6330>.

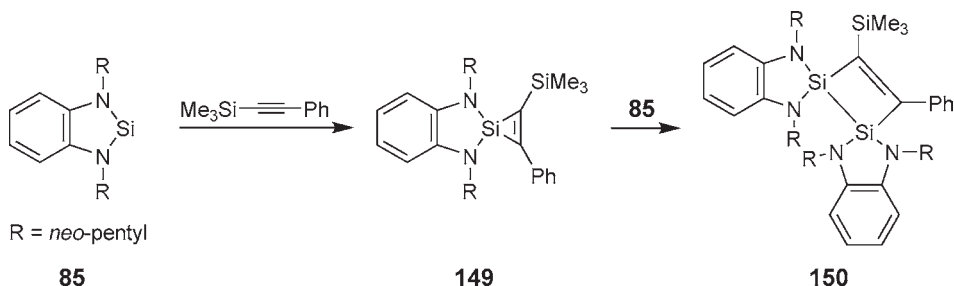


Reduction of silylene **84** with strong reducing agents such as potassium, potassium/sodium alloy, or potassium graphite yields either the 1,2-disilanyl dianion **123** or the silyl dianion **124**, depending on the stoichiometry (Scheme 12) <2000CJC1526, 2001CL68>. At room temperature reaction of silyl dianion **124** with the solvent gives the silyl monoanion **125**. All three anionic compounds **123–125** were detected directly by ^{29}Si NMR and by trapping with electrophiles <2001CL68>.

In contrast, the reaction of unsaturated 1,3,2(λ^2)diazasilole **83** with alkali metals results in its decomposition <1998JA12714, 2001CL68>. EPR results obtained after electrochemical reduction indicate however the formation of a trimeric cyclic anion radical <2004JOM4165>. In agreement with this result is the finding that careful reduction of the silylene **85** with sodium gives the radical anion **85 $^{\cdot-}$** in 86% isolated yields. Further reduction of **85 $^{\cdot-}$** with excess sodium eventually results in the formation of disilyl dianion **126** in 67% yield <2005CC5112>. It is noteworthy that the attempted synthesis of a silylene from the less bulky-substituted silyl dichloride **127** by reduction with potassium metal results in the formation of a tetrameric radical anion **128** and dianion **129** <2004AGE1124>.

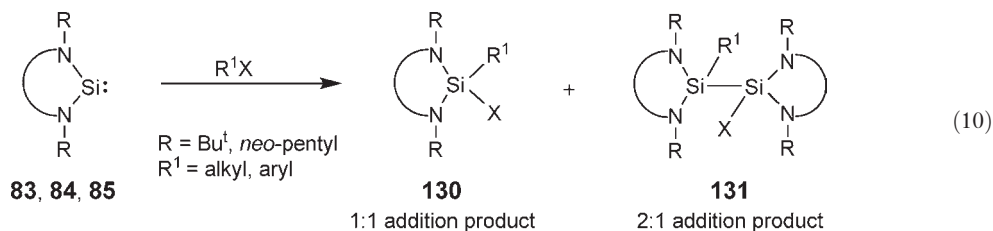


The reaction of bisaminosilylenes **83–85** with alkyl and aryl halides yields the formal product of oxidative addition, **130** and the disilane **131**, the product of a formal 2:1 addition (Equation 10) <1996JOM211, 1998JA12714, 2000CJC1526, 2002JA4186, 2005JA14730, 2005JCD2945>. Which type of product is eventually formed depends strongly on the type of silylene and nature of the halide X or the organic group R^1 and on the actual reaction conditions. The mechanism of this reaction is not clearly understood, but increasing experimental evidence is



Scheme 17

accumulated in favor of a radical mechanism <2005JA14730, 2005JCD2945>. Quantum mechanical computations, which are in accord with experimental results, suggest that this type of reaction proceeds via a radical chain mechanism <2005PCA3728>.



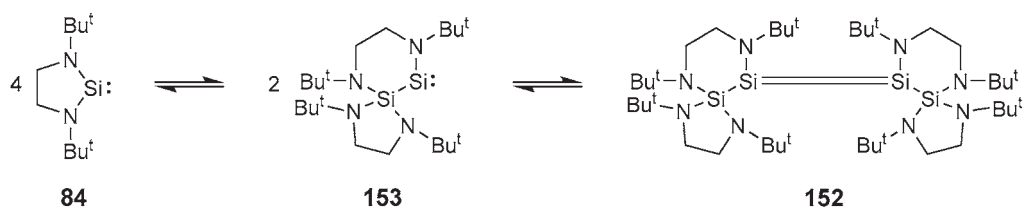
Interestingly, in the case of the reaction of silylene **85** with halocarbons the thermal rearrangement of the disilane **132** to the 1:1 addition product **133** with extrusion of the silylene was found to be a general follow-up reaction (Scheme 13) <2005JCD2945>.

Reaction of silylene **85** with silyl halides is believed to proceed via a similar reaction mechanism. The reactions are however less clean giving other products as well, such as silyldihalides **85X₂**. Similarly, during the reaction with germanium or tin(IV) chlorides, the dichloride **85Cl₂** and the element(II) chloride are formed <2006JOM811>.

6.16.2.4.6 Reactions with cyclic transition states

Many of the addition reactions of the silylenes **83–85** with molecules having multiple bonds and also many of their insertion reactions into activated σ -bonds are thought to proceed via cyclic transition states. For that reason these reactions are summarized in this section. It should be emphasized, however, that in only a few cases mechanistic investigations either by theoretical means or by experimental methods have been undertaken to substantiate the claim for a one-step cycloaddition.

6.16.2.4.6(i) Addition reactions to multiple bonds



Scheme 18

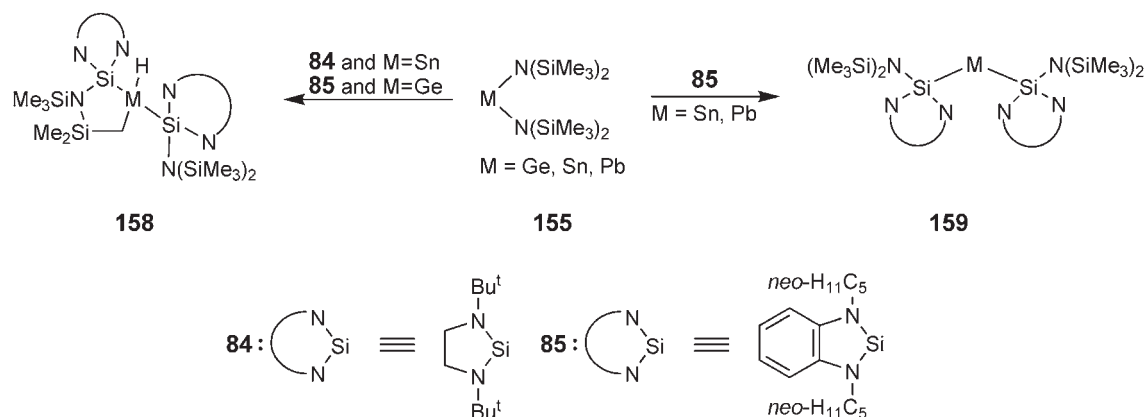
The stable silylenes **83–85** do not react with conventional C=C double bonds; however, diazasilole **83** is an efficient catalyst for the polymerization of alkenes, terminal alkynes, and 1,3-butadienes <2000ACR704, 2002USP028920, 2004JOM4165>. The stable bisaminosilylene **85** reacts with the activated double bond in 1*H*-phosphirenes **134**. The heterobicyclobutane **135** is however only a transient species and after addition of a second silylene **85** phosphasiletes **136** were isolated. Use of more sterically demanding substituted phosphirenes hampered the attack of the second silylene and the phosphasiletes **137** and **138**, which are valence isomers of bicyclobutane **135**, were obtained (Scheme 14) <2004AGE3474>.

Reaction with ketone and imine functionalities was studied in detail for silylene **85**. Reaction of this silylene with ketones such as benzophenone, 3,3-dimethylbutan-2-one, and 2-adamantan-2-one afforded the disilaoxetane compounds **139** in high yields (Scheme 15). The formation of these products most likely occurs via a [2+1] cycloaddition to form a short-lived oxasilacyclopropane intermediate **140**, which further reacts with a second silylene to form the final product <1997OM4861, 1997PS537>.

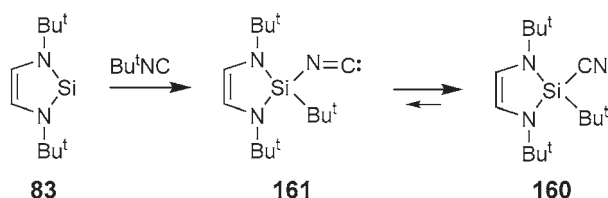
Silylene **85** reacts also with imines to give 1:1 adducts or 2:1 adducts, depending on the imine used and on the reaction conditions <1998OM1378>. Reaction of silylene **85** with pyridine gave the 1-aza-2,3-disila-cyclobutane **141**,

which is labile and partially dissociates in solution into the reactants. Upon extended heating in benzene the stable pyridyldisilane **142** is obtained as a thermally stable final product (Scheme 16) <2004JOM1350>.

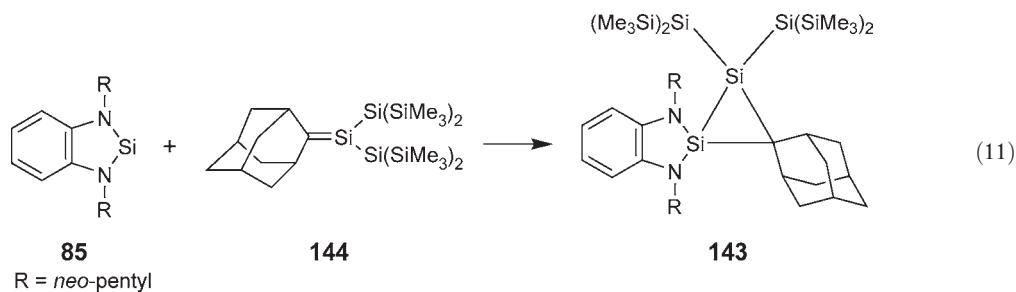
In a [2+1] cycloaddition reaction the disilacyclopropane **143** is formed from silylene **85** and the ephemeral silene **144** (Equation 11) <2004OM2848>.



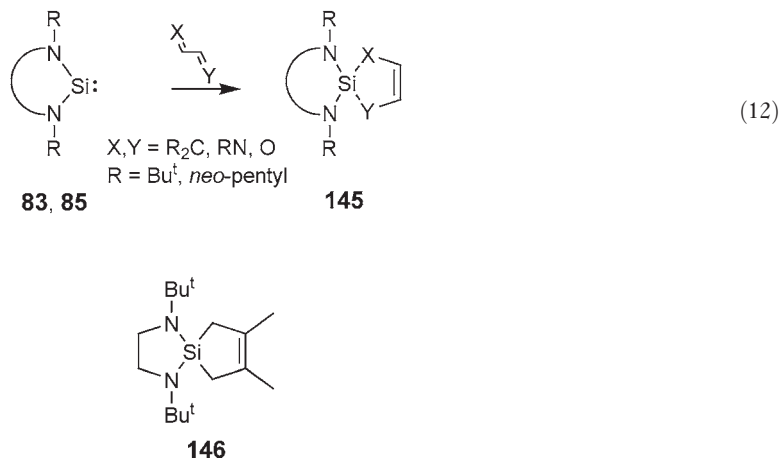
Scheme 19



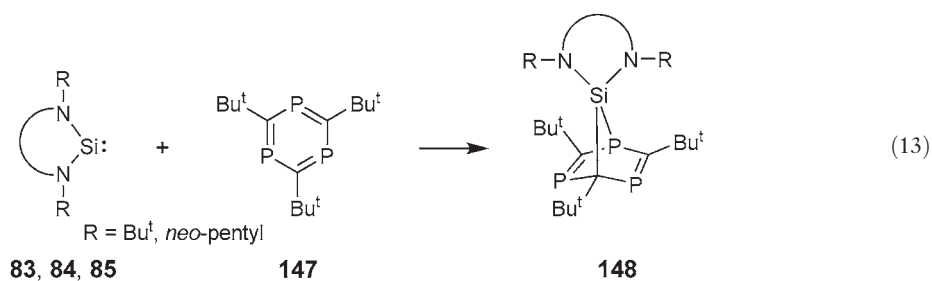
Scheme 20

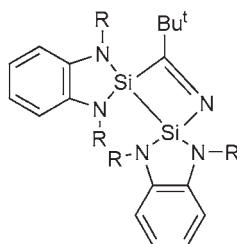


Reaction of silylenes **83** or **85** with compounds having conjugated double bonds such as butadienes, 1-aza-, 1-oxa-, 1,4-diaza-, or 1,4-dioxabutadienes yielded the corresponding spirocompounds **145** (Equation 12) <1996PAC785, 1997OM4861, 1998OM1378, 1998JA12714, 2000ACR704>. It is noteworthy that although diazasilole **83** gave the expected silacyclopentene from the reaction with 1,4-diphenylbutadiene, it acts as a polymerization catalyst in the case of 2,3-dimethyl-1,3-butadiene <1996PAC785, 2000ACR704>. In contrast, the CC saturated analogue of **83**, that is, silylene **84**, gives the expected product of a [1+4] cycloaddition, the spiro-silacyclopentene **146** <2000CJC1526>.



Also, 2,4,6-tri-*t*-butyl-1,3,5-triphospha-benzene **147** undergoes [1+4] cycloaddition with the stable bis(amino)silylenes **83–85** to afford the structurally characterized 1,3,5-triphospha-7-silanorbornadienes **148**. In the case of silylene **85** this reaction was shown to be reversible (Equation 13) <1999CC2451, 2002JCD484>. The higher reactivity of benzo[*b*]-diazasilole **85** compared to silylene **83** is also demonstrated in the reaction with alkynes. While diazasilole **83** is unreactive toward alkynes such as bis(trimethylsilyl)ethyne <2000ACR704>, silylene **85** affords with phenyl-trimethylsilyl-ethyne disilacyclobutene **149** <1998POL999>. The product formation is thought to proceed via a [1+2] addition which yields a silacyclopentene intermediate **150** followed by insertion of a second silylene **85** (Scheme 17) <1998POL999, 2001JOM209>. Similarly, with pivaloylnitrile the disilaazetine **151** is formed <2001ZFA1048>.

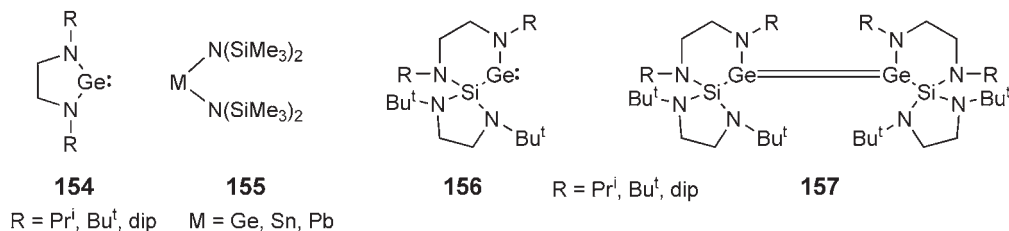


**151**R = *neo*-pentyl6.16.2.4.6(ii) Insertion reaction into σ -bonds

Several of the reactions described in Section 6.16.2.4.6.1 are two-step reactions. After the initial [2+1] addition of the silylene to the multiple bond, a second insertion reaction of a silylene into a reactive Si-X bond of the cyclopropane derivative takes place yielding four-membered ring compounds. Examples are the reactions with alkynes, nitriles, imines, and ketones.

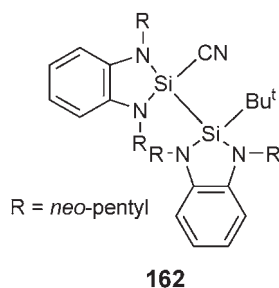
The ability of silylene **84** to insert into M(II)–N bonds (M = Si, Ge, Sn, Pb) allows for the synthesis of M(II) compounds with a novel substitution pattern and for the synthesis of a series of M=M bonded species (M = Si, Ge) with unusual bonding properties. For example, colorless crystals of silylene **84** transform over a period of days to a red powdery material, which has been characterized as the disilene **152** <1999JA9479, 2000CJC1526>. Density functional computations suggest that the reaction proceeds via silylene **153**, formed by insertion of silylene **84** into the Si–N bond of a second molecule of silylene **84**. The aminosilyl-substituted silylene **153** then dimerizes to give product **152** (Scheme 18). The silylene **153** was detected by trapping with methanol and with triphosabenzene **147** <1999JA9479, 2002JCD484>. The complete reaction sequence **84** $\rightarrow$ **152** is reversible and in a dilute THF solution of disilene **152** only silylene **84** is present <2000CJC1526>. Interestingly, the 4,5-dimethyl-substituted silylene **88** does not give this insertion reaction <2006OM3802>.

Similar insertion reactions of silylene **84** into the M(II)–N bond took place with germylenes **154** or with stannylenes **155** (M = Sn) <1997CB1733, 1998ZFA1405>. For the germylenes **154** the substituents R attached to the nitrogen atoms of the *N*-heterocyclic germylenes control if the reaction is stopped at the stage of the germylenes **156** (for R = dip (2,6-diisopropylphenyl)) or if dimerization reaction to the digermene **157** follows (for R = Prⁱ, Bu^t).

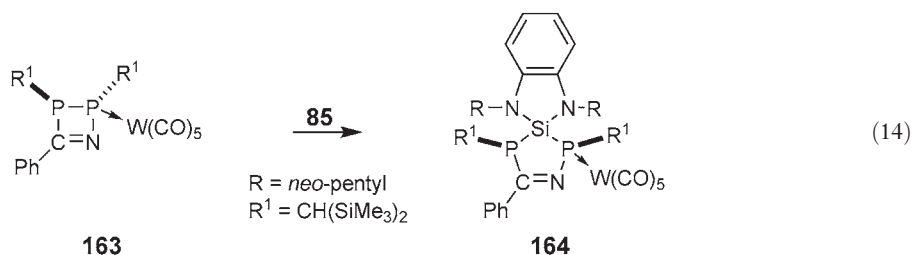


In the case of stannylene **155** (M = Sn) an intramolecular C–H insertion took place, which affords the spirocyclic compound **158** (M = Sn) <1997CB1733>. Similarly, the benzo condensed silylene **85** undergoes insertion reactions into the M(II)–N bond of the persilylated amides **155**. In this case the tin and lead compound gave the product of double insertion into the M(II)–N bond **159**, while the germanium compound undergoes a subsequent intramolecular C–H insertion reaction to give **158** (M = Ge) (Scheme 19) <1997AGE2514>. This reaction pattern was also found for the reaction of silylene **85** with other Sn(II) compounds <1997CC1845, 2004ZFA2090>.

Stable bisamino silylenes such as **83** and **85** react with organo substituted isocyanides by insertion into the N–C bond to afford exclusively silanitriles (e.g., **160**) which have tetracoordinated silicon atoms <1998POL999, 2000ACR704>. In particular, no silaketenes, the products of simple addition of the silylenes to the isocyanides, were detected. The reaction between **83** and pivaloyl isocyanide is thought to proceed via insertion of the silylene in the N–C bond and isomerization of the silanitrile **161** to the silanitrile **160** (Scheme 20). In the case of silylene **85** the outcome of the reaction depends on the actual conditions. Excess of silylene **85** during the course of the reaction affords product **162**, which results from the addition of 2 equiv of silylene **85** to the isocyanide <2001JOM209>.



Insertion of a silylene into a P-P single bond was observed for the reaction of silylene **85** with the diphosphaetidin complex **163**. The tungsten complex of 1,2,4,3-azadiphosphasilol-5-ene, **164**, was obtained in high isolated yields (Equation 14) <2005CC4842>.



6.16.2.4.7 Reactions of substituents

No reactions of the silylenes **83–90** have been reported in which the substituents of the five-membered ring are essentially involved.

6.16.2.5 Synthesis

6.16.2.5.1 Synthesis by reduction of compounds with tetravalent silicon atoms

The general method for the synthesis of stable cyclic bisdiaminosilylenes **83–90** involves the reductive dehalogenation of the appropriate dihalogenosilane. This was employed for the generation of compound **83** from the dichloride **83Cl₂** with potassium in THF at 65 °C <1998JA12714>. The use of potassium-graphite as reducing agent at ambient temperature was found to be more effective for the synthesis of silylenes **83**, **85**, and **86** from the appropriate dichlorosilane <2001CC2372, 2005ZFA1383> than the reaction with potassium in THF at 65 °C <1995CC1931>. Potassium/sodium alloy as well as lithium naphthalide has found application as reductant in this chemistry <1998ZFA295>, and for the synthesis of silylene **84** originally the cyclic silicondifluoride was reduced with Rieke magnesium in THF <1994JCD2405>. More suitable, however, is the reduction of the dichloride **84Cl₂** with sodium/potassium alloy in a 10:1 mixture THF/triethylamine at ambient temperature. The amine is added to avoid over-reduction of the silylene <2000CJC1526>. For the synthesis of compound **88** the dibromide **88Br₂** and potassium graphite were used in a 5:1 mixture THF/triethylamine at room temperature <2006OM3802>. The importance of the flanking bulky N-substituents in the synthesis of stable cyclic amino silylenes was demonstrated by the potassium reduction of the dichloride **127**, a less bulky-substituted analogue of **85Cl₂**. The reduction yielded the thermally stable cyclotetrasilane radical anion **128** and a similar dianion **129** <2004AGE1124>.

Clearly, synthetic alternatives to the reductive elimination are missing. It is noteworthy that the application of photochemical methods, common for the synthesis of transient silylenes, have not been described for the generation of 1,3,2(λ²)-diazasilacyclopentenes and -pentanes. A potential alternative to the described reduction chemistry could be the formal disproportionation reaction of a 1-halo-2-alkyl disilane with extrusion of a silylene as shown in Scheme 13. The scope and the limitation of this chemistry has however not been tested.

6.16.2.6 Possible Applications

Despite considerable advances during the last 10 years, the chemistry of stable silylenes still remains in its infancy. Their chemistry has been explored for some very specific examples and much work still has to be done to demonstrate the generality of this chemistry. In particular, their use as ligands in transition metal chemistry and their possible potential in catalyst design has not been tested. Some preliminary results in direction of application are, however, promising. Silylene **83** has been shown to be an efficient catalyst for alkene polymerization <2002USP028920> and recently binuclear Pd(0) complexes of silylene **83** were shown to be active in Suzuki cross-coupling reactions <2001CC2372>.

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6.17

Three or Four Heteroatoms including at least One Other Element

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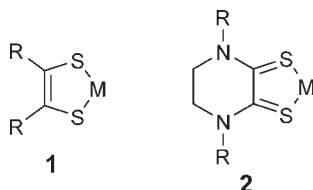
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6.17.1	Introduction	692
6.17.2	Theoretical Methods	693
6.17.3	Experimental Structural Methods	693
6.17.3.1	X-Ray Single Crystal Structures	693
6.17.3.1.1	Aluminium heterocycles	693
6.17.3.1.2	Indium heterocycles	694
6.17.3.1.3	Gallium heterocycles	694
6.17.3.1.4	Germanium heterocycles	695
6.17.3.1.5	Tin heterocycles	695
6.17.3.1.6	Lead heterocycles	695
6.17.3.2	Mass Spectrometry	695
6.17.3.3	UV-Vis Spectroscopy	716
6.17.3.4	NMR Spectroscopy	716
6.17.3.4.1	Aluminium heterocycles	716
6.17.3.4.2	Gallium heterocycles	716
6.17.3.4.3	Indium heterocycles	716
6.17.3.4.4	Germanium heterocycles	717
6.17.3.4.5	Tin heterocycles	717
6.17.3.4.6	Lead heterocycles	717
6.17.3.5	IR and Raman Spectroscopy	718
6.17.3.6	Mössbauer Spectroscopy	718
6.17.3.7	Other Spectroscopic Methods	718
6.17.4	Thermodynamic Aspects	719
6.17.5	Reactivity of Fully Conjugated Rings	719
6.17.6	Reactivity of Nonconjugated Rings	719
6.17.6.1	Reactions Involving Ring Carbon or Heteroatom Other than Group III or IV Metal	719
6.17.6.2	Reactions Involving Ring Group III or IV Metal	720
6.17.7	Reactivity of Substituents Attached to Ring Carbon Atoms	721
6.17.8	Reactivity of Substituents Attached to Ring Heteroatoms Including Metals	721
6.17.9	Ring Synthesis from Acyclic Compounds Classified by the Number of Ring Atoms Contributed by Each Component	723
6.17.9.1	Formation of One Bond between Two Heteroatoms	723
6.17.9.2	Formation of Two Bonds: Four-Atom Fragment and a Group III or IV Element	723
6.17.9.3	Formation of Two Bonds: Four-Atom Fragment and a Nitrogen, Phosphorus, or Group VIII Element	725
6.17.9.4	Formation of Two Bonds: [3+2] Atom Fragments by Cycloaddition	726
6.17.9.5	Formation of Two Bonds: [3+2] Atom Fragments by Other Processes	726
6.17.9.6	Formation of Three Bonds	726
6.17.9.7	Formation of Four Bonds	726

6.17.10	Ring Synthesis by Transformation of Another Ring	727
6.17.10.1	Ring Synthesis from Three-Membered Heterocycles	727
6.17.10.2	Ring Synthesis from Four-Membered Heterocycles	729
6.17.10.3	Ring Synthesis from Five-Membered Heterocycles	729
6.17.10.4	Ring Synthesis from Six-Membered Heterocycles	730
6.17.10.5	Ring Synthesis from Seven-Membered Heterocycles	731
6.17.11	Synthesis of Particular Classes of Compounds	731
6.17.12	Applications and Important Compounds	731
6.17.12.1	Biologically Active Compounds	731
6.17.12.2	Applications in Research and Industry	732
References		733

6.17.1 Introduction

The chemistry of five-membered rings with three or four heteroatoms including at least one group IV heteroelement other than silicon was reviewed in CHEC-II(1996) <1996CHEC-II(4)829> for the literature between 1982 and the beginning of 1994, while it was not discussed in CHEC(1984) because of the limited data available on these systems. In this chapter, the literature between 1995 and mid-2006 is considered together with information on five-membered rings with three or four heteroatoms including at least one group III or IV metal for the same period of time. The numerous transition metal-based five-membered heterocycles, that is, traditional transition metal dithiolates **1** or dithionates **2** <B-2004MI738, 2006IC3557> are not included in the scope of this chapter.



The major types of parent heterocycles discussed in this chapter are presented in **Figure 1** and can, at least theoretically, generate a large variety of specific compounds, which represent not only ‘classic’ organometallic compounds with M–C bonds, but also a variety of heterocycles with homolytic or heterolytic M–M bond and those with C–M–X or X–M–Y fragments (X and Y are N, O, S, and P donor atoms). The last group of the compounds predominates over other types and is similar to open-chain group III or IV alkoxides, thiolates, and amides. Moreover, group IV metals can form ‘carbenoid’-type compounds in addition to usual tetravalent complexes. Available literature data on these systems, however, are distributed quite unevenly and heavily depend on the type of the metal in the heterocycle favoring germanium, tin, and aluminium compounds.

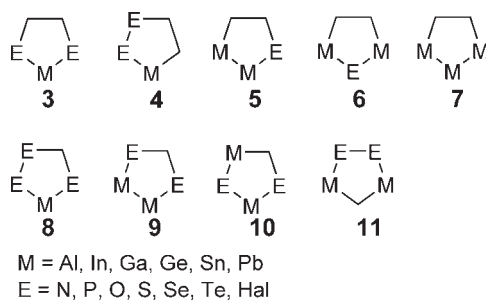


Figure 1 Major types of heterocycles discussed in this chapter.

The five-membered heterocycles presented in this chapter reflect some specific unanswered questions. One of the most interesting problems, which should be addressed in the future, is the possible aromaticity or antiaromaticity in the heterocycles under consideration.

6.17.2 Theoretical Methods

The ability of the semi-empirical PM3 method to predict the correct structures in tin(IV) compounds of general formula LSnX_2R_2 (L = phen or bipy; R = Et, Bu, Ph, and Tol) has recently been tested <2005AOM479>. In all cases tested, Sn–N bonds were significantly (0.17–0.26 Å) overestimated, probably reflecting underestimation of the tin-neutral ligand interactions. As a result of the overestimation of all Sn–N bonds, the calculated respective N–Sn–N angles are significantly underestimated. Use of double-zeta quality effective core potential (LANL2DZ) at *ab initio* Hartree–Fock theoretical level leads to a dramatic improvement in the calculated geometries with typical error of 0.03–0.04 Å for Sn–N bond distances in the similar compounds <1998PCA2472>.

Based on the comparison between crystallographically observed and calculated geometries, it has been concluded that crystal-packing forces can affect the first coordination sphere geometry around the tin center. The close approach method, which utilizes *ab initio* Møller Plesset perturbation theory (MP2) coupled with a LANL2DZ basis set, has been proposed <2004IC5529> for the conformational energy search in lead(II) cysteine complexes.

Satisfactory geometries with an average deviations of ~3% for distances and angles in the numerous tin-containing five-membered heterocycles have also been reported for density functional theory (DFT) calculations conducted using a B3LYP exchange-correlation functional and all-electron double-zeta valence plus polarization (DZVP) basis set <2005CEJ6185>. These geometries were then used for the calculation of the electric field gradients (EFGs) on the tin nuclei at the same level of theory and thus predict quadrupole splitting in Mössbauer spectra of organotin(IV) compounds. The observed high correlation coefficient ($R = 0.982$) between calculated EFG values and experimentally observed quadrupole splitting allowed the authors to determine solid-state conformations in several organotin(IV) compounds and thus to address the choice among possible structural hypotheses. Interestingly, effective core potential basis sets lead to significantly poorer results as compared to the full-electron basis sets.

Three-dimensional quantitative structure–activity relationship (3-D QSAR) studies on several organotin(IV) anticancer agents of general formula LSnX_2R_2 (L = Bipy or Phen; X = halide or pseudohalide; R = benzyl) by comparative molecular field analysis have been reported recently <2002BML61> and provide insight into the mechanism and toxicity of these drugs. The electron paramagnetic resonance (EPR) hyperfine coupling constants were accurately predicted for the paramagnetic aluminium complexes using the DFT approach <2005JA17204>.

Overall, the recent improvements in the field of computational chemistry demonstrate the ability of modern approaches to support structural interpretations and predict spectroscopic properties in the nontraditional metal-containing heterocycles described in this chapter.

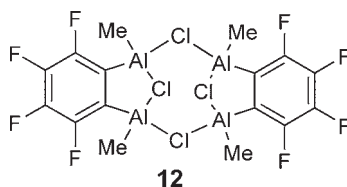
6.17.3 Experimental Structural Methods

6.17.3.1 X-Ray Single Crystal Structures

In CHEC-II(1996), a significant number of X-ray structures with aluminium, indium, gallium, germanium, tin, and lead heterocycles were reported. Since 1995, many new publications on X-ray studies appeared and these are listed in Table 1. The large number makes a detailed discussion impossible within the limited space available. Instead, only illustrative examples will be discussed for each metal of interest. It should be noted that the indium- and lead-containing structures with heterocycles of interest are still rare, while those with aluminium, gallium, germanium, and especially tin atoms appear more frequently in the current literature.

6.17.3.1.1 Aluminium heterocycles

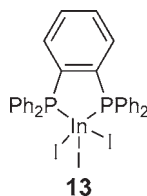
The five-membered heterocycle in compound 12 is almost planar with the short range of metal-bridging chlorine atom distances within 2.272–2.288 Å <1999CC1367>.



Besides the traditional tetrahedral coordination around aluminium center, a number of penta- and hexacoordinated structures have been reported including trigonal bipyramidal $(\text{LAlEt}_2\text{O})_2$ and L_3Al ($\text{HL} = 2\text{-methyl-8-oxoquinolin}$) compounds <2002JOM229>. On the other hand, salen-type ligands enforce a square pyramidal coordination around the aluminium center with a significant number of structures reported recently (salen = *N,N'*-bis(salicylaldehyde)ethylenediamine) <1997JOM189, 2005IC1433, 2006JA1147>. The same types of complex can form hexacoordinated dimers as well as polymers by reaction with phenylphosphinic acid <2000CC1799, 2002IC558>.

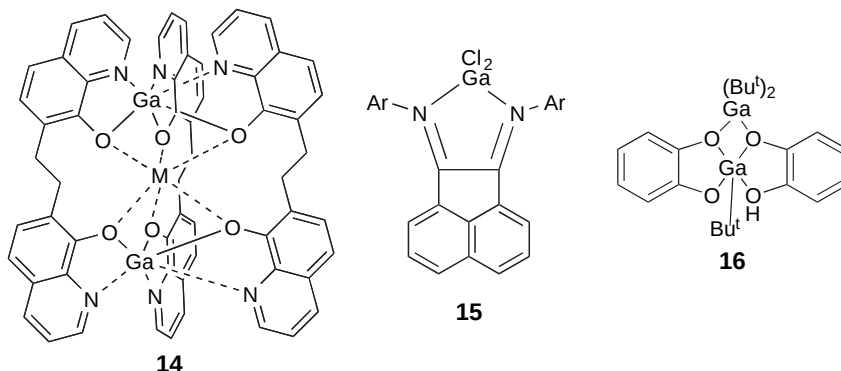
6.17.3.1.2 Indium heterocycles

The pentacoordinated indium(III) compound **13** has a quasi-square-pyramidal environment rather than trigonal bipyramidal with a short indium–axial iodine bond distance (2.713 Å) as compared to those in equatorial positions (2.780 Å) <1998EJI203>. An example of pseudooctahedral coordination around an indium(III) center can be given by the $[(\text{bipy})\text{InCl}(\text{SC}(\text{O})\text{Ph})_2]$ structure in which the indium center is coordinated to a planar bipyridine ligand, a chloride ion, and two thiobenzoate anions <2002MI467>. Of the latter, one thiobenzoate ligand binds in a bidentate fashion, while the other is bonded mainly through the sulfur atom.

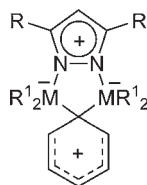


6.17.3.1.3 Gallium heterocycles

An interesting triple-stranded dinuclear gallium helicate has been found in the solid-state structure of cryptate **14**. In this structure, two gallium centers ‘preset’ the molecular cavity, which can adopt sodium or potassium ions <1999CEJ48>. The gallium complexes with aromatic chelate ligands are usually planar as represented by complexes **15** and **16** <2002CJC1398, 2005JOM722>. The unusually short Ga–N distance (1.985 Å) in complex **15** has been explained by the sp^2 -hybridization of the nitrogen donor atoms.



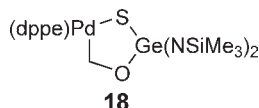
A set of unique molecules of general formula **17** reveals a nonplanar $\text{N}_2\text{M}_2\text{C}$ heterocycle with slightly different metal-bridging phenyl bond distances <2005OM6184>.



17: M = Ga, In

6.17.3.1.4 Germanium heterocycles

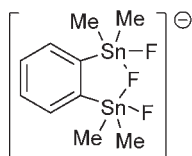
The five-membered heterocycle **18** is nonplanar and combines square planar palladium and tetrahedral germanium centers in the same cycle <2004OM2370>.



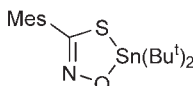
18

6.17.3.1.5 Tin heterocycles

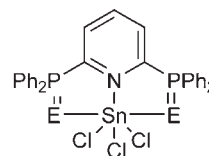
In analogy to aluminium heterocycles **12**, dinuclear tin(IV) complex **19** has a fluorine bridging atom resulting in an Sn–F–Sn fragment with almost equal Sn–F bonds and a trigonal bipyramidal geometry at tin centers <2000ZK309>. Similar chloro-bridged compounds possess a nonplanar heterocycle <1998OM5858>. The five-membered ring in 2,2-di-*tert*-butyl-1,3,5,2-oxathiazastannole **20** is planar with Sn–S and Sn–O bond distances of 2.508 and 2.127 Å, respectively <2001TL7063>. As expected, in the complexes **21**, the Sn–E bond distances increase and the E–Sn–E angle decreases in the series O, S, and Se <2003POL1585>. Overall, these examples demonstrate that the tin center in five-membered heterocycles can have tetrahedral, trigonal bipyramidal, and octahedral coordination.



19



20



21

E = O, S, Se

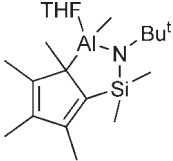
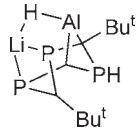
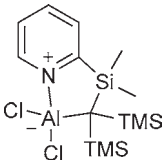
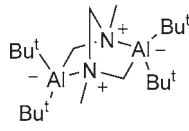
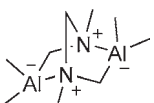
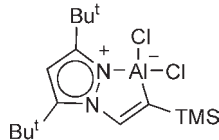
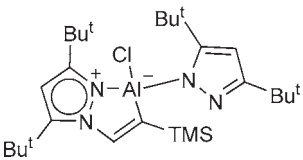
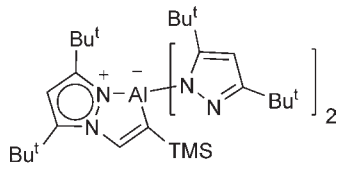
6.17.3.1.6 Lead heterocycles

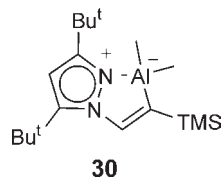
Three different cysteamine complexes of lead(II) were recently structurally characterized <2004IC5529>. The lead(II) center in PbCl(SCH₂CH₂NH₂) forms covalent Pb–Cl and Pb–S bonds, along with intramolecular Pb–N coordinative bond and two intermolecular Pb–S contacts resulting in octahedral configuration with a stereochemically active lone pair. On the other hand, the lead center in Pb(SCH₂CH₂NH₂)₂ complex is tetracoordinated with lone pair of electrons occupying the same plane as the sulfur donor atoms.

6.17.3.2 Mass Spectrometry

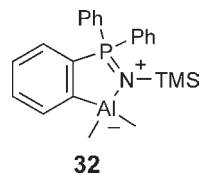
The fragmentation pattern often allows determination of the correct structure of the target heterocyclic system. For instance, the regiochemistry of [3+2] cycloaddition, which results in the formation of compound **170** (see Section 6.17.10) was tentatively assigned on the basis of the fragment peaks of mesitylisothiocyanate and germanone Tbt(Tip)Ge=O (Tbt = 2,4,6-tris[bis(trimethylsilyl)]-phenyl; Tip = 2,4,6-triisopropylphenyl) <1999JA8811>. Under electron ionization/mass spectrometry (EI/MS) conditions, complex **200** (see Section 6.17.10) eliminates an O=CCH₂O fragment <2004OM2370>. On the other hand, soft ionization methods result in the observation of a single [M]⁺ ion <2002POL563>. The fast atom bombardment (FAB) MS method has been widely used for the characterization of numerous heterocycles presented in this chapter <1995JOM43>. The FAB spectra of R₂SnL₂ complexes (HL = 4-X-benzoyldioxamic acid; R = Me, Et, Buⁿ, Ph, or Cl) clearly show the respective [M]⁺ ions and

Table 1 X-Ray crystal structures of five-membered rings with three or four heteroatoms including at least one group III or IV metal deposited to CCDC between 1995 and 2005

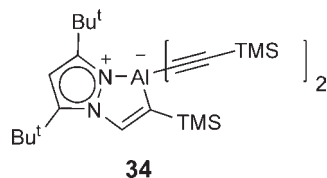
Compound	CCDC entry	Reference	Compound	CCDC entry	Reference
<i>One aluminium atom in heterocycle</i>					
 22	AFIPAG	2001JA7713	 23	BEYGIW	2004JCD1971
 24	FOFNAQ	2005JOM69	 25	IWIKAA	2004ZNB269
 26	MENHAO	2000CC1393	 27	MIXGUV	2001OM3299
 28	MIXHAC	2001OM3299	 29	MIXHEG	2001OM3299



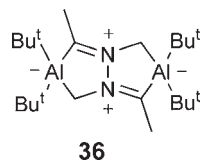
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VARREM 2003JCD3804

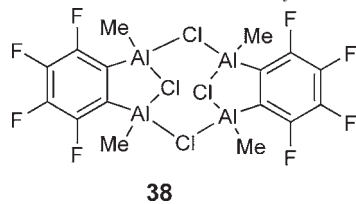


WONSIB 2000AGE3099

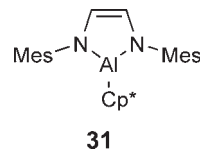


XEYPUM 2001ZFA909

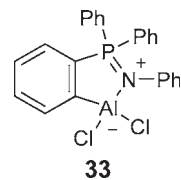
Two aluminium atoms in heterocycle



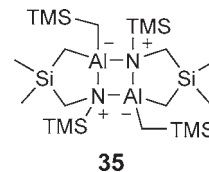
GOTNEI 1999CC1367



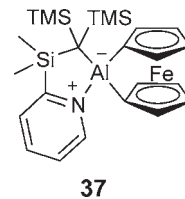
PUNROF 1998JCD1937



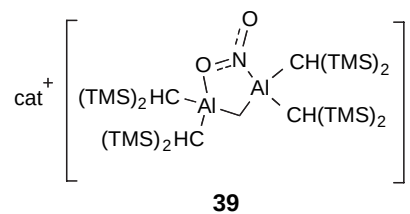
VARROW 2003JCD3804



XEDQAY 2000ZFA2284



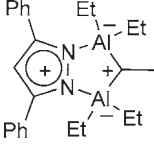
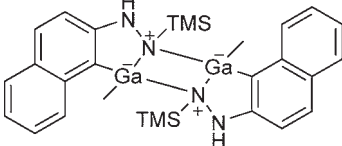
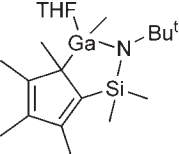
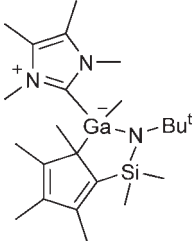
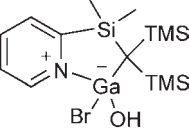
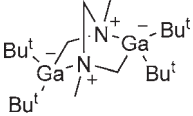
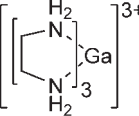
YANHUR 2005OM785

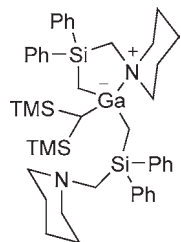


NUZYOW
NUZYUC
NUZZAJ 1998EJI921

(Continued)

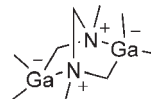
Table 1 (Continued)

Compound	CCDC entry	Reference	Compound	CCDC entry	Reference
 40 <i>One gallium atom in heterocycle</i>	QOPNUE	2001CC353			
 41	AFAKIB	2002EJI602	 42	AFIPEK	2001JA7713
 43	AFIPOU	2001JA7713	 44	FOFNEU	2005JOM69
 45	KALRUL	2005ZNB243	 46	JADGEB	1999ZFA1225



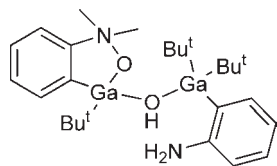
47

MASLUN [2000ZFA1526](#)



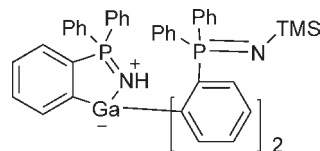
48

MENHES [2000CC1393](#)



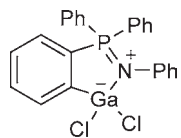
49

NOKKIH [1997POL3407](#)



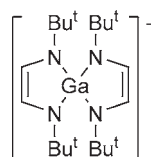
50

VARRIQ [2003JCD3804](#)



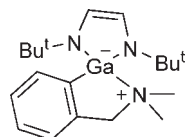
51

VARRUC [2003JCD3804](#)



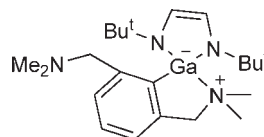
52

VORQIC [2001ZNB937](#)



53

YUVJAA [1995JA5421](#)

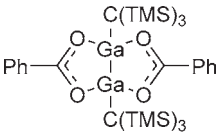
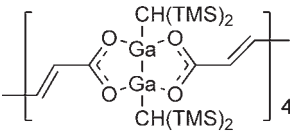
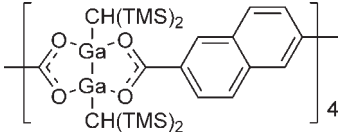
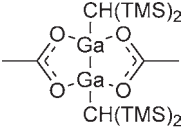
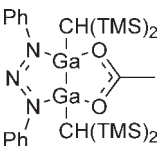
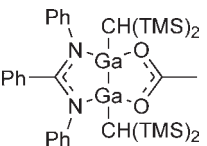
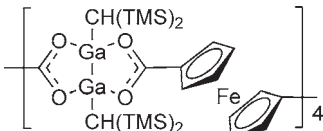
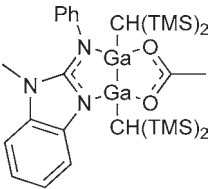


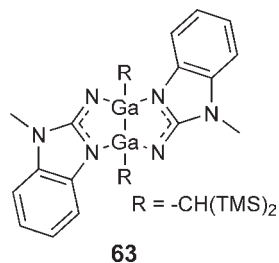
54

YUVJEE [1995JA5421](#)

(Continued)

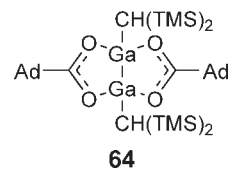
Table 1 (Continued)

Compound	CCDC entry	Reference	Compound	CCDC entry	Reference
<i>Two gallium atoms in heterocycle</i>					
 55	ATOHIA	2004EJI969	 56	EGANUV	2002POL511
 57	EREMAP	2004OM72	 58	HOJNOJ	1999JCD2385
 59	HOJNUP	1999JCD2385	 60	HOJPAX	1999JCD2385
 61	KIDXUQ	2000OM1128	 62	MASLEX	2000ZFA1526



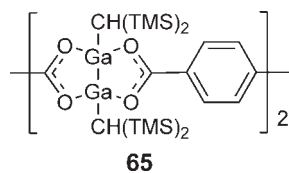
MASLIB
MASLOH

2000ZFA1526



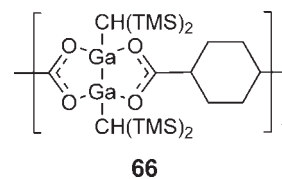
SUJBAA

1998EJI1661



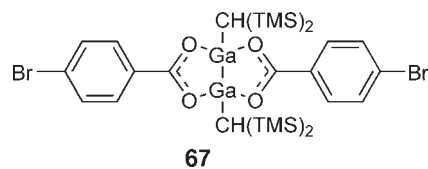
SUJDIK

1998EJI1661



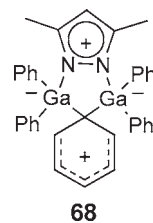
SUJDOQ

1998EJI1661



TIQSUH

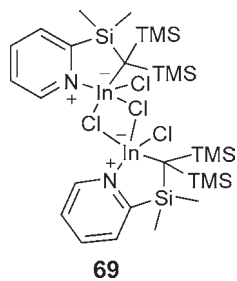
1996CB1425



ELOCOX

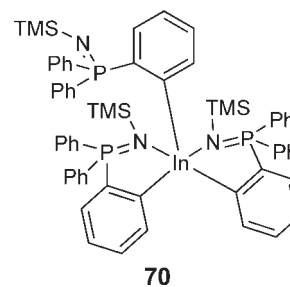
2003JA11152

One indium atom in heterocycle



FOFNIY

2005JOM69

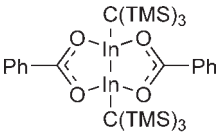
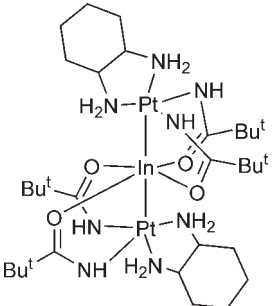
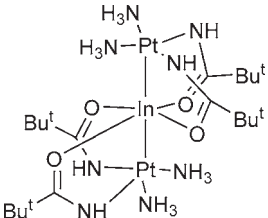
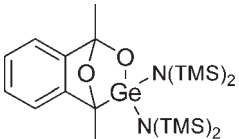
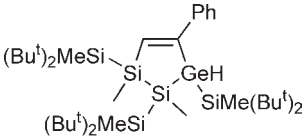


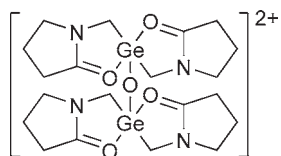
VIQXAU

2001OM2730

(Continued)

Table 1 (Continued)

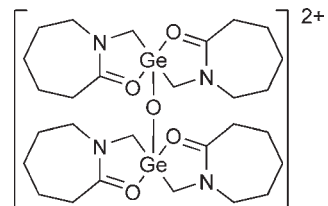
Compound	CCDC entry	Reference	Compound	CCDC entry	Reference
<i>Two indium atoms in heterocycle</i>					
 71	ATOHOH	2004EJI969			
<i>One indium and one platinum atom in heterocycle</i>					
 72	UNEKON	2003EJI4234	 73	UNEKUT	2003EJI4234
<i>One germanium atom</i>					
 74	AKELUX	2003OM3222	 75	EROLOM	2004CL84



76

EVOCIB
EVOCUN

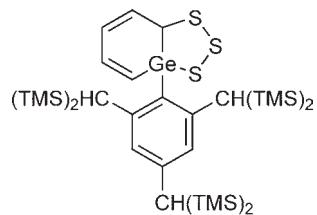
2003IZV1632



77

EVOCOH

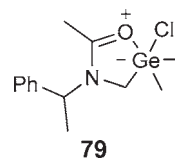
2003IZV1632



78

IMOVEL

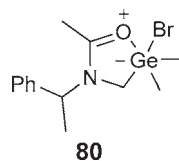
2003JOM66



79

LOHHOF

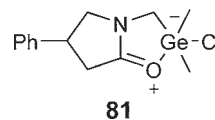
2000IZV137



80

LOHHUL

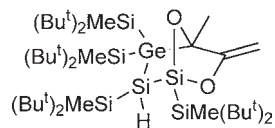
2000IZV137



81

LOHJAT

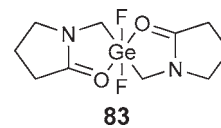
2000IZV137



82

OCEXID

2001CC2146



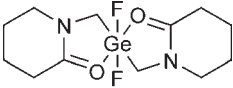
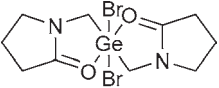
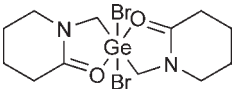
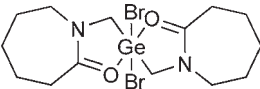
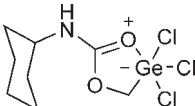
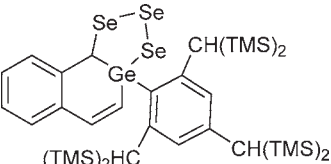
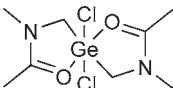
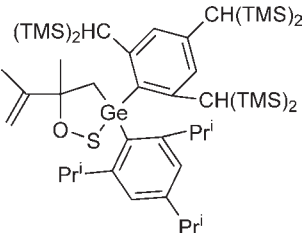
83

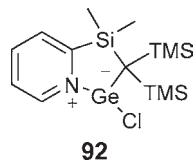
QEQVOX

2000IZV1799

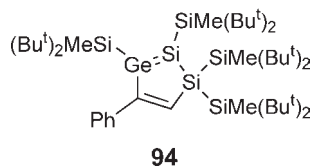
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Table 1 (Continued)

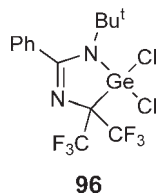
Compound	CCDC entry	Reference	Compound	CCDC entry	Reference
 84	QEQVUD	2004AXB252 2000IZV1799	 85	QEQWAK	2000IZV1799
 86	QEQWEO	2000IZV1799	 87	QEQWIS	2000IZV1799
 88	SANDOB	2004DOK342	 89	VADWIH	2003OM481 2002CL818
 90	WOKGOS	2000ZOB571	 91	XERQOA	1999CL129



XIDLEB [2001OM1223](#)

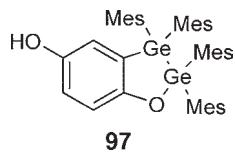


YERQIV [2000JA12604](#)
[2001JOM41](#)

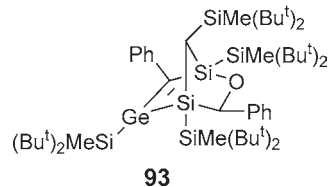


YIXNUO [1995ZNB289](#)

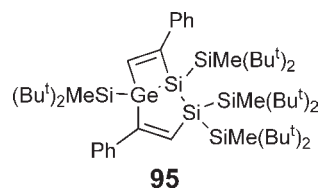
Two germanium atoms in heterocycle



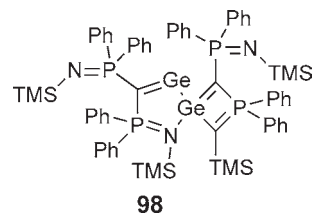
DUBBAD [1999MI599](#)



XOZGUO [2002JA9962](#)



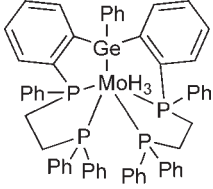
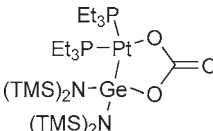
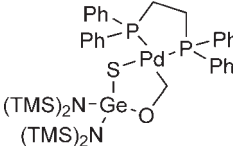
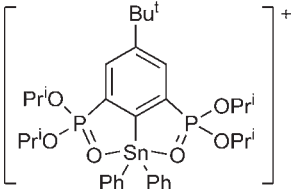
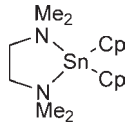
YERQOB [2000JA12604](#)
[2001JOM41](#)

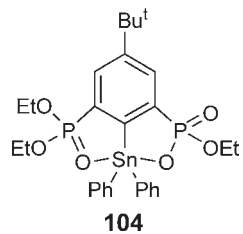


TIFHEV [2001AGE2501](#)

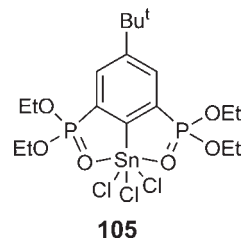
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Table 1 (Continued)

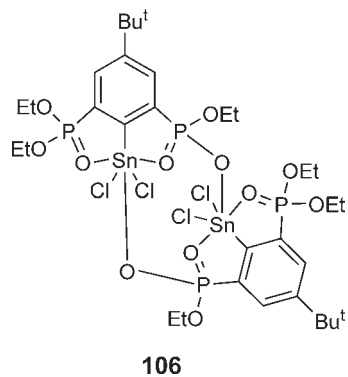
Compound	CCDC entry	Reference	Compound	CCDC entry	Reference
<i>One germanium and one molybdenum atom in heterocycle</i>					
 99	FADTIO	2001CL960			
<i>One germanium and one platinum atom in heterocycle</i>					
 100	JOLQUW	1998IC6461			
<i>One germanium and one palladium atom in heterocycle</i>					
 101	AYITEH	2004OM2370			
<i>One tin atom in heterocycle</i>					
 102	EYURUL	2004OM1501	 103	GALJUY	1998OM3176



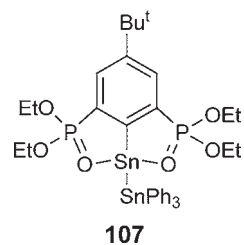
GORDIA [1999EJI887](#)



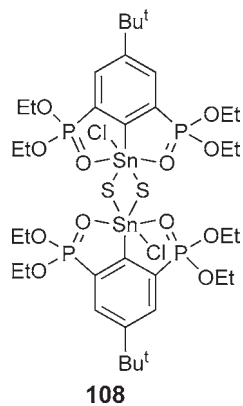
GORDUM [1999EJI887](#)



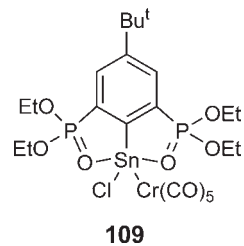
GORFAU [1999EJI887](#)



HUCGUH [2000OM4613](#)



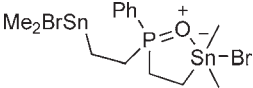
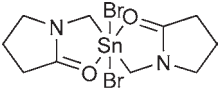
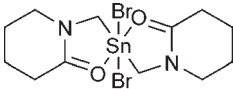
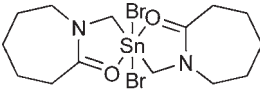
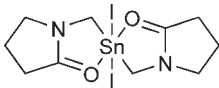
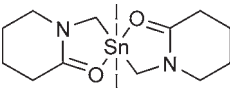
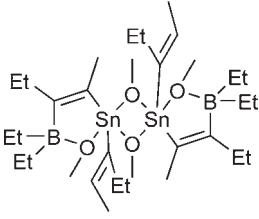
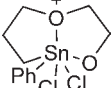
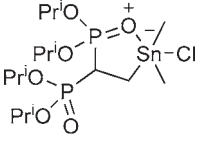
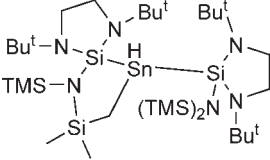
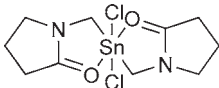
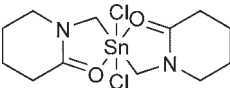
HUCHAO [2000OM4613](#)

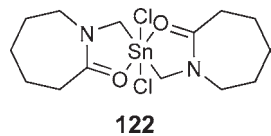


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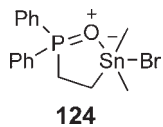
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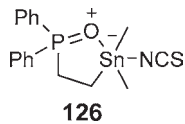
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 112	LEBMUA	1999IZV1988	 113	LEBNOV	1999IZV1988
 114	LEBNUB	1999IZV1988	 115	LEBPOX	1999IZV1988
 116	LORJEH	1999KGS1185	 117	MEVFIC	2001JOM55
 118	NASNIE	1996JOM233	 119	NECJAG	1997CB1733
 120	RIMZES	1996IZV2768	 121	RIMZIW	1996IZV2768



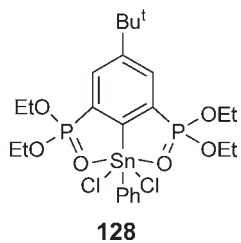
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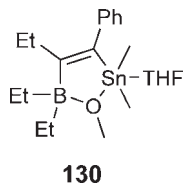
RIQXAQ 2001JCD2593



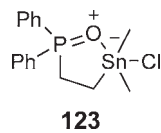
RISCAX 2001JCD2593



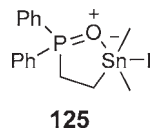
SANQUT 1998OM1227



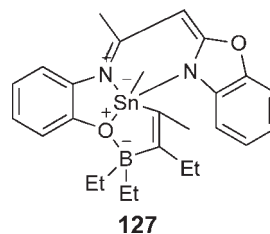
SUSFER 1996PC1, 1996ZK859



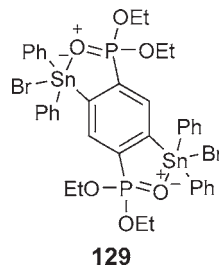
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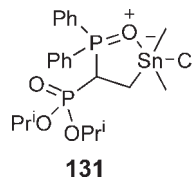
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ROHTOX 1997MI231



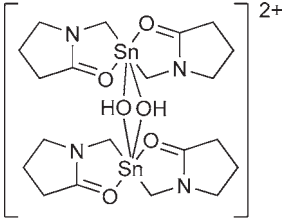
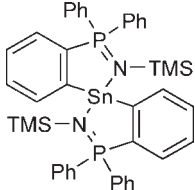
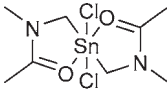
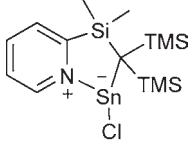
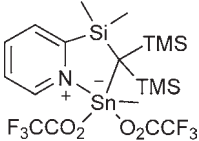
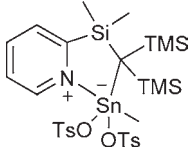
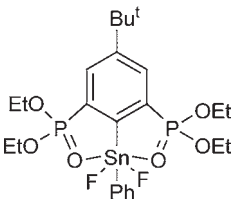
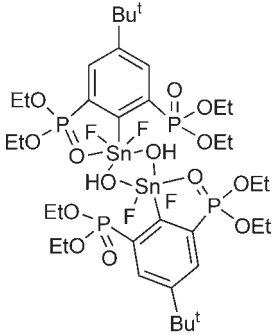
SANTOQ 1998OM1227

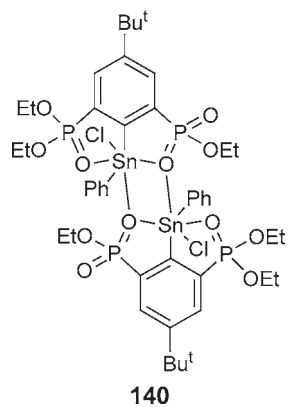


TUKSIB 1996ZK859

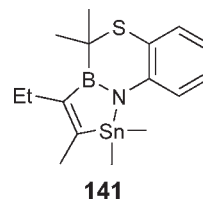
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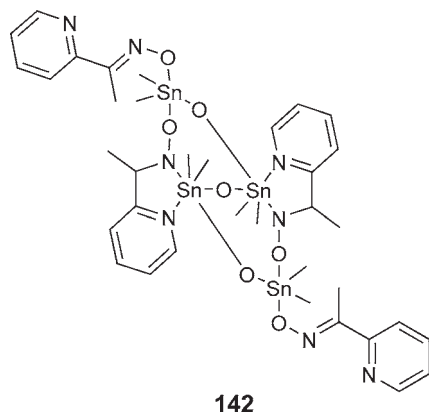
Compound	CCDC entry	Reference	Compound	CCDC entry	Reference
 132	WITNAO	2000IZV754	 133	WOHSUH	2000OM3890
 134	WOKGUY	2000JGUC571	 135	XIDLIF	2001OM1223
 136	XIDLUR	2001OM1223	 137	XIDMAY	2001OM1223
 138	XIMWAR	2001OM4647	 139	XIMWEV	2001OM4647



XIMWIZ [2001OM4647](#)

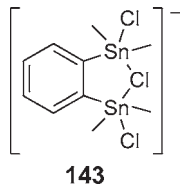


YOVPEE [1995JOM197](#)

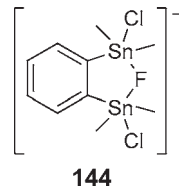


MUWBEL [2002JOM66](#)

Two tin atoms in heterocycle



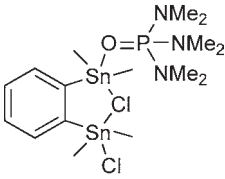
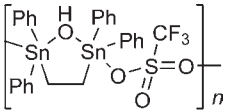
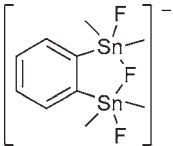
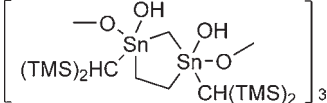
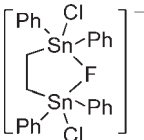
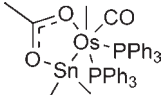
BAXYEE [1998OM5858](#)



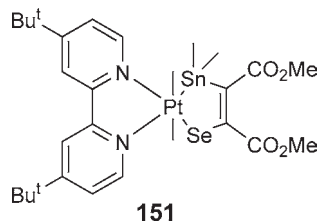
BAXYII [1998OM5858](#)

(Continued)

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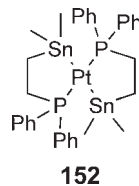
Compound	CCDC entry	Reference	Compound	CCDC entry	Reference
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 147	FUQGUT	2000NCS309	 148	HAQFOU	1998OM4096
 149	ZAFRON	1995OM2512			
<i>One tin and one osmium atom in heterocycle</i>					
 150	FODQOE	1999CC1101			

One tin and one platinum atom in heterocycle



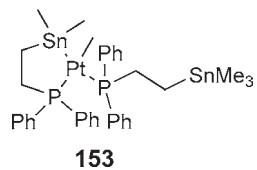
GOXPEO

[2002OM1257](#)
[1999JCD1713](#)



NIDVEB

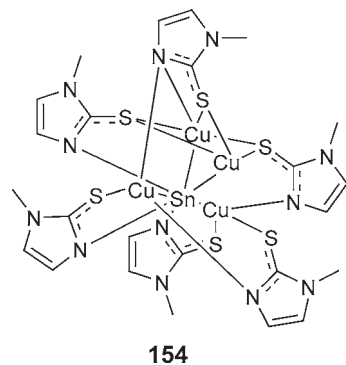
[1998AXC333](#)



NUZWAG

[1998EJI897](#)

One tin and one copper atom in heterocycle

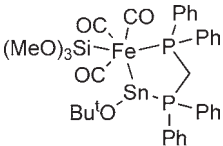
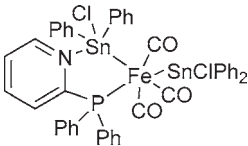
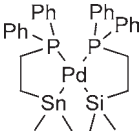
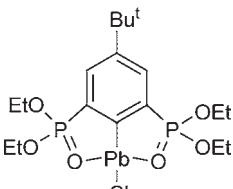
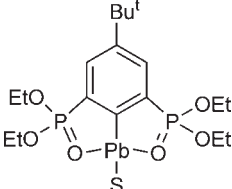


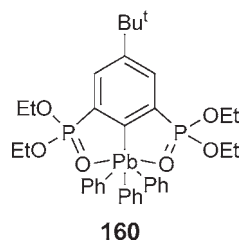
NIWTUI

[1997CC1975](#)

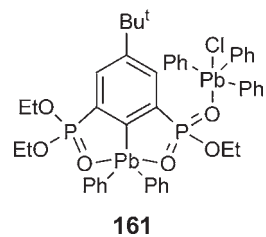
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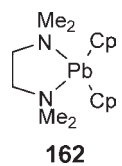
<i>Compound</i>	<i>CCDC entry</i>	<i>Reference</i>	<i>Compound</i>	<i>CCDC entry</i>	<i>Reference</i>
<i>One tin and one iron atom in heterocycle</i>					
 155	QIQNIN	2001OM627	 156	ROJTIT	1997CC1911
<i>One tin and one palladium atom in heterocycle</i>					
 157	ZAGHEU	1995JA6408			
<i>One lead atom in heterocycle</i>					
 158	ALIHUY	2003EJI3563	 159	ALIJAG	2003EJI3563



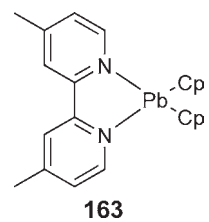
IGUJUP [2002ZFA2435](#)



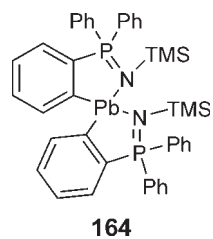
IGUKAW [2002ZFA2435](#)



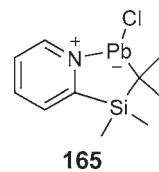
TODHOJ [1996CC1977](#)



TODHUP [1998OM3176](#)
[1996CC1977](#)



WOHTAO [2000OM3890](#)



XIDLLOL [2001OM1223](#)

fragments formed upon sequential loss of ligands <2004CEJ1456, 2004JOM4584>. Interestingly, in some cases, $[\text{SnL}_3]^+$ peaks were also detected under FAB MS conditions, which is indicative of a possible gas-phase reaction of these compounds.

The complexation behavior of the bidentate *o*-bis(dimethylchlorostannyl)benzene (**188**) and *o*-bis(methyldichlorostannyl)benzene toward chlorine and fluorine ions has been monitored using the negative electrospray ionization (ESI) method <1998OM5858>. The data clearly support the formation of 1:1 complexes with molecular ions of [**188** or **188** + Cl or F] $^-$. These molecular ions had the largest intensity and were accompanied by less intense fragmentation as well as dimeric molecular ions.

Electron impact mass spectrometry with the electron beam energy of 20 eV has been used for the detailed determination of the fragmentation patterns in 24 2,2-di-*n*-butyl- and 2,2-diphenyl-6-aza-1,3-dioxo-2-stannabenzocyclonon-4-ones derived from amino acids <2003CEJ2291>. In general, it was found that the molecular ion is unobservable in mass spectra, while the common fragmentation pattern includes losses of *n*-butyl or phenyl substituents as well as decarbonylation of amino acid fragment.

6.17.3.3 UV-Vis Spectroscopy

Since all of the metals discussed in this chapter have closed-shell configuration, the observable bands in ultraviolet-visible (UV-Vis) spectra of compounds mentioned below belong to the intraligand transitions. For instance, the ligand's $\pi-\pi^*$ transition has been reported at 345, 317, and 314 nm for $[\text{Sn}(\text{DTCA})\text{Cl} \cdot \text{H}_2\text{O}]$, $[\text{Sn}(\text{DTCA})\text{Cl}_3 \cdot \text{H}_2\text{O}]$, and $[\text{Al}(\text{DTCA})\text{Cl}_2 \cdot 2\text{H}_2\text{O}]$ complexes (DTCA = dithiocarbazate), respectively (see Section 6.17.9.2 <2001SRI115>). The first ligand $\pi-\pi^*$ excitation has been used as an excitation band for luminescent and phosphorescent experiments in several organotin and organolead complexes <2003OM4070>.

6.17.3.4 NMR Spectroscopy

6.17.3.4.1 Aluminium heterocycles

^{27}Al nuclear magnetic resonance (NMR) spectroscopy helps to differentiate between five- and six-coordinated salen-based aluminium complexes <2002IC558, 1999JA6747, 2006JA1147, 2000OM4416>. Indeed, ^{27}Al NMR spectra of all five-coordinated monomeric and dimeric salen-type complexes contain a single resonance at ~ 50 ppm, while all six-coordinated compounds have a single signal observed at ~ 0 ppm. Interestingly, in the case of monomeric complexes with bromine as an axial ligand, the observed chemical shifts (32–38 ppm) are shifted upfield as compared to those in respective chloride-containing complexes (43–57 ppm) <2006JA1147>. Moreover, ^{27}Al NMR spectroscopy clearly indicates that six-coordinate solid-state structure of $[\text{Salophen}(\text{Bu}^t)\text{Al}(\text{Ph}_3\text{PO})_2]\text{Br}$ complex changes into five coordinated in solution ($\text{Salophen}(\text{Bu}^t) = N,N'$ -*o*-phenylenebis(3,5-di-*tert*-butylsalicylideneimine)) <2006JA1147>. On the other hand, four-coordinated aluminium complexes of 2-pyridinecarboxaldehyde phenyl hydrazone and 2-acetylpyridine phenyl hydrazone ligands have chemical shifts ~ 150 ppm <2000OM4036>.

6.17.3.4.2 Gallium heterocycles

The negative signals observed in ^1H NMR spectrum of tetrahedral $[\text{Me}_2\text{Ga}(\text{TMEDA})][\text{Me}_2\text{GaCl}_2]$ complex have been assigned to the protons in the Ga–Me groups (TMEDA = tetramethylethylenediamine) <2003ZFA2509>. In the set of catechol-based gallium mono- and dinuclear systems, ^1H NMR spectroscopy has been used for determination of all possible isomers <2005JOM722>.

6.17.3.4.3 Indium heterocycles

The complexation of bis(amino thiol) ligand with indium centers has been investigated using ^1H NMR spectroscopy and supports metal-tetradentate N_2S_2 binding <1996IC6656>. ^1H and ^{13}C NMR data on $[\text{Me}_2\text{InCl}(\text{TMEDA})]$ complex reveal pentacoordinate geometry with equivalent methyl groups both on the TMEDA ligand and those directly attached to the metal center with the latter having a signal at -0.32 ppm in ^1H and -0.1 ppm in ^{13}C NMR spectra <2003ZFA2509>. Interestingly, in the case of $[(\text{CO})_n\text{M}-\text{GaR}(\text{TMEDA})]$ complexes ($\text{R} = \text{Me}$ or Et), the signals of the $\text{M}-\text{CH}_n$ protons were observed in the 0.09–0.73 ppm range with the exception of $[(\text{CO})_5\text{Cr}-\text{Ga}(\text{Me})(\text{TMEDA})]$ for which it was found at -0.01 ppm <1998JA1237>. Using ^{31}P NMR spectroscopy in the set of 1:1 neutral and cationic 1,2-bis(diphenylphosphanyl)benzene indium complexes it has been found that the ligand's

signals in the complexes shifted upfield as compared to the free ligand, which is opposite to the expected complexation shift observed in the most transition metal and main group metallocomplexes <1998EJI203>.

6.17.3.4.4 Germanium heterocycles

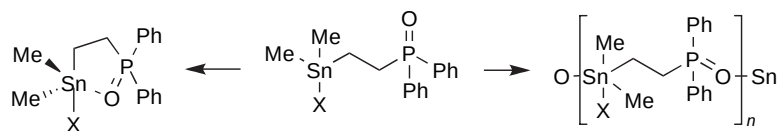
Compounds **170** and **100** (see Section 6.17.6) and similar complexes were characterized by ^1H , ^{13}C , and ^{31}P NMR spectroscopy <2004OM2370, 2005JOM2967>. ^1H , ^{13}C , and (in some cases) ^{77}Se NMR data available for germanium-containing compounds originated from Okazaki's group <1995JOM43, 1995OM1008, 1996OM4531, 1997JA2337, 1999JA8811, 2002POL563>.

Tris(hydroximato) germanium compounds have been successfully characterized by the solid-state ^{13}C and ^{15}N variable-amplitude cross-polarization/magic angle spinning (VACP/MAS) NMR approach because of their low solubility in organic solvents <2002IC3901>.

6.17.3.4.5 Tin heterocycles

$^{31}\text{P}\{^1\text{H}\}$ NMR spectra of tin complexes of general formula $[2,6\text{-}(\text{Ph}_2\text{P}(\text{E}))_2\text{Py-SnCl}_3]$ ($\text{E} = \text{O}, \text{S}, \text{Se}$) show splitting due to ^{31}P – ^{119}Sn coupling, which monotonically decreases with increase of the 'softness' of atom E <2003POL1585>. The value of the θ (C-Sn-C) angle in Me_2SnL_2 complexes ($\text{HL} = 4\text{-X-benzhydroxamic acid}$; $\text{X} = \text{Cl}, \text{F}$) has been estimated on the basis of the Lockhart and Manders equation ($\theta(\text{C-Sn-C}) = [^1J(\text{Sn}, \text{C}) + 875]/11.4$) and found to be in excellent agreement with that found in the X-ray structure <2004CEJ1456, 2004JOM4584>. In the series of tin(IV) heterocycles with a direct Sn–Pt bond, ^{119}Sn NMR spectra contain only one resonance with a large coupling due to $^1J(\text{PtSn})$ with the values between 9904 and 10031 Hz <1999JCS(D)1713>. The only single resonance of ^{119}Sn (from -287 to -489 ppm) has been observed in NMR spectra of other R_2SnL_2 complexes ($\text{HL} = 4\text{-X-benzhydroxamic acid}$; $\text{R} = \text{Me}, \text{Et}, \text{Bu}^n, \text{Ph}$, or Cl) confirming their hexacoordinated nature and absence of positional isomers <2004CEJ1456, 2004JOM4584>. On the other hand, the ^{119}Sn NMR spectra of dinuclear $[\text{R}_2\text{SnL}]_2\text{O}$ complexes fall into two categories. $[\text{Me}_2\text{SnL}]_2\text{O}$ complex with $\text{HL} = 4\text{-aminohydroxamic acid}$ shows lower field chemical shift at -196.36 ppm with agreement with the pentacoordinated structure of this complex. However, the other tested dinuclear compounds reveal ^{119}Sn chemical shifts outside the values of pentacoordinated tin(IV) complexes but are typical for hexacoordinated Sn(IV) compounds. Based on this observation, the authors proposed possible coordination of the solvent molecule for the central atom <2004JOM4584>.

Unsolvated $\text{XMe}_2\text{SnCH}_2\text{CH}_2\text{P}(\text{O})\text{Ph}_2$ ($\text{X} = \text{Cl}, \text{Br}, \text{I}$) can form in the solid state both chelate and linear chain forms depending on the nature of the recrystallization solvent <2001JCD2593>. A ^{119}Sn NMR experiment in CD_3OD and CDCl_3 , however, was not sensitive enough to determine which out of the two possible forms is predominant in solution because in both cases the characteristic of the pentacoordinated Sn(IV) center signal was observed between -49 and $+16$ ppm with only ~ 5 ppm difference between chloroform and methanol solutions (Scheme 1).



Scheme 1

The similar pentacoordinated Sn(IV) centers were postulated for the chelates formed by intramolecular cyclization in $\text{Ph}_2\text{P}(\text{E})\text{CH}_2\text{CH}_2\text{SnCl}_3$ compounds <2002JOM25>.

The complexation behavior of the bidentate *o*-bis(dimethylchlorostannyl)benzene and *o*-bis(methyldichlorobenzene) toward chlorine, fluorine, and hexamethylphosphoramide (HMPA) has been monitored using ^{119}Sn and ^{19}F NMR methods <1998OM5858>. The data clearly support the formation of 1:1 complexes with trigonal-pyramidal tin(IV) centers. Unlike complexation with chlorine and fluorine ions, the reaction with HMPA leads to the formation of two nonequivalent tin(IV) trigonal pyramidal centers, which show fast exchange at room temperature (single ^{119}Sn peak at -71 ppm), while two peaks at -52.9 and -98.9 ppm were observed at -80°C .

6.17.3.4.6 Lead heterocycles

Examples of the use of ^{207}Pb NMR spectroscopy for the study of coordination and stability of lead-containing five-membered heterocycles are rare. For instance, the differences in coordination number for different macrobicyclic

lead(II) complexes result in a ca. 1000 ppm shift in ^{207}Pb NMR spectra <2005IC5428>. As usually, ^1H and ^{13}C NMR spectroscopy can be successfully applied to the characterization of lead-containing complexes <2003OM4070, 2005POL865, 2004IC5529>.

6.17.3.5 IR and Raman Spectroscopy

In general, M–X (X is the atom within the five-membered heterocycle) bond frequencies are rarely used for characterization of target compounds. Instead, characteristic group frequencies of organic ligands and organic groups are commonly used for identification purpose. The infrared (IR) spectrum of compound **102** (see Table 1) contains a characteristic $\nu(\text{C}=\text{O}-\text{Ge})$ band at 1032 cm^{-1} <2004OM2370>. The complexation of chelate dithiocarbazate ion to Sn^{2+} , Sn^{4+} , and Al^{3+} centers with the formation of $[\text{Sn}(\text{DTCA})\text{Cl} \cdot \text{H}_2\text{O}]$, $[\text{Sn}(\text{DTCA})\text{Cl}_3 \cdot \text{H}_2\text{O}]$, and $[\text{Al}(\text{DTCA})\text{Cl}_2 \cdot 2\text{H}_2\text{O}]$ (see Section 6.17.9.2) has been supported by IR spectroscopy <2001SRI115>. Indeed, the C=S band of the DTCA ligand is virtually unchanged, while the absence of –SH vibrations is clearly indicative of complexation. A similar idea has been used for establishing the coordination sites in a series of R_2SnL_2 complexes (HL = 4-X-benzhydroxamic acid; R = Me, Et, Bu^n , Ph, or Cl) <2004CEJ1456>. Indeed, disappearance of the CO–NHOH group frequency, along with a significant shift of the C=O group (from 1680 to 1600 cm^{-1}) and the presence of a N–H band at ca. 3200 cm^{-1} , clearly indicate the coordination of the tin(IV) ion to two oxygen atoms in the ligand. In addition, the presence of two Sn–O bands in the $400\text{--}535\text{ cm}^{-1}$ region reflects different Sn–O bond lengths as supported by X-ray crystallography.

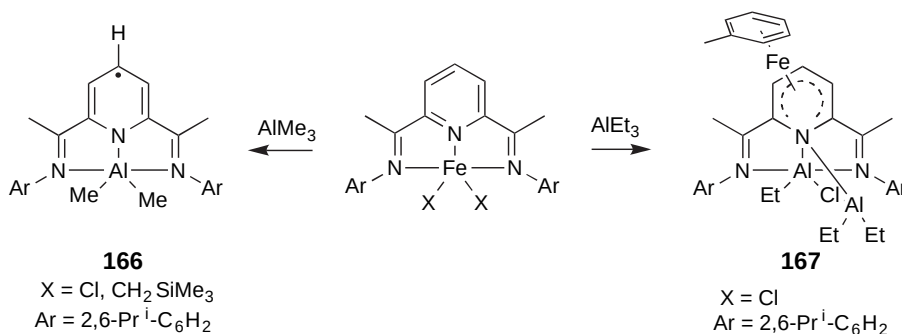
6.17.3.6 Mössbauer Spectroscopy

^{119}Sn Mössbauer spectroscopy has been used for the characterization of tin-containing five-membered heterocycles with three or four heteroatoms <1999POL3005, 1999JOM103, 2003ICA8>. Thus distorted octahedral LSnCl_2R_2 complexes (L = 2-(2'-pyridyl)quinoxaline; R = Me, Et, Bu^n) have $\sim 1.6\text{ mm s}^{-1}$ isomer shift and large ($3.85\text{--}4.08\text{ mm s}^{-1}$) quadrupole splitting at 77 K <1999POL3005>. The increase of coordination number from 6 to 7 in the $(\text{Ox})_3\text{SnR}$ complexes (OxH = 8-hydroxyquinoline; R = Ar) decreases both isomer shift ($0.59\text{--}0.63\text{ mm s}^{-1}$) and quadrupole splitting ($1.57\text{--}2.02\text{ mm s}^{-1}$) at 77 K <1999JOM103>. So large differences in the observed isomer shifts probably reflect the differences of total s-electron densities in the two sets of compounds. The same variability has been illustrated for the numerous $[(\text{DMPP})\text{SnX}_4]$ and $[(\text{DMPP})\text{SnX}_2\text{R}_2]$ complexes (X = Cl, Br, I; R = Me, Et, Bu^n , Ph) <2003ICA8>. Indeed, in the case of $[(\text{DMPP})\text{SnX}_4]$ complexes, the isomer shift follows electronegativity of X and varies from 0.59 (X = Cl) to 1.28 mm s^{-1} (X = I). Replacement of ligand X on organic group R significantly increases isomer shifts and decreases the difference in isomer shift between chloro- and bromo-containing analogues.

6.17.3.7 Other Spectroscopic Methods

The luminescent and phosphorescent properties of several pentacoordinate tin(IV) and lead(IV) complexes of general formula LMPh_2 (L = 2,6-bis(2'-indolyl)pyridine or 2,6-bis[2'-(7-azaindolyl)]pyridine) were investigated at room temperature as well as at 77 K <2003OM4070>. The complexes display both blue-green fluorescent and orange-red phosphorescent emissions originating from the ligand $\pi\text{--}\pi^*$ excitation. It has been suggested that tin(IV) and lead(IV) centers play a key role in enhancing fluorescent properties.

The reaction of LFeCl_2 with 10 equiv of trialkylaluminum in toluene at -35°C leads to the formation of unique paramagnetic aluminium complexes **166** and **167** (Scheme 2) <2005JA17204>. These complexes were characterized by room temperature EPR spectroscopy in toluene. A satisfactory simulation of the experimental spectrum was obtained using parameters consistent with a substantial delocalization of the unpaired electron over the diiminepyridine part with hyperfine couplings at the aluminium center, all three nitrogen atoms, and hydrogens located at pyridine ring as well as the ligand's methyl groups. The ligand's electron delocalization has also been confirmed by DFT calculations, which indicated that the singly occupied molecular orbital (SOMO) predominantly consists of the diiminepyridine π^* orbital.



Scheme 2

6.17.4 Thermodynamic Aspects

The bridge-terminal phenyl site exchange process that occurs in the set of gallium and indium complexes **17** has been investigated using ^{13}C NMR spectroscopy [<2005OM6184>](#). It has been shown that the signals of the *ipso*-carbon atoms of terminal and bridging ligands broaden with increase of temperature and eventual coalescence is consistent with bridge-terminal phenyl exchange. Eyring analysis of the data afforded the activation enthalpies, entropies, free energies, and rate constants for this process.

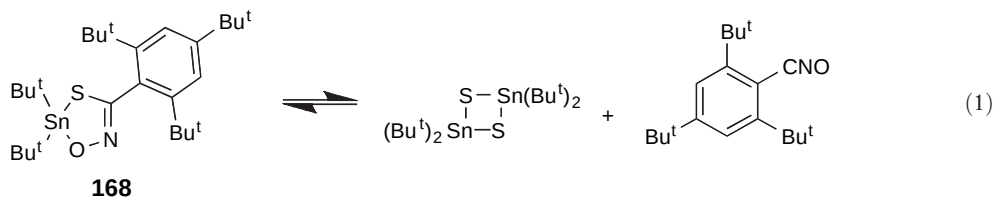
6.17.5 Reactivity of Fully Conjugated Rings

Since the degree of conjugation in group III and IV metal-containing heterocycles has not been investigated, the reactivity of all systems of interest is discussed in the following section.

6.17.6 Reactivity of Nonconjugated Rings

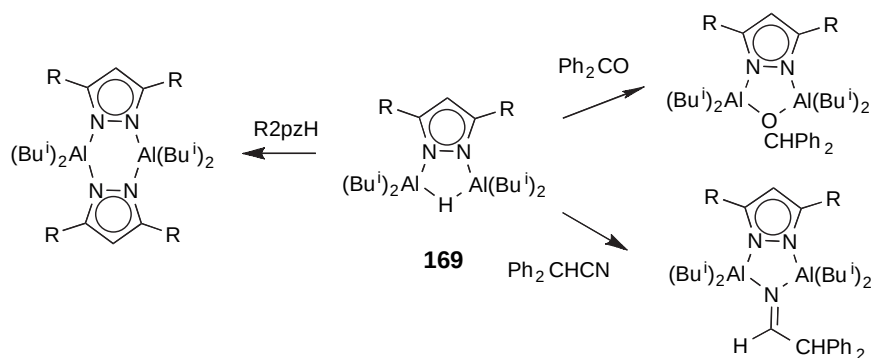
6.17.6.1 Reactions Involving Ring Carbon or Heteroatom Other than Group III or IV Metal

Heating a solution of stannole **168** in benzene- d_6 at 80°C leads to thermal cleavage of the S–C bond and the formation of four-membered 2,2,4,4-tetra-*t*-butyl-1,3,2,4-dithiadistannetane. Interestingly, this reaction is reversible. Cooling down the resulting solution leads to a quantitative re-formation of stannole **168** ([Equation 1](#)) [<2001TL7063>](#).

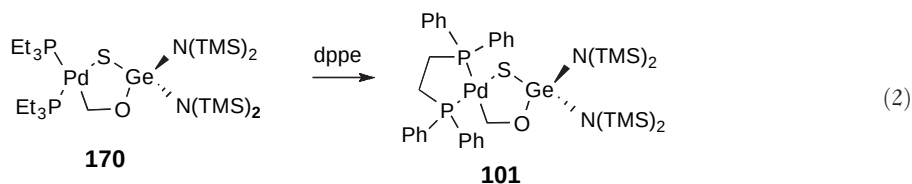


Selected reactions of hydride-bridged dialuminium complex **169** are presented below [<2001OM4301>](#). The reactions between complex **169** and 1 equiv of diphenylacetonitrile or benzophenone result in the bridged hydride transfer to the nitrile or carbonyl carbon atom, while those between compound **169** and 1 equiv of 3,5-diphenylpyrazole or diphenylmethanol cause elimination of the bridged hydride ion ([Scheme 3](#)).

Both ligands in complex **170** can easily be substituted by the chelating bis(diphenylphosphino)ethane (DPPE) group resulting in formation of product **100** ([Equation 2](#)) [<2004OM2370>](#).

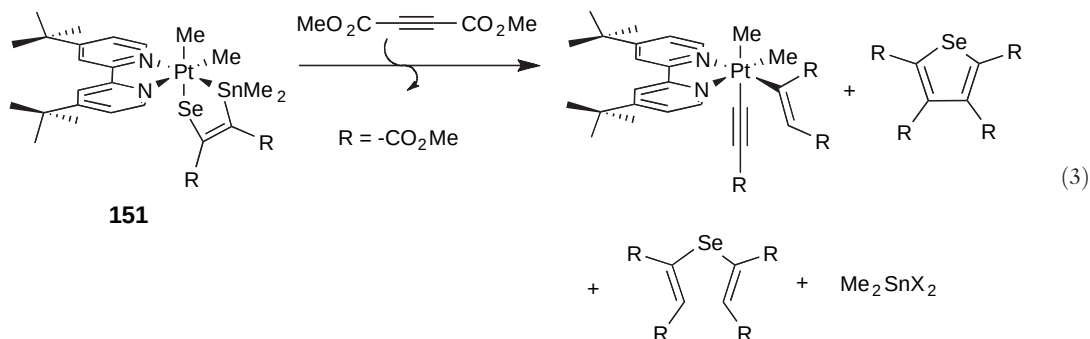


Scheme 3

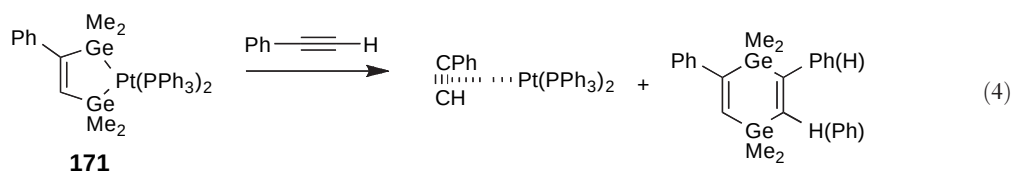


6.17.6.2 Reactions Involving Ring Group III or IV Metal

Complex **151** readily reacts with an excess of dimethyl acetylenedicarboxylate [<1999JCD1713, 2002OM1257>](#). The resultant reaction products are organoselenium compounds (Equation 3) and an uncharacterized organotin product. When the same reaction was conducted with an excess of $[\text{Me}_2\text{SnSe}]_3$ and alkyne, the observed ratio of organoselenium and organotin products was found to be 1:1:2 with a turnover frequency of 0.06 h^{-1} at 40°C .



The platinum complex **171** easily reacts with excess of phenylacetylene with the formation of a 1:1 mixture of 1,4-digermacyclohexa-2,5-diene and $(\eta\text{-acetylene})\text{bis}(\text{triphenylphosphine})\text{platinum}$ in quantitative yields ([Equation 4](#) [<2005JOM2967>](#)).

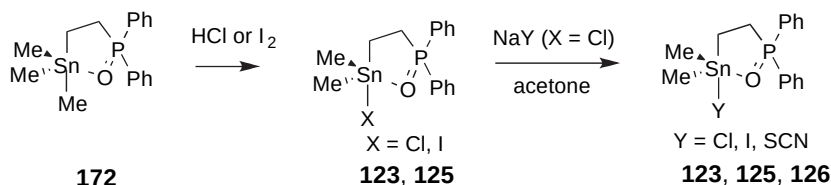


6.17.7 Reactivity of Substituents Attached to Ring Carbon Atoms

Since the reactivity of the substituents at ring metal center(s) is much higher than that at ring carbon atoms, examples of the latter are not discussed in the literature.

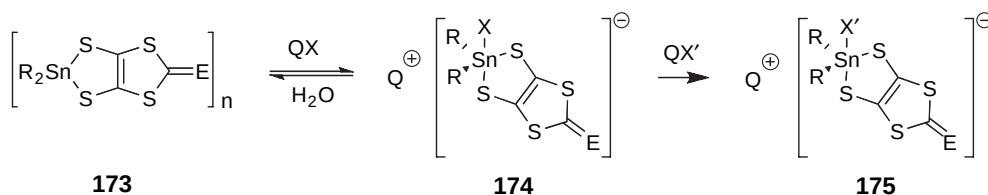
6.17.8 Reactivity of Substituents Attached to Ring Heteroatoms Including Metals

The methyl group in compound **172** can be easily replaced by chlorine or iodine by reaction with HCl or I₂. The chlorosubstituted compound has found to be a good precursor for nucleophilic substitution reactions with NaX (X = Br, I, or SCN) in acetone (**Scheme 4**) <2001JCD2593>.



Scheme 4

Several complexes between tin(IV) centers and the 1,3-dithiole-2-thione-4,5-dithiolato or 1,3-dithiole-2-one-4,5-dithiolato ligands have been prepared by Wardel's group by methathesis reactions involving addition, elimination, and substitution at the metal atom (**Scheme 5**) <1998POL4475, 1999JOM140>.

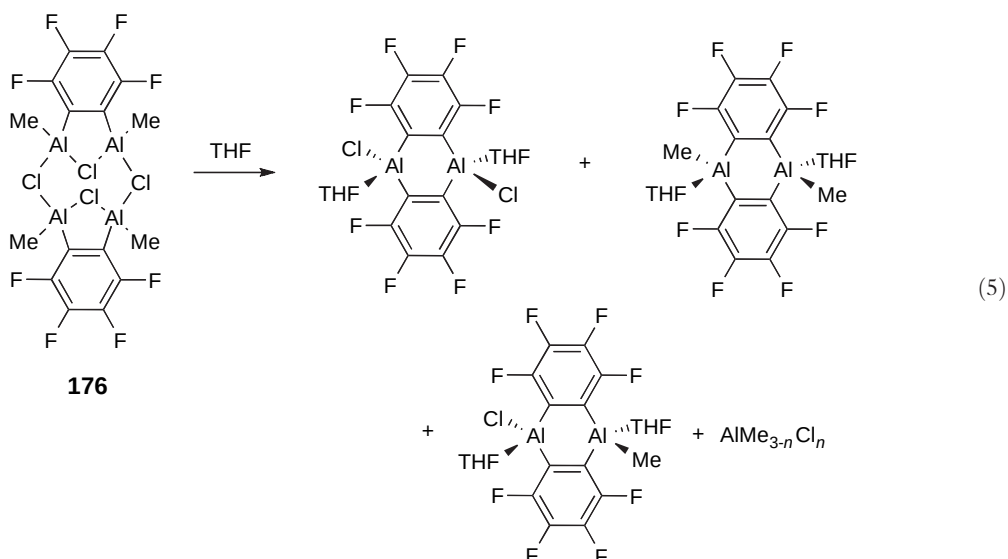


Scheme 5

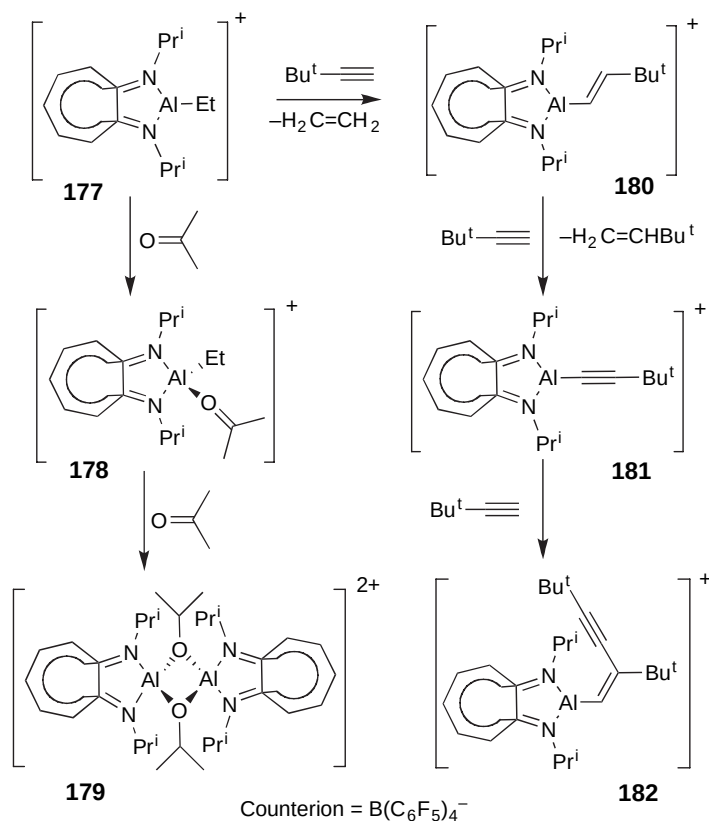
In all cases, the neutral compounds are considerably more soluble in coordinating solvents than in noncoordinating solvents in agreement with the available solid-state structures, which reveal the polymeric nature of these compounds. Interestingly, solution ¹¹⁹Sn NMR data suggest that both neutral and anionic complexes (E = O) are pentacoordinated, indicating that the possible intermolecular interactions are still appreciable in solution.

It has been demonstrated that the bromine ligand can be easily substituted in the series of [Salen(Bu^t)AlBr] compounds with different salen ligands by triphenylphosphine oxide or triphenylphosphate with the formation of monomeric six-coordinate complexes of general formula [SalenAlL₂]⁺ (L = OPPh₃ or OP(OPh₃)₃) (Salen = *N,N'*-ethylenebis(3,5-di-*tert*-butylsalicylideneimine)) <2006JA1147>. On the other hand, the treatment of similar [Salen(Bu^t)AlMe] complex with phenylphosphinic acid leads to the formation of polymeric chains with hexacoordinated aluminium centers of formula [SalenAl(PhHPO₂)_n] <2000CC1799, 2002IC558>. The reaction of monomeric [Salomphen(Bu^t)AlCl] with GaCl₃ in dichloromethane leads to the formation of a dimeric [Salomphen(Bu^t)₃Al]₂²⁺ 2[GaCl₄]⁻ complex, which has been characterized by spectroscopic and crystallographic methods (Salomphen = *N,N'*-(3,4-dimethylbenzylidene)bis(3,5-di-*tert*-butyl-salicylideneimine)) <1999JA6747>.

Addition of tetrahydrofuran (THF) to a solution of dimeric 1,2-bis(chloromethylalumino)tetrafluorobenzene **176** induces a ring contraction process that results in the formation of a mixture of three dialacycles (9-methyl-10-chloro-9,10-dihydro-9,10-diala-octafluoroanthracene, 9,10-dimethyl-9,10-dihydro-9,10-diala-octafluoroanthracene, and 9,10-dichloro-9,10-dihydro-9,10-diala-octafluoroanthracene) as confirmed by ¹H and ¹⁹F NMR spectroscopy (**Equation 5**) <2000JOM132>.

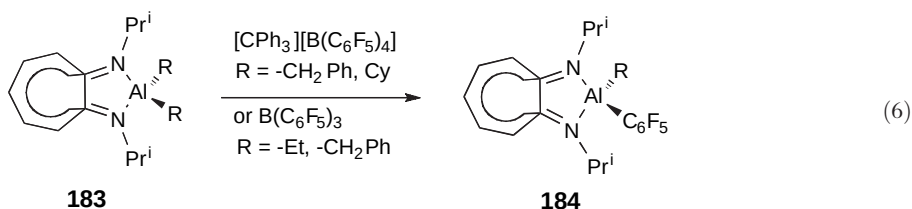


The ethyl group in complex **177** can easily be substituted by an acetone ligand, via the tetrahedral intermediate **178**, leading to the formation of the dimeric compound **179**. The initial compound **177** can also react with *tert*-butylacetylene. The reaction with 1 equiv of *tert*-butylacetylene involves β -H transfer and results in the formation of product **180**. The treatment of this vinylic compound with an excess of *tert*-butylacetylene leads to the formation of products **181** and **182** (Scheme 6) <1999JA11605>.



Scheme 6

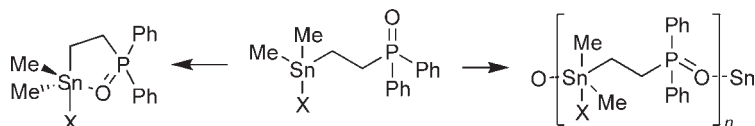
In the case of neutral analogues of cation **177**, the substituents coordinated to the aluminium center also show high reactivity <2001JA8291>. Thus $(\text{Pr}^i)_2\text{ATI})\text{AlCl}_2$ can be cleanly alkylated by Grignard reagents with the formation of $(\text{Pr}^i)_2\text{ATI})\text{AlR}_2$ ($\text{Pr}^i_2\text{ATI} = N,N'$ -diisopropylaminotroponimate; $\text{R} = \text{Cy}, \text{CH}_2\text{Ph}$). Interesting realkylation products were observed when compound **183** reacted with $(\text{CPh}_3)(\text{B}(\text{C}_6\text{F}_5)_4)$ or $\text{B}(\text{C}_6\text{F}_5)_3$ in pentane at 25°C . In both cases, substituent R in the $\text{Al}-\text{R}$ bond was substituted by a C_6F_5 group eliminated from $[\text{B}(\text{C}_6\text{F}_5)_4]^-$ or $\text{B}(\text{C}_6\text{F}_5)_3$ (Equation 6).



6.17.9 Ring Synthesis from Acyclic Compounds Classified by the Number of Ring Atoms Contributed by Each Component

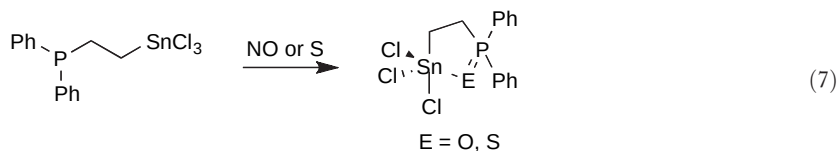
6.17.9.1 Formation of One Bond between Two Heteroatoms

Unsolvated $\text{XMe}_2\text{SnCH}_2\text{CH}_2\text{P}(\text{O})\text{Ph}_2$ ($\text{X} = \text{Cl}, \text{Br}, \text{I}$) can form both the chelate and linear chain forms dependent on the nature of recrystallization solvent <2001JCD2593>. Thus crystallization from protic solvents (EtOH and MeOH) results in the formation of polymer chains, while use of nonhydroxylic solvents such as hydrocarbons and acetone leads to the stabilization of the chelated form (Scheme 7).



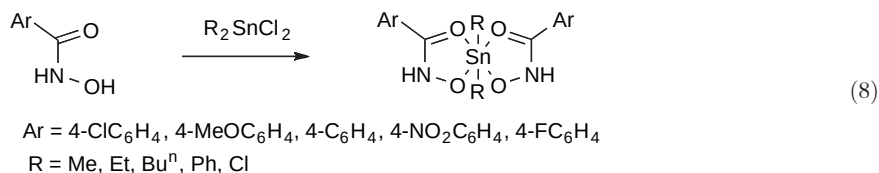
Scheme 7

The reaction of $\text{Ph}_2\text{P}(\text{CH}_2)_2\text{SnCl}_3$ with nitrogen monoxide in acetone or sulfur in dichloromethane results in the formation of pentacoordinated chelates, which can form dimeric hexacoordinated structures in the solid state (Equation 7) <2002JOM25>.

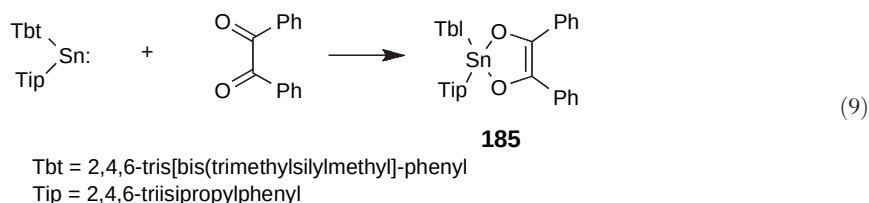


6.17.9.2 Formation of Two Bonds: Four-Atom Fragment and a Group III or IV Element

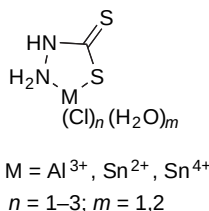
Hydroxymato(2-) type ligands can be conveniently used for the preparation of the *fac*-tris[benzohydroxymato(2)]-germinate complex in 73% yield by the reaction between benzohydroxamic acid and tetramethoxygermane <2002IC3901>. A series of diorganotin(IV) and dichlorotin(IV) derivatives of 4-X-benzohydroxamic acids (HL ; $\text{X} = \text{Cl}, \text{OMe}, \text{NH}_2, \text{NO}_2, \text{or F}$) of general formula R_2SnL_2 were prepared by the reaction between the appropriate R_2SnCl_2 ($\text{R} = \text{Me}, \text{Et}, \text{Bu}^n, \text{Ph}, \text{or Cl}$) with HL in the presence of potassium hydroxide in methanol at room temperature (Equation 8) <2004CEJ1456, 2004JOM4584>. Most of these complexes are stable in air, soluble in polar organic solvents, insoluble in water, and gradually decompose in polar solvents.



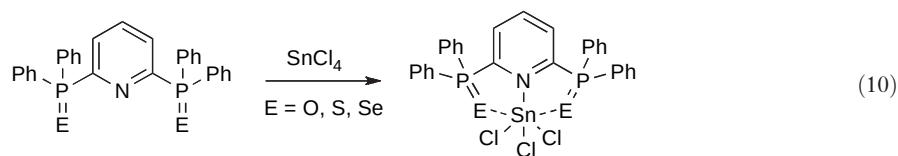
The [4+1] cycloaddition between benzil and a kinetically stabilized diarylstannylene leads to formation of the unsaturated heterocycle **185** in 22% yield (Equation 9) <1996OM4531>.



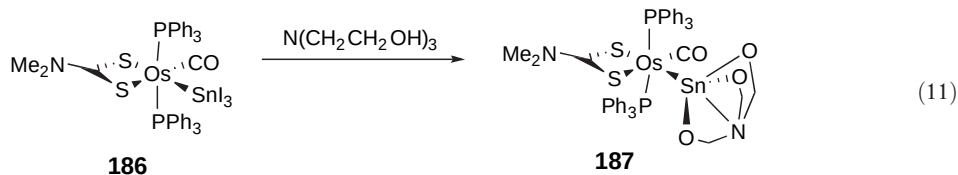
Complexation of the well-known dithiocarbazate chelate ligand (DTCA[−]) with Al³⁺, Sn²⁺, and Sn⁴⁺ ions leads to the formation of hexacoordinated complexes with 1:1 (Mⁿ⁺:DTCA) ratio, which were investigated for antimicrobial activity <2001SRI115>. These compounds, however, were found to be thermally unstable.



The reaction between 2,6-pyridine tetraphenylimidodiphosphonates with SnCl₄ leads to the formation of the complexes shown in Equation (10), which have been characterized by X-ray crystallography, IR, and ³¹P NMR spectroscopy <2003POL1585>. All the complexes are unstable in solution when exposed to moisture or oxygen or higher than room temperatures and decompose back to the starting ligands. As expected, stability of these complexes decreases with increasing ‘softness’ of the donor chalcogen atoms in the ligands.



A rare case of the formation of the first metal-bound stannatrane complex **187** has been reported as the result of the reaction between triethanolamine and organometallic compound **186** (Equation 11) <1999CC837>. As confirmed by a X-ray single crystal diffraction study, the Sn–N distance is significantly shorter compared to the sum of the tin(IV) and nitrogen van der Waals radii.



Numerous examples of complexation of group III and IV metals with simple chelate ligands were reported between 1995 and 2006. Those include, but are not limited to, the formation of Sn(etma)₂Cl₂ (etma = ethylmaltol), Sn(mepp)Cl₃(H₂O) (mepp = 1-methyl-2-ethyl-3-hydroxy-4-pyridinone) <2000POL399>, 24 tin(IV) 2,2-di-*n*-butyl- and 2,2-diphenyl-6-aza-1,3-dioxo-2-stannabenzocyclononen-4-ones derived from amino acids <2003CEJ2291>, mono- and polynuclear lead complexes with cysteamine ([Pb₂Cl(SCH₂CH₂NH₂)₃], [Pb₂(SCH₂CH₂NH₂)₃](NO₃)_{0.67}Cl_{0.33}), Pb(SCH₂CH₂NH₂)₂ · 2PbCl(SCH₂CH₂NH₂)₂, and Pb(SCH₂CH₂NH₂)₂) <2005POL865, 2004IC5529>, Pb(SCH₂CH₂OH)₂ <2005CM2448>, indium(III) and gallium(III) complexes of N₂S₂ bis(amino thiol)-type ligands <1996IC6656>. This group also includes several catechol-based chelate complexes, that is, [(3,5-*tert*-butylcatechol)₂Ge] <2000JOM69>, dinuclear and trinuclear catechol complexes of indium and gallium <2005JOM722>, tris(oxalate)gallium complexes <2005SM373>. Another set of ligands is based on 8-hydroxyquinoline-containing moieties, which can coordinate to aluminium(III) <2002JOM229> or gallium(III) ions <1999CEJ48>.

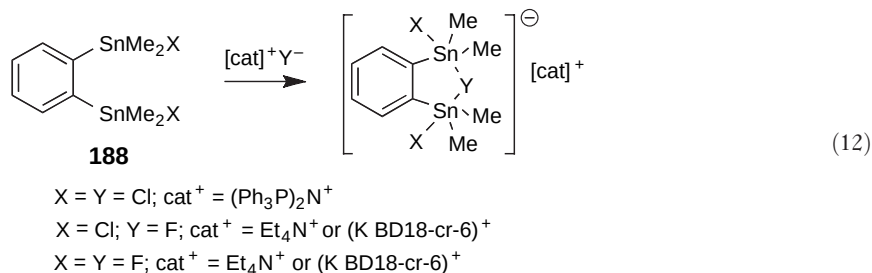
Another general group of complexes includes chelates with common aromatic and aliphatic dinitrogen bases such as bipy(2,2'-bipyridine), phen(1,10-phenanthroline), and analogues. The examples include [(phen)PbX₂] (X = Cl, Br, I), [(bipy)PbI₂] <1996AJC1089>, [(phen)Pb(OAc)(NCS)]₂ <2002POL1223>, [(BTZ)₂Pb(NO₃)₂]₂, [(BTZ)-Pb(SCN)₂]_n (BTZ = 4,4'-bithiazole, in both cases lead ion coordinated to nitrogen rather than sulfur atoms of chelate ligand) <2002POL197>, [(pydim)Pb(NCS)][BF₄] (pydim = 2,6-bis[(2,6-dimethylphenylimino)methyl]pyridine) <2002POL1795>, TMEDA complexes of gallium, indium, and aluminium of formula [(TMEDA)GaMe₂]-[Me₂GaCl₂], [(TMEDA)InMe₂Cl] <2003ZFA2509>, [(TMEDA)AlCl-M(CO)_n], [(TMEDA)Al(Et)-M(CO)_n], [(TMEDA)GaCl-M(CO)_n], [(TMEDA)Ga(R)-M(CO)_n] (M = Cr, Mo, W, and Fe) <1998JA1237>, dinuclear 2-pyridinecarboxaldehyde phenyl hydrazone aluminium and gallium complexes [(Me₂M){NC₅H₄C(R)NNPh}-(MMe₃)] (R = H, Me) <2000OM4036>, dinuclear gallium complexes of tris(2-pyridylmethyl)amine <2001ICA113>, aluminium and gallium complexes of *o,o'*-Prⁱ₂C₆H₃-bis(imino)acenaphthene ligand <2002CJC1398>, and aluminium μ -oxo-trimethylethylenediamide complex <2005AOM204>.

The reaction of 2-acetylpyridine phenylhydrazone or 2-pyridinecarboxaldehyde phenylhydrazone with trimethylaluminium or trimethylgallium in toluene at room temperature affords the air-sensitive dinuclear metal complexes of general formula [(Me₂M){NC₅H₄C(R)NNC₆H₅}(MMe₃)] (M = Al, Ga; R = H, Me) <2000OM4036>. The decagallium complex (GaMe₂)₈(GaMe₂)₂(μ_4 -O)₂(μ_3 -O)₄(C₁₂H₁₀N₃)₂ was also isolated in this reaction as a minor product.

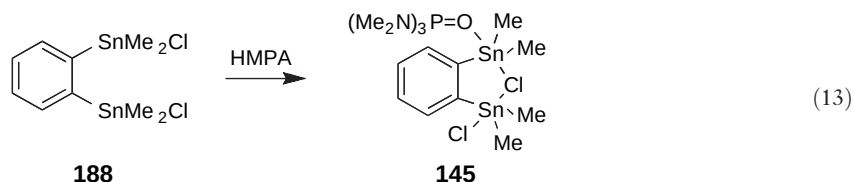
The diphosphine-type ligands provide an opportunity for the complexation with group III and IV metals. For instance, the reaction of gallium or indium trihalides with 1,2-bis-(diphenylphosphanyl)benzene (DP) leads to the formation of [(DP)₂MCl₂]⁺[MX₄]⁻ complexes.

6.17.9.3 Formation of Two Bonds: Four-Atom Fragment and a Nitrogen, Phosphorus, or Group VIII Element

The treatment of *o*-bis(dimethylchlorostannyl)benzene **188** with fluoride or chloride ions gave in high yield a variety of μ -halo bis(stannyl)-containing complexes shown in Equation (12) <1998OM5858>. The reaction is selective toward fluoride ions. Indeed, reaction of the starting complex **188** with fluoride ions leads only to the formation of the μ -fluoro product, while the μ -chloro product has not been detected.



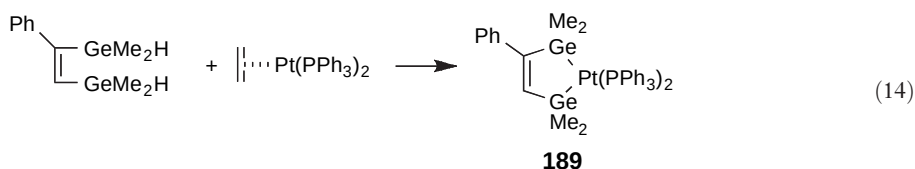
The treatment of *o*-bis(dimethylchlorostannyl)benzene **188** with HMPA afforded the neutral complex **145**, which arises from the intramolecular cyclization reaction between the chlorine atom at terminal position and the neighboring tin(IV) center (Equation 13) <1998OM5858>.



Interestingly, when 1,2-bis(trimethylstannyl)tetrafluorobenzene, a close analogue of compound **188**, was introduced into the reaction with Me₂AlCl, the dimeric 1,2-bis-(chloromethylalumino)tetrafluorobenzene was obtained and characterized by spectroscopy and X-ray crystallography <1999CC1367>. The reaction requires exchange between the SnMe₃ and MeAlCl groups.

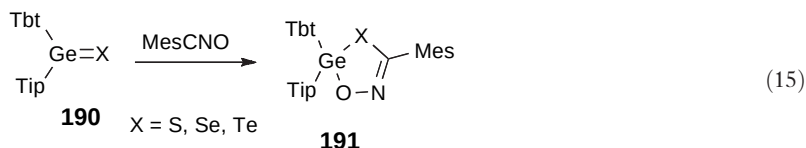
1,4-Digermabut-2-ene-1,4-diylplatinum **189** was obtained by the reaction between (η -ethylene)bis(triphenylphosphine)platinum with excess (*Z*)- α,β -bis(dimethylgermyl)styrene at room temperature for 10 min (Equation 14)

<2005JOM5700>. The structure of product **189** was confirmed by NMR, IR, and mass spectra. The target platinum complex is air and moisture sensitive.



6.17.9.4 Formation of Two Bonds: [3+2] Atom Fragments by Cycloaddition

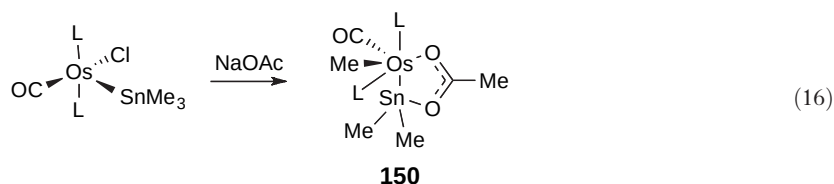
An interesting example of [3+2] cycloaddition between germanestellone **190** (X = Te) and mesitonitrile oxide results in formation of product **191**, which has a Te-Ge-O-N motif, in 94% yield (Equation 15) <1997JA2337>. This method was later extended to the preparation of sulfur- and selenium-containing oxachalcogenazagermole from germanethiones and germaneselonones, respectively, which were prepared in quantitative yields <1999JA8811>.



Similarly, [3+2] cycloaddition of the Tbt(Tip)Sn=Se or Tbt(Tip)Sn=S and mesitonitrile oxide results in formation of the tin(IV) heterocycles (X=Se or S; M=Sn) in only 12% and 39% yield <1995JOM43, 1996OM4531>. In addition, a similar [3+2] cycloaddition between Tbt(Mes)Ge=O (Mes = 2,4,6-trimethylbenzene) and mesitonitrile oxide gives the oxygen analogue of compound **191** (X = O) in only 34% yield <2002POL563>.

6.17.9.5 Formation of Two Bonds: [3+2] Atom Fragments by Other Processes

Treatment of the coordinatively unsaturated osmium trimethylstannyl complex Os(SnMe₃)Cl(CO)(PPh₃)₂ with sodium acetate results in methyl group migration from tin to osmium with formation of the Os-Sn-O-C-O heterocycle **150**, which has been characterized by NMR, IR, and X-ray crystallography (Equation 16) <1999CC1101>.

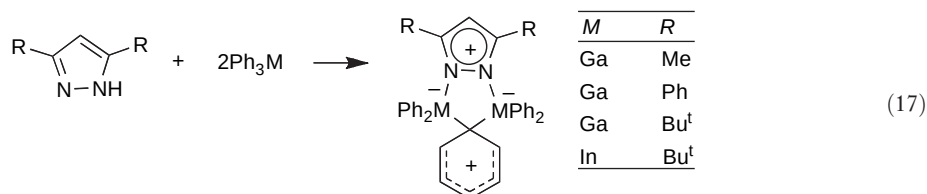


6.17.9.6 Formation of Three Bonds

The straightforward formation of five-membered heterocycles with three or four heteroatoms and at least one group III or IV metal is unknown.

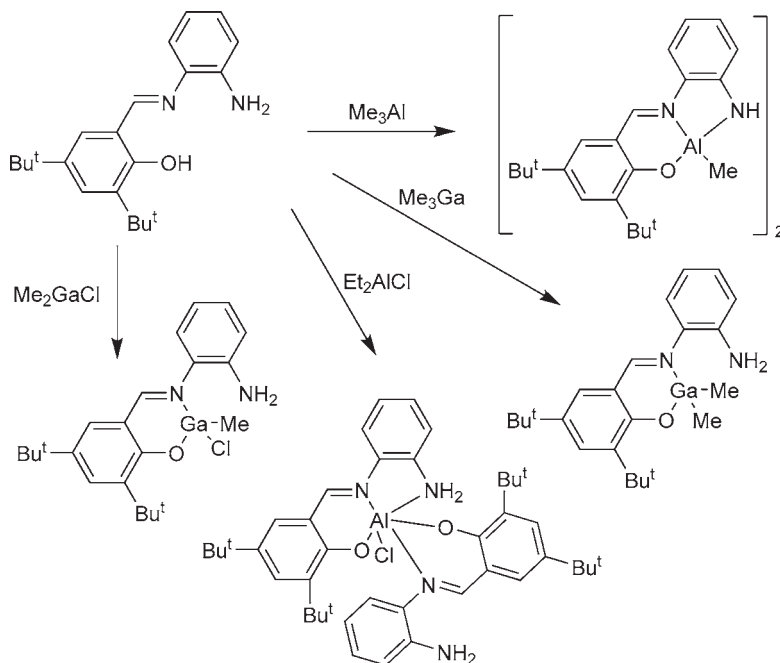
6.17.9.7 Formation of Four Bonds

Treatment of triphenylgallium or triphenylindium with 3,5-disubstituted pyrazoles in a 2:1 stoichiometry results in formation of unusual phenyl-bridged complexes in which a phenyl group acts as a bridge between the two metal atoms (Equation 17). The bridging phenyl group is exchangeable in solution and the kinetics of bridge-terminal phenyl group exchange has been determined by variable-temperature NMR spectroscopy <2005OM6184>.



The analogous reaction between diisobutylaluminium hydride and 3,5-disubstituted pyrazoles in 2:1 stoichiometry results in formation of bridging hydride complexes of general formula $[(\mu, \eta^1 \eta^1 - R_2 \text{pz})(\text{AlBu}^i_2)_2(\mu\text{-H})]$ [\(<2001OM4301>\)](#). Unlike the gallium and indium complexes described above, the aluminium hydride bridging complexes appear to have a static structure as confirmed by variable-temperature NMR spectra in the range -80 and 20°C in toluene- d_8 .

The well-known salen-type ligands are very useful chelates for coordination with group III and IV metals. The classical tetradentate salen-type ligands with N_2O_2 coordination sphere provide a conformationally rigid platform for the preparation of group III and IV complexes. It is interesting, however, that the reactivity of recently discussed 'half' salen-like ligands with N_2O donor atoms toward the complexation with the metal center heavily depends not only on the type of the metal ion but also on the composition of the initial metal precursor. For instance, when MMe_3 ($\text{M} = \text{Al}, \text{Ga}$) is mixed with phensal(Bu^t) H_3 two (in the case of aluminium) or one (in the case of gallium) moles of methane are eliminated and red-colored 1:1 complexes are formed. The aluminium complex, however, is dimeric in nature with all phensal donor atoms coordinated to the central metal, while in the case of the gallium compound, the first coordination sphere is O, N, 2C. On the other hand, if Et_2MCl was used as a metal precursors, the formation of a 1:1 complex was observed only for the gallium complex, while the 1:2 complex formed in the case of aluminium ([Scheme 8](#)) [\(<2000OM4416>\)](#).



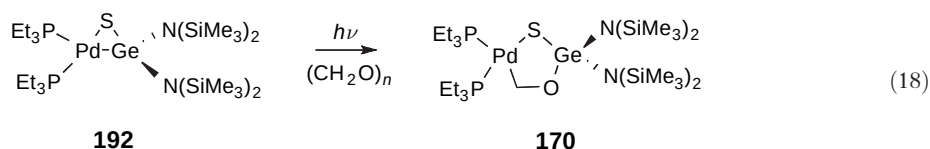
Scheme 8

6.17.10 Ring Synthesis by Transformation of Another Ring

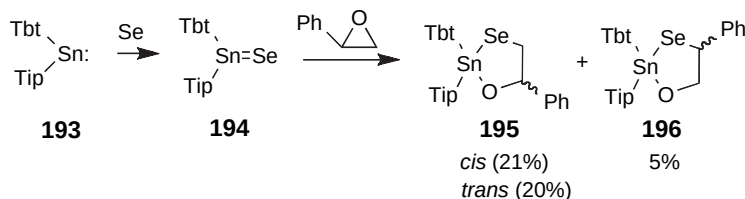
6.17.10.1 Ring Synthesis from Three-Membered Heterocycles

Photolysis of a mixture of three-membered heterocycle [192](#) and paraformaldehyde leads to the formation of product [170](#) as a result of insertion of formaldehyde into the Pd–Ge bond ([Equation 18](#)). The addition of CO (1 atm) to a

solution of compound **170** results in the formation of a new cyclic system and the reduction of the Pd center <2004OM2370>.

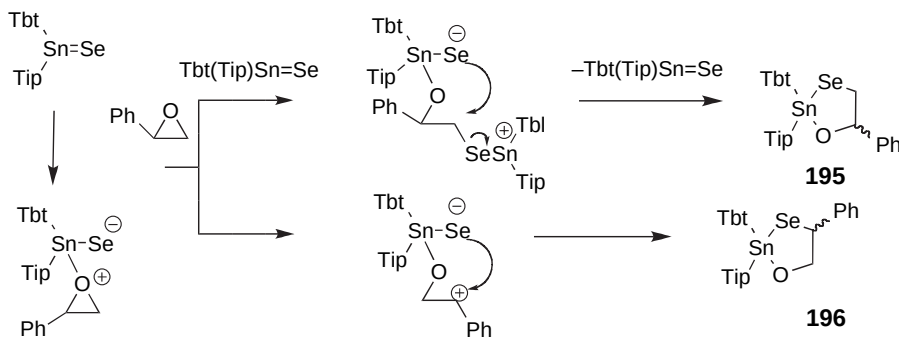


The reaction between styrene oxide and stannaneselone **194** (generated from sterically crowded stannylene **193**) leads to the formation of products **195** and **196** in 46% total yield. Compound **195** exists as a mixture of *cis*- and *trans*-isomers, which can be separated using chromatography (Scheme 9) <1995JOM43>.



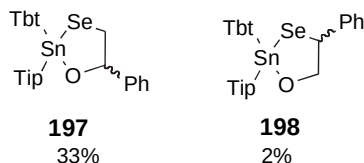
Scheme 9

The proposed mechanism for this reaction involves the initial coordination of styrene oxide to Tbt(Tip)Sn=Se followed by nucleophilic attack of a second Tbt(Tip)Sn=Se molecule on the less substituted carbon with the formation of *cis*- and *trans*-**195**. Alternatively, the unimolecular cyclization of the initial styrene oxide–Tbt(Tip)Sn=Se complex leads to the formation of compound **196** as a minor product (Scheme 10).



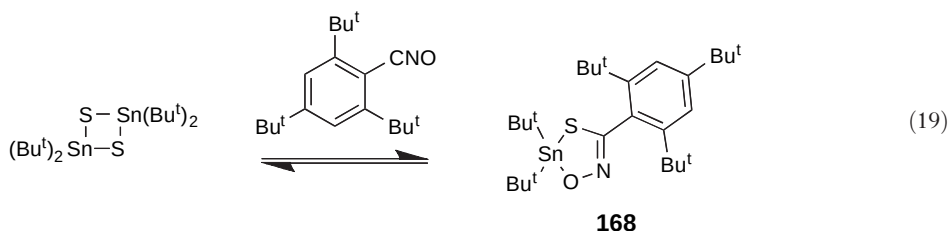
Scheme 10

Interestingly, the minor product **196** in this reaction became a major product if the Tbt(Tip)Sn=Se precursor was generated using triphenylphosphine and tetraselenostannolane as starting reactants <1993OM2573>. In analogy with this mechanism, the Tbt(Tip)Sn=S precursor leads to the formation of respective sulfur analogues **197** and **198** with complex **197** being again (as a mixture of *cis*- and *trans*-isomers) the major product <1996OM4531>.

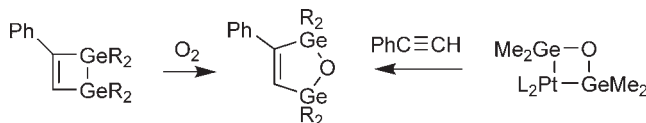


6.17.10.2 Ring Synthesis from Four-Membered Heterocycles

The reaction of 2,2,4,4-tetra-*t*-butyl-1,3,2,4-dithiadistannetane with 2,4,6-tri-*t*-butylbenzonitrile oxide slowly forms 2,2-di-*t*-butyl-1,3,5,2-oxathiazastannole **168**, which has been characterized by NMR spectroscopy and X-ray crystallography (Equation 19) <2001TL7063>.



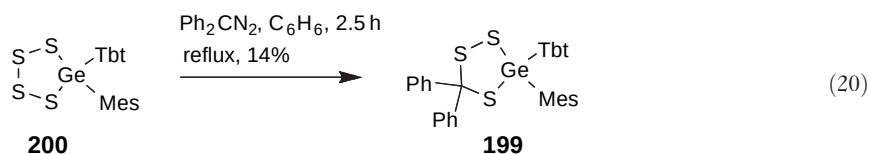
A ring expansion reaction has been used for the preparation of 1,3-digerma-2-oxacyclopent-4-enes and related palladium and platinum compounds <1995OM5700, 2005JOM2967>. In the first variation, the oxygenation of the Ge–Ge bond with dioxygen at room temperature results in formation of the target five-membered metallocycle. The product of insertion of the Pd(PPh₃)₂ fragment into Ge–Ge bond was also suggested as the reactive intermediate in the reaction between four-membered digermene and Pd(PPh₃)₄ <2005JOM2967>. In the second variation, the target compound was prepared by the reaction between platinum digermanate and phenylacetylene at 100 °C (Scheme 11) <1995OM5700>.



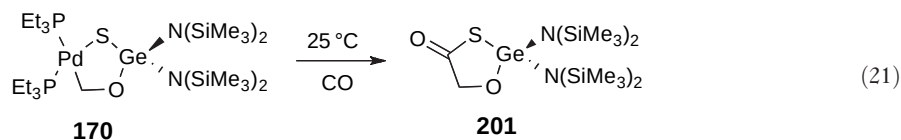
Scheme 11

6.17.10.3 Ring Synthesis from Five-Membered Heterocycles

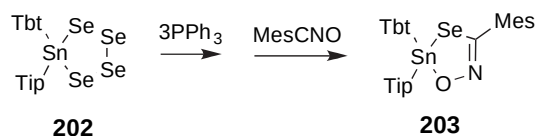
The preparation of the various 1,2,4-trithia-3-germacyclopentanes by transformation of another ring can be illustrated by the synthesis of 3-{2,4,6-tris[bis(trimethylsilyl)methyl]-phenyl}-3-mesityl-1,2,4-trithia-3-germacyclopentane **199** <1995OM1008>. This compound can be prepared in low yield by the reaction between tetrathiagermolane **200** and diphenyldiazomethane (Equation 20).



The addition of carbon monoxide (1 atm) to a solution of compound **170** results in the formation of the new cyclic system **201** as a result of insertion of carbon monoxide into the Pd–S bond (Equation 21) <2004OM2370>.



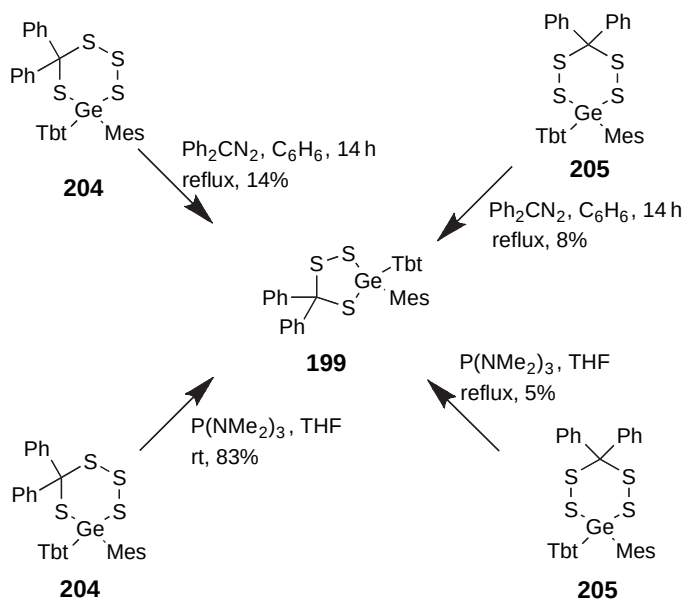
The deselenation reaction of heterocycle **202** with triphenylphosphine followed by addition of mesitronitrile oxide results in the formation of product **203** in 83% yield (Scheme 12) <1995JOM43>. This compound is thermally very stable and does not decompose even at 200 °C in toluene. This reaction has been extended to the use of Tbt(Ditp)Sn=E, Tbt(Dmtp)Sn=S, and Tbt(Tcp)Sn=E precursors (E = S, Se) in the reaction with mesytonitrile oxide (Ditp = 2,2''-diisopropyl-*m*-terphenyl-2'-yl; Dmtp = 2,2''-dimethyl-*m*-terphenyl-2'-yl; Tcp = 2,4,6-tricyclohexylphenyl) <2004JA15572>.



Scheme 12

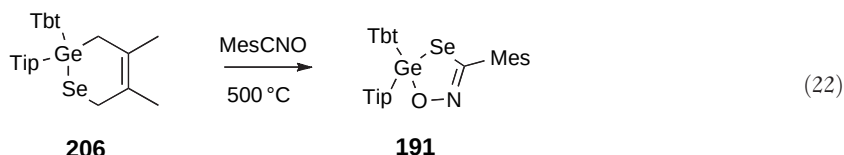
6.17.10.4 Ring Synthesis from Six-Membered Heterocycles

The preparation of the various 1,2,4-trithia-3-germacyclopentanes by transformation of a six-membered ring can be illustrated on the basis of synthesis of 3-{[2,4,6-tris[bis(trimethylsilyl)methyl]-phenyl]-3-mesityl-1,2,4-trithia-3-germacyclopentane **199** (Scheme 13) <1995OM1008>. This compound can be prepared in low yield by the reaction between 1,2,3,5-tetrathia-4-germacyclohexane **204**, or 1,2,4,5-tetrathia-3-germacyclohexane **205**, with diphenyldiazomethane in refluxing benzene for several hours. The yield of this ring transformation reaction was dramatically improved when desulfurization of compound **204** was conducted in the presence of hexamethylphosphorus triamide in THF at room temperature. Interestingly, no yield improvement for the preparation of compound **199** was observed if compound **205** was reacted with hexamethylphosphorus triamide under the same reaction conditions.



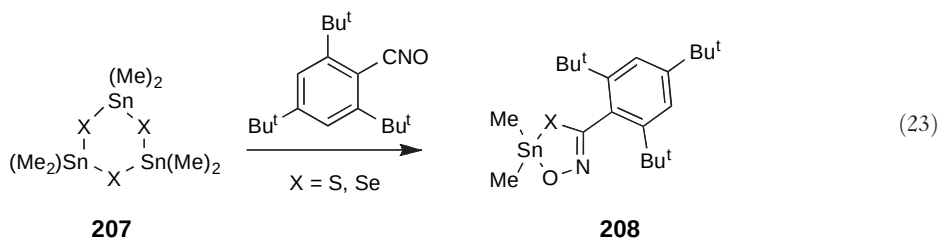
Scheme 13

As an alternative to [3+2] cycloaddition, product **191** (X=Se) can be prepared in 90% yield using a [4+2] cycloreversion reaction of the six-membered heterocycle **206** in the presence of mesitronitrile oxide (Equation 22) <1999JA8811>.



As has been shown by Saito *et al.* <2001TL7063>, steric constraints at the metal center can be significantly reduced. Indeed, the monitoring of the reaction of 1,3,5,2,4,6-trithiatristannine **207** (X=S) and 2,4,6-tri-*t*-butylbenzonitrile oxide

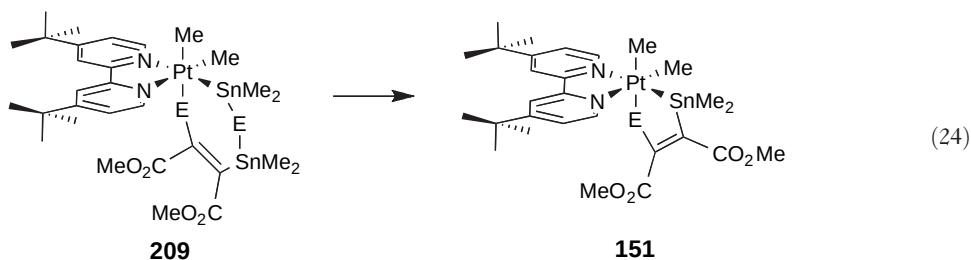
using NMR spectroscopy in benzene-*d*₆ at room temperature suggests that quantitative transformation of these reagents into the target 2,2-dimethyl-1,3,5,2-oxathiazastannole **208** (X = S) occurs (Equation 23).



The analogous reaction of the 2,2,4,4,6,6-hexamethyl-1,3,5,2,4,6-triselenatristannin **207** (X = Se) and 2,4,6-tri-*t*-butylbenzonitrile oxide (3 equiv) leads to the formation of equilibrium mixture consisting of 1,3,5,2-oxaselenazastannole, along with starting nitrile oxide and tristannine in 3:3:1 ratio, in sharp contrast to the complete reaction with the sulfur analogue.

6.17.10.5 Ring Synthesis from Seven-Membered Heterocycles

The room temperature slow elimination of an [Me₂SnE]₃ fragment (identified by ¹H NMR) from the methylene chloride solutions of seven-membered heterocycles **209** results in the formation of five-membered metallocycles **151** <1999JCD1713, 2002OM1257>. The complexes are yellow and air stable if E = S or Se, while it is brown and air sensitive for E = Te (Equation 24).



6.17.11 Synthesis of Particular Classes of Compounds

The major synthetic routes for the preparation of five-membered group III and IV metal-containing heterocycles with three or four heteroatoms are illustrated in the text and in Table 1.

6.17.12 Applications and Important Compounds

6.17.12.1 Biologically Active Compounds

The antimicrobial properties of [Sn(DTCA)Cl H₂O], [Sn(DTCA)Cl₃ H₂O], and [Al(DTCA)Cl₂ 2H₂O] complexes (see Section 6.17.9.2) were evaluated against *Pseudomonas aeruginosa* and *Bacillus cereus* cultures <2001SRI115>. It has been found that the aluminium complex has a strong antimicrobial activity with the minimum inhibitory concentrations (MICs) of 300 and 700 µg ml⁻¹ against *P. aeruginosa* and *B. cereus* cultures, respectively.

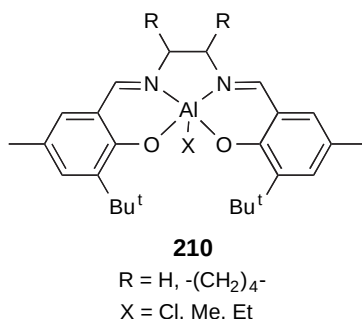
The R₂SnL₂ complexes (HL = 4-X-benzoyldioxamic acid; R = Me, Et, Buⁿ, Ph, or Cl) (see Equation (8), Section 6.17.9.2) exhibit *in vitro* antitumor activities against a series of human tumor cell lines, which in some cases are identical to, or even higher than, the activity of cisplatin <2004CEJ1456, 2004JOM4584>. For Alk₂SnL₂ complexes, the activity increases with the length of the alkyl chain. The most active compounds *n*-Bu₂SnL₂, which bear an electron-withdrawing substituent (Cl, NO₂, or F) in the hydroxamic ligand, display high *in vivo* activity against H22 liver and BGC-823 gastric tumors and have relatively low toxicity.

6.17.12.2 Applications in Research and Industry

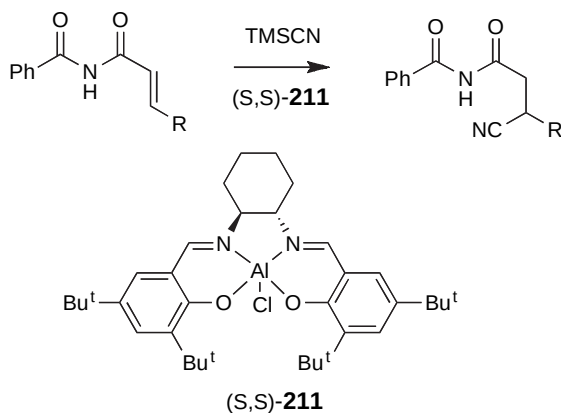
The macrobicyclic ligand derived from 4,13-diaza-18-crown-6 and Schiff-base spacer (e.g., 1,2-phenylenediamine or 1,2-ethylenediamine) forms stable lead(II) complexes of general formula $[\text{LPb}(\text{X})_2 \cdot (\text{solv})_n]$ in the presence of different counterions <2005IC5428>. The double protonation of the resulting compounds causes the demetalation of the complex without receptor destruction. Since this demetalation process is reversible and very fast, receptor L has been suggested as potential compound for lead(II) extraction.

Several pentacoordinate Schiff-base gallium complexes of formula $(R)\text{salemGaX}$ ($\text{X} = \text{Cl}, \text{N}_3$; $(R)\text{salem} = N,N'$ -bis-(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexyldiimine or N,N' -bis-(3,5-di-*tert*-butylsalicylidene)-1,2-ethylenediimine) were tested as potential catalysts for the copolymerization of carbon dioxide and epoxides <2004MI755>. In the presence of a Lewis-base cocatalyst, *N*-methylimidazole (Meim) or phosphine, formation of polymer is not observed. In the absence of Meim, a low molecular weight homopolymer is observed when the chloride species is the catalyst. Substitution of the ethylenediimine bridging group to the 1,2-phenylenediimine results in another series of aluminium complexes which are potentially useful in the production of polycarbonates from CO_2 and cyclohexene oxide <2005IC1433>. By studying the reactivity of these complexes it has been found that the introduction of the electron-withdrawing substituents in the Salen backbone increases the catalytical activity of aluminium complexes. For instance, the complex derived from $\text{salen}(\text{Bu}^t)_4 = N,N'$ -bis-(3,5-di-*tert*-butylsalicylidene)-1,2-ethylenediimine is essentially inactive when compared to the analogous derivative containing nitro substituents in the 3-positions of the phenolate groups. While $(\text{Salen})\text{AlX}$ complexes are capable of producing poly(cyclohexene oxide) carbonate with low amounts of polyether linkage along with the small quantities of cyclic carbonate byproducts, their reactivities are greatly reduced when compared to their $(\text{Salen})\text{CrX}$ analogues under identical reaction conditions <2005IC1433>.

Another series of aluminium complexes with sterically hindered Schiff bases of general formula $[\text{AILX}]$ (L = sterically hindered Schiff base; $\text{X} = \text{Cl}, \text{Me}, \text{Et}$) **210** proved to be active in catalytic polymerization of ϵ -caprolactone <1997JOM189>.

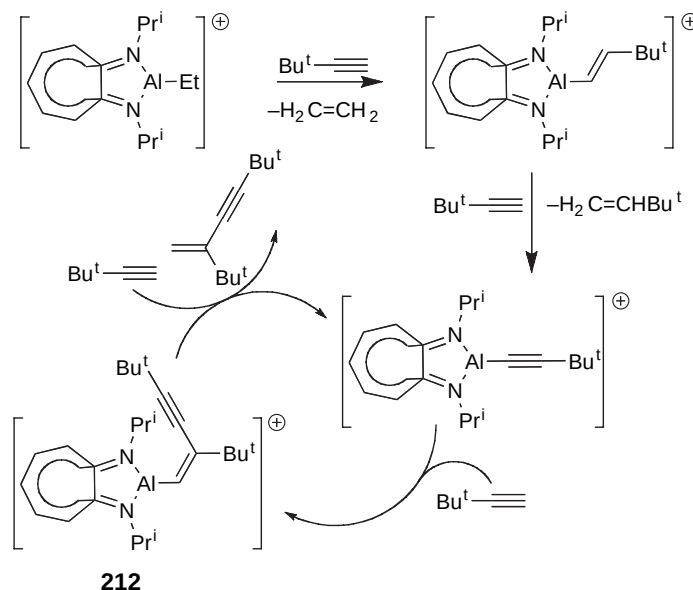


Salen-based aluminium complexes were tested as catalysts for the dealkylation reaction of a series of organophosphates with and without a cocatalyst <2006JA1147>, while chiral 1,2-cyclohexanediamine-containing $[\text{Salen}(\text{Bu}^t)_4\text{AlCl}]$ complex **211** was found to be a highly efficient enantioselective catalyst for catalytic conjugate addition of cyanide to α,β -unsaturated imides <2003JA4442>. The isolated yields of the target cyanides vary between 70% and 96%, while ee values were found to be between 87% and 98% as determined by chiral high-performance liquid chromatography (HPLC) (Equation 25).



(25)

Cationic organoaluminium aminotroponimate compounds catalytically dimerize *tert*-butyl acetylene to the head-to-tail dimer 2-*tert*-butyl-5,5-dimethyl-1-hexen-3-yne with >90% selectivity, while only small amounts of trimer and tetramer products were detected by gas chromatography–mass spectrometry (GC-MS) <1999JA11605>. The proposed reaction mechanism has been supported by NMR, GC-MS, and in one case X-ray crystallography. The first vinylic intermediate is stable in CDCl₃ solution at 23 °C in the absence of *tert*-butyl acetylene and its *trans*-stereochemistry has been established by a vinyl ³J_{HH} value of 21 Hz. The structure of the first alkynyl intermediate has been established by NMR in solution and by X-ray crystallography in the solid state <1999JA11605, 2001JA8291>. Interestingly, this compound is dimeric in the solid state, while the question about solution dimerization remains open. This alkynyl intermediate reacts with an excess of *tert*-butyl acetylene with formation of final intermediate **212**, which has been characterized by solution NMR spectroscopy and GC–MS method (Scheme 14).



Scheme 14

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6.18

Pentazoles

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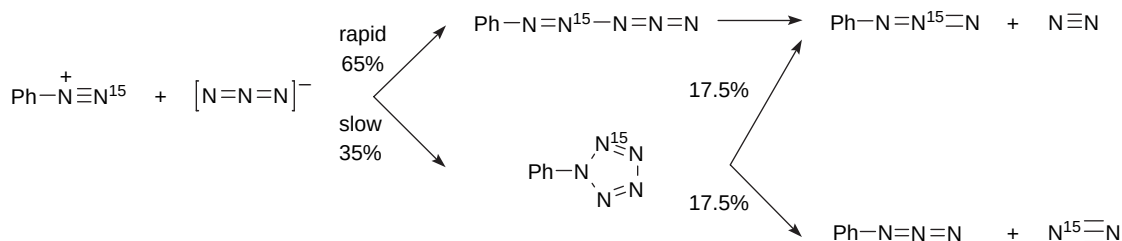
6.18.1 Introduction and History	739
6.18.2 Theoretical Methods	740
6.18.2.1 Pentazole HN_5 and the Pentazole Anion N_5^-	740
6.18.2.2 Polynitrogen Compounds Including the Pentazole Ring	741
6.18.2.2.1 Azidopentazole and octaazapentalene	742
6.18.2.2.2 Dipentazole	743
6.18.2.2.3 Azopentazole	743
6.18.2.2.4 Other polynitrogen compounds containing the pentazole ring system	743
6.18.2.3 Pentazole Attached to Substituted Phenyl Rings	744
6.18.2.4 Pentazole Attached to Azoles	745
6.18.2.5 Pentazoles with Nonaromatic Substituents	747
6.18.2.6 Complexation	747
6.18.2.7 Basicity	748
6.18.2.8 Aromaticity	748
6.18.3 Experimental Structural Methods	749
6.18.3.1 Molecular Dimensions	749
6.18.3.2 NMR Spectroscopy	749
6.18.3.3 Mass Spectrometry	750
6.18.3.4 IR and UV Spectra	750
6.18.4 Decomposition Temperatures and Decomposition Rates	750
6.18.5 Reactivity of Fully Conjugated Rings	752
6.18.6 Ring Syntheses from Acyclic Compounds	753
6.18.7 Important Compounds and Applications	754
References	754

6.18.1 Introduction and History

Pentazole is the all-nitrogen member of the azole series, which consists of the isoelectronic nitrogen analogues of the cyclopentadienylidene anion. The successful synthesis of N_5^+ <1999AGE2004> increased the interest in nitrogen-rich and polynitrogen compounds as potential energetic materials <1999MI304> and inspired an increased interest in the investigation of pentazoles, whose chemistry has been summarized in several reviews <1964AHC373, 1984CHEC(5)839, 1994HOU796, 1996CHEC-II(4)897, 1993AG242, 2004HOU917>. The chemistry of pentazoles was covered previously in CHEC(1984) by I. Ugi <1984CHEC(5)839> and in CHEC-II(1996) by R. N. Butler <1996CHEC-II(4)897> and these chapters contain reference to earlier comprehensive reviews. This chapter updates the previous work and reviews the literature from 1995 onward, concentrating on major new advances, preparations, reactions, uses, and concepts.

The early days of pentazole chemistry were characterized by many unsuccessful attempts to synthesize pentazole <1903CB2061, 1910CB2904, 1932G716>, mistakes <1915CB410>, misinterpretations <1954HCA798> and violent disputes <1915CB1614>, even though as early as 1893 <1893CB86> Noelting and Michel had unknowingly produced the first arylpentazoles from the reaction of aryl diazonium compounds with sodium azide.

Huisgen and Ugi recognized that the nitrogen evolution in the reaction of phenyldiazonium ion with aluminium and lithium azide at low temperatures takes place in two stages with different reaction rates. They were able to prove the existence of phenylpentazole by quantitative measurement of the dinitrogen gas evolved during the reaction of phenyldiazonium chloride with sodium azide <1956AG705, 1956AG753> in combination with ^{15}N labeling experiments (Scheme 1) <1957CB2914, 1956HCA1469, 1957MI16>.



Scheme 1

Later, they synthesized differently substituted phenylpentazoles and isolated several crystalline derivatives <1958CB2324, 1959CB1864>. The history of the discovery of the pentazole ring system has been summarized very concisely in the following articles <1964AHC373, 1984CHEC(5)839, 1994HOU796, 2005HCA1154>.

For a long time, pentazole chemistry only involved the study of the chemical and physical properties of the pentazole compounds discovered by Huisgen and Ugi. More than 40 years later, the first pentazole attached to a five-membered ring system, tetrazolypentazole, was reported by Hammerl and Klapötke <2002IC906>. Unfortunately, this compound decomposes below -50°C . Imidazolypentazole is reported to be stable up to -30°C . Recently, the first dipentazole, 1,4-bis(*p*-pentazolyl)butane, has been observed by nuclear magnetic resonance (NMR) spectroscopy <2004ZNB716>.

Another goal of pentazole research in recent years has been the isolation of pentazole or its anion. The first attempts to isolate the pentazole anion by ozonation of *p*-dimethylaminophenylpentazole or reduction of phenylpentazole with sodium in liquid ammonia had failed <1964AHC373>. Recently, the cleavage of the C–N bond in *p*-dimethylaminophenylpentazole and the NMR spectroscopic identification of a zinc pentazolate salt in the reaction solution was reported <2003CC1016>. It was later shown that the reported compound does not contain a pentazole <2005CC1607>, which shows that the controversial history of pentazole is not yet finished. By using different ionization techniques it was possible to cleave the C–N bond in *p*-dimethylaminophenylpentazole and detect the pentazole ring mass spectrometrically.

The availability of ever faster computers is responsible for the continuously improving quality in the calculations of the stability and the properties of pentazole compounds. Azidopentazole has been identified as the most stable of the known N_8 polynitrogen compounds and considerable work has gone into the question whether a pentazole salt of the N_5^+ ion would be stable.

6.18.2 Theoretical Methods

Due to its elusive nature as the last member of the azole series and the fact that pentazole is a homoaromatic system of nitrogen atoms, theoretical methods have been applied very early to investigate the properties of pentazole. Soon after the discovery, the first linear combination of atomic orbitals (LCAO) calculations were made for the synthesis of pentazole <1961CB273>. The fascination of the pentazole system inspired calculations at ever higher levels of theory <1969BSF1097, 1970BSF273, 1979NJC607, 1983CJC1435>.

6.18.2.1 Pentazole HN_5 and the Pentazole Anion N_5^-

Pentazole HN_5 has a C_{2v} structure with an N(1)–H bond length of 101.0 pm, and N–N bond lengths of 130.6, 130.4, and 136.0 pm at the CCSD level for the N(1)–N(2), N(2)–N(3), and N(3)–N(4) bonds <1992JA8302>. The dissociation of pentazole HN_5 to HN_3 and N_2 is exothermic with $-43.3 \text{ kcal mol}^{-1}$ and an activation barrier of $20.1 \text{ kcal mol}^{-1}$.

<1996JPC13447, 1979NJC607>. Further calculations at the CCSD(T) level resulted in an activation barrier of $14.9 \text{ kcal mol}^{-1}$ and a reaction energy of $-43.3 \text{ kcal mol}^{-1}$ <2003CEJ5511>.

The calculation of the deprotonation reaction of HN_5 suggests that HN_5 is a stronger acid than HNO_3 <2000IJQ27> with a gas-phase acidity ΔG^0 of $309.6 \text{ kcal mol}^{-1}$ <1998IJM51>. At the CCSD(T) level, the proton affinity is $332(2) \text{ kcal mol}^{-1}$ <2003CCR93>.

The pentazole anion ($\tilde{X}^1A'_1$) has a D_{5h} structure with five equal N–N bond distances of 133.09 pm and an NNN bonding angle of 108° at the CCSD(T) level of theory extrapolated to the basis set limit. The decomposition of the pentazolate anion to dinitrogen N_2 and the azide ion N_3^- is exothermic by $14.3 \text{ kcal mol}^{-1}$ and the activation energy for this decomposition is $27.2 \text{ kcal mol}^{-1}$ <2004JA834, 2003CCR93, 2002PCA4639, 1997JMT9>. The heat of formation is $\Delta H_f(298 \text{ K}, \text{N}_5^-) = 59.6 \text{ kcal mol}^{-1}$ at the CCSD(T) level of theory. Since the calculated imaginary frequency for the transition state is rather large with $862i \text{ cm}^{-1}$, the pentazole ion might be able to tunnel through the barrier to reach the products. A crude estimate using the Wigner expression leads to an enhancement of the dissociation rate by 1.7 at 298 K . Thus, tunneling has to be considered for the estimation of the stability of N_5^- , especially at lower temperatures, where a larger tunneling effect is expected.

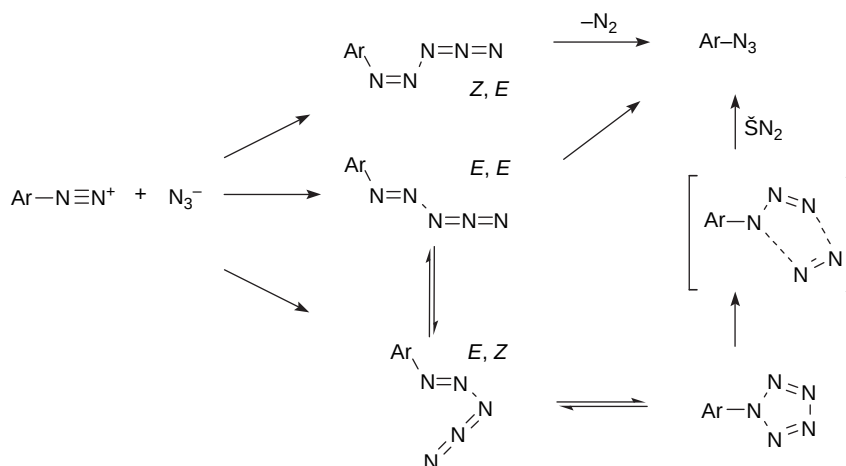
The vertical ionization energy of the N_5^- pentazole anion refers to the formation of neutral N_5 <2001CPL311> with the geometry of the pentazole anion and was calculated to be 5.6 eV <2002PCA4639>. On this basis, it was proposed that a salt of the type N_5^+N_5^- should be stable toward charge recombination, as the vertical electron affinity of N_5^+ is 3.0 eV . Minima for an N_5^+N_5^- salt were reported at the CCSD(T) level of theory <2001CPL311, 2002PCA4639, 2001CPL311>. In order to give an exact assessment of the stability of N_5^+N_5^- , the electron affinity has to be examined more thoroughly. The neutral pentazole radical $\text{N}_5^\cdot$ is not vibrationally stable <2000CPL483, 2001CPL311> and undergoes spontaneous decomposition. Since this decomposition does not involve a significant activation barrier, its adiabatic ionization energy has to be considered for the evaluation of the stability of an N_5^+N_5^- salt <2004JA834>. The adiabatic ionization energy takes into account the dissociation energy of neutral N_5 to form N_3 and N_2 . Based on the adiabatic ionization potential, an N_5^+N_5^- salt has a reaction enthalpy for the decomposition reaction of $-65 \pm 7 \text{ kcal mol}^{-1}$ at the CCSD(T) level. The calculated Born–Haber cycle leads the authors to the conclusion that a N_5^+N_5^- salt is not stable <2004JA834>.

The reaction of the N_5^+ ion with N_2H_2 was calculated to lead to a $\text{N}_5\text{-NHNH}$ pentazole species that is $5.5 \text{ kcal mol}^{-1}$ lower in energy than the starting materials at the MP2 level <2002CPL87>. The polarizability in the azole series is correlated to the molecular structures and the number of nitrogen atoms <1990JPC1755, 1995JPC12790>. The out-of-plane component of the quadrupole moments of the azoles increases with increasing aza substitution of the azoles from pyrrole to pentazole as the nitrogen atoms hold the π -electrons more tightly than carbon atoms and thus flatten the electron density distribution <1999PCA10009>.

Huisgen already favored an arylpentazene intermediate in the formation of arylpentazoles <1958CB531>. NMR spectroscopical monitoring of the reaction of *p*-chlorophenyldiazonium chloride with sodium azide at -85°C showed that the ratio of azide to pentazole at the start of the reaction is 10:1 and lowers to a final value of about 4:1 <1998J(P1)2243>. Thus the pentazole is formed late in this reaction. Prior to the appearance of the pentazole signals in the ^1H NMR, two proton resonances, which were assigned to the (*E,E*) and (*E,Z*) pentazene isomers, were detected. ^{15}N NMR signals were not detected due to the fast disappearance of the signals. Calculations were used for further elucidation of the mechanism of formation. While four possible pentazene isomers can be formed in the reaction of the diazonium ion with azide ions, only three minima were found for arylpentazenes at the MP2 level: (*Z,E*), the (*E,E*), and (*E,Z*) (Scheme 2). The (*Z,E*) isomer, which has a twisted structure with the azide out of the plane of the arylazo group, almost immediately loses N_2 with steric assistance from the aryl group to form the aryl azide. The barrier for the isomerization to the (*E,E*) isomer is higher than 60 kcal mol^{-1} . The (*E,E*) and (*E,Z*) isomers, which are similar in energy, are formed concomitantly. The isomerization barrier between these isomers was calculated to be around 8 kcal mol^{-1} and the activation energy for the formation of an arylpentazole was calculated to be around 6 kcal mol^{-1} . Integration of the ^1H NMR spectra shows that about 60% of the (*E,E*) and (*E,Z*) isomer mixture reacts to form the pentazole and 40% react to form the azide. The decomposition follows a different mechanism: here phenylpentazole is involved in a 1,3-dipolar cycloreversion with elimination of dinitrogen to form phenyl azide.

6.18.2.2 Polynitrogen Compounds Including the Pentazole Ring

Due to its comparatively high stability for a polynitrogen compound, the pentazole ring has been used as a building block for higher polynitrogen clusters. Generally, neutral polynitrogen clusters are more stable with an even number



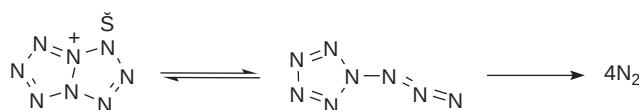
Scheme 2

of nitrogen atoms. Polynitrogen ions are more stable with an odd number of nitrogen atoms. Azidopentazole is the only pentazole compound that has a considerable decomposition barrier. All other compounds show only a very small decomposition barrier, which might prevent their experimental observation.

6.18.2.2.1 Azidopentazole and octaazapentalene

Several N_8 isomers have been investigated theoretically: azidopentazole <1995JPC2324, 1996CB1157, 1996IC7124, 2001JCC1334, 2001CPL565, 2003JMT135, 2004JMT153>, octaazacubane <1995JPC2324, 1996IC7124, 1997THA136>, octaazapentalene <1995JPC2324, 1996CB1157, 1996IC7124, 1997THA136, 2000IJQ311, 2001JCC1334>, diazidodiimide ($\text{N}_3-\text{N}=\text{N}-\text{N}_3$) <1996CB1157, 1996IC7124, 2001JCC1334>.

Azidopentazole is the global N_8 minimum structure and decomposes to four dinitrogen molecules ($\Delta E = 197.2 \text{ kcal mol}^{-1}$) with an activation barrier of $19.3 \text{ kcal mol}^{-1}$ at the CASSP2 level of theory (Scheme 3) <2000IJQ311>. At the same level of theory, octaazapentalene is $1.5 \text{ kcal mol}^{-1}$ higher in energy than azidopentazole and decomposes by rearrangement to azidopentazole with an activation energy of $8.8 \text{ kcal mol}^{-1}$ <2000IJQ311>. Octaazapentalene is not formed in the rearrangement of octaazacubane, as dissociation to N_6 and N_2 is energetically more favorable <1997THA136>.



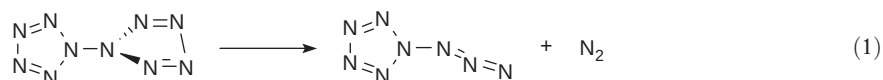
Scheme 3

A theoretical investigation of the reaction path connecting N_5^+ and N_3^- to azidopentazole yielded a maximum barrier height of $38.6 \text{ kcal mol}^{-1}$, indicating that this synthesis pathway is theoretically possible <2001JCC1334>. The violently explosive tetrazolyl azide <2003MI165, 2005MI17>, which is derived from azolypentazole by the exchange of one nitrogen with a carbon atom and the addition of a hydrogen atom, demonstrates the high energy content of pentazole azide and clearly highlights the hazards involved in an attempt to synthesize pentazole azide. It was shown that ^{15}N -labeled nitrogen atoms of the azide group of azidotetrazolate anion migrated into the tetrazole ring system after one month. A heptaazapentalene anion is considered to be involved in this reaction <1986CC959>.

Calculations indicate that azidopentazole can form charge-transfer complexes with aromatic ring systems. The complexation energy for the benzene charge-transfer complex is $-4.57 \text{ kcal mol}^{-1}$ and for a 1,3,5-trinitrobenzene charge-transfer complex the complexation energy is $-4.62 \text{ kcal mol}^{-1}$ <2004JMT153>. In the benzene complex azidopentazole acts as an electron acceptor, whereas in the charge-transfer complex with the electron acceptor trinitrobenzene azidopentazole acts as an electron donor.

6.18.2.2.2 Dipentazole

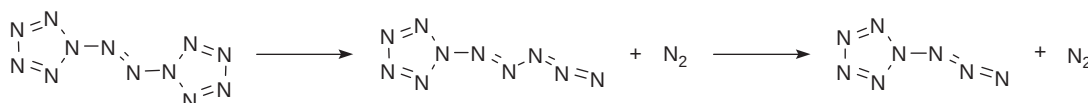
The global minimum structure for N_{10} species is dipentazole. It has a D_{2d} structure with two perpendicular pentazole ring systems <1992JA8302>. The activation energy for the decomposition to azidopentazole and dinitrogen is $5.2 \text{ kcal mol}^{-1}$ and the reaction energy of $-45.2 \text{ kcal mol}^{-1}$ at the CCSD(T) level of theory (Equation 1) <2003CEJ5511>.



At the quadratic configuration interaction with single and double excitations (QCISD) level, the bond energy of the bond connecting the two tetrazole ring systems is 93 kcal mol^{-1} , indicating a strong bond. The difference in energy between dipentazole and five dinitrogen molecules was calculated to be $286 \text{ kcal mol}^{-1}$ <1986CC959>. The reaction of a hypothetical N_4^{2+} dication with azide ions to form dipentazole is exothermic with $584 \text{ kcal mol}^{-1}$ <2001JA3308>. The series of azolypentazoles from cyclopentadienylpentazole to dipentazole shows a decreasing stability of the respective pentazoles. The difficulty of an azidopentazole synthesis is illustrated by the very unstable analogue tetrazolypentazole, which has a calculated barrier of $11.6 \text{ kcal mol}^{-1}$ for the decomposition and decomposes already at 223 K <2002IC906>, whereas imidazolypentazole, which has an activation energy of $13.5 \text{ kcal mol}^{-1}$, decomposes above 248 K . Therefore, dipentazole is not expected to be stable above 200 K .

6.18.2.2.3 Azopentazole

The azopentazole molecule consists of two pentazole rings linked by an azo group. It is favored by $20.7 \text{ kcal mol}^{-1}$ over an open-chain N_{12} molecule with a heat of formation of $315.9 \text{ kcal mol}^{-1}$ at the B3LYP level. The reaction of a hypothetical N_6^{2+} with two azide molecules to form azopentazole is exothermic with $503.7 \text{ kcal mol}^{-1}$ <2001JA3308>. The dinitrogen elimination from azopentazole leads to an N_{10} molecule consisting of a pentazole ring attached to a chain of five nitrogen atoms, which in turn decomposes to azidopentazole and dinitrogen. The activation energy for this decomposition is $8.1 \text{ kcal mol}^{-1}$ and the reaction energy is $-57.9 \text{ kcal mol}^{-1}$. The resulting N_{10} decomposes virtually without activation energy to azidopentazole and dinitrogen (Scheme 4) <2001JMT237>.



Scheme 4

6.18.2.2.4 Other polynitrogen compounds containing the pentazole ring system

The controversial history of pentazole continues in regard to the question whether larger polynitrogen compounds containing the pentazole ring system are stable. Calculations at lower levels of theory do not lead to accurate results; thus, many polynitrogen compounds reported as stable are not stable at higher levels of theory. The example of hexazine has shown <2001PCA4107> that the results of lower-level calculations have to be interpreted very carefully. An N_7 compound with a five-membered ring was reported to be stable with the Gaussian-3 method <2001CPL367>, but decomposes at the B3LYP level <2002CPL204>. No minima were found for N_9 compounds containing the pentazole ring system <2000THA67>. Two pentazole rings bound to a nitrogen atom with C_2 symmetry form the minimum energy N_{11} compound at the B3LYP level <2003CPL204>, which has a decomposition barrier of $5.6 \text{ kcal mol}^{-1}$. For N_{13} , N_{14} , and N_{15} , C_{2v} symmetric isomers with two pentazole rings connected by a chain of three, four, and five nitrogen atoms are the most stable isomers (Figure 1) <2003CPL204, 2004IJQ933>. The most stable N_{13}^+ isomer consists of two chains of four nitrogen atoms connected to a pentazole ring and is $6.3 \text{ kcal mol}^{-1}$ lower in energy than an open-chain structure, which has a decomposition barrier of $8.2 \text{ kcal mol}^{-1}$ to form N_{11}^+ and N_2 at the B3LYP level. The lowest-energy N_{13}^- was reported to contain a pentazole ring that is linked by two nitrogen atoms to a six-membered nitrogen ring. It is $6.8 \text{ kcal mol}^{-1}$ lower in energy than an open-chain N_{13}^- structure and has a decomposition barrier to N_{11}^- and N_2 of $31.5 \text{ kcal mol}^{-1}$ at the B3LYP level.

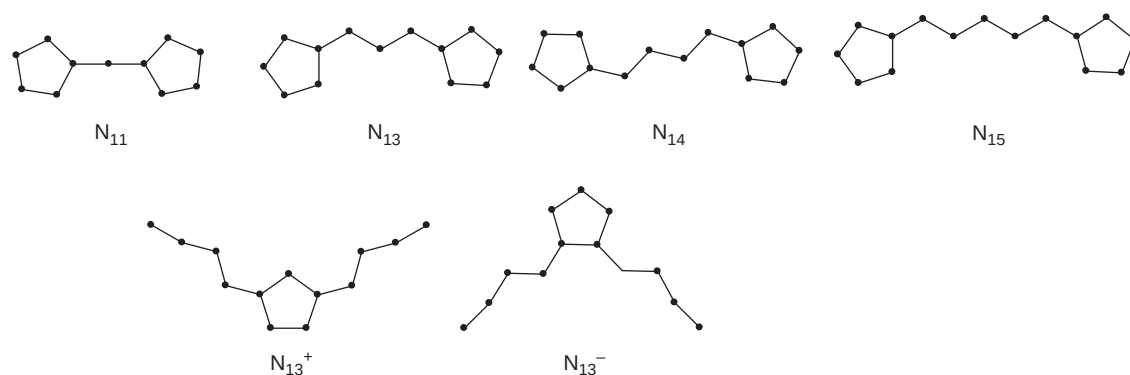


Figure 1 Reported minimum energy isomers for polynitrogen species containing the pentazole ring.

The extraordinary stability of anionic azide clusters like $\text{Sb}(\text{N}_3)_6^-$, $\text{Te}(\text{N}_3)_5^-$, $\text{Te}(\text{N}_3)_6^{2-}$, and $\text{Si}(\text{N}_3)_6^{2-}$ suggests a similar stability of pentazolid compounds. Investigation of $\text{A}(\text{N}_5)_n^q$ pentazolides at the B3LYP level (**Table 1**) showed that neutral and cationic pentazolides are not very stable, whereas the anionic complexes show higher activation energies than phenylpentazole, which can be handled at low temperatures <2003IC8241>. A nitrogen analogue of the fullerene C_{60} -containing alternating five- and six-membered nitrogen rings has also been reported <2000CPL262>.

Table 1 Activation energies for the decomposition of $\text{A}(\text{N}_5)_n^q$ pentazolides in kcal mol^{-1} at the B3LYP level <2003IC8241>

	E_{act}		E_{act}
$\text{B}(\text{N}_5)_2^-$	10.7	$\text{Al}(\text{N}_5)_4^-$	18.4
$\text{B}(\text{N}_5)_3$	8.9	$\text{Si}(\text{N}_5)_3^+$	2.0
$\text{B}(\text{N}_5)_4^-$	19.5	$\text{Si}(\text{N}_5)_4$	10.4
$\text{C}(\text{N}_5)_3^+$	1.0	$\text{Si}(\text{N}_5)_6^{2-}$	21.2
$\text{C}(\text{N}_5)_4$	11.4	$\text{P}(\text{N}_5)_3$	10.4
$(\text{N}_5-\text{N}-\text{N}_5)^-$	16.1	$\text{P}(\text{N}_5)_4^+$	2.1
$\text{N}(\text{N}_5)_3$	8.2	$\text{P}(\text{N}_5)_6^-$	16.3
$\text{N}(\text{N}_5)_4^+$	2.2	$\text{S}(\text{N}_5)_6$	8.6
$\text{Al}(\text{N}_5)_3$	12.1		

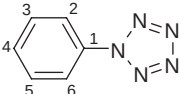
The activation energy data for these larger systems have to be viewed with a certain respect. Due to computational cost, only very few of the possible dissociation pathways have been investigated, so that there might be dissociation pathways that are lower in energy than the reported values. An example is the activation energy for the decomposition of octaazacubane, where the spin-forbidden dissociation into four N_2 molecules has a high activation barrier but a non-least-motion pathway reduces the dissociation barrier to less than 20 kcal mol^{-1} .

6.18.2.3 Pentazole Attached to Substituted Phenyl Rings

In almost all experimentally known pentazoles, the pentazole ring is attached to a substituted phenyl ring. Calculations using these well-known pentazoles were used to determine the mechanism of the formation and decomposition of the pentazoles (see Section 6.18.2.1). Here the theoretical data can be compared to experimental data for verification. As the calculated data for the known pentazole derivatives model their characteristics quite well, calculations can also be used to extrapolate the stability of yet unknown pentazole derivatives. The high sensitivity of these compounds makes calculations a fast and safe route for the evaluation of the properties of potential new compounds.

The calculated data at the B3LYP <2004PCA7463> and MP2 level <2003CEJ5511> (Table 2) show the same trend for the substituted arylpentazoles as the early experimental data by Huisgen and Ugi <1958CB531>. In general, electron-withdrawing substituents decrease the activation energy for the decomposition and make the arylpentazole less stable and electron-donating substituents increase the activation barrier for the decomposition and make the arylpentazoles more stable. The decomposition energies decrease with electron-donating substituents and increase with electron-withdrawing substituents.

Table 2 Calculated data for the decomposition of substituted phenylpentazoles at the B3LYP level in kcal mol⁻¹



	4	2	6	ΔE_{act}	$\Delta E_{\text{act}} (MP2)^a$	$\Delta G_{\text{act}} (solv.)$	$\Delta G_{\text{act}} (exp.)$	ΔE_{dec}	$\Delta E_{\text{dec}} (MP2)$	$\Delta G_{\text{dec}} (solv.)$
NO ₂	H	H	H	18.6	17.8	17.9	18.7	-37.4	-45.0	-49.9
HSO ₃	H	H	H	18.8		18.3		-37.0		-48.1
CN	H	H	H	19.0		18.5		-36.9		-47.6
N ₅	H	H	H	19.1		18.4		-36.8		-47.3
CF ₃	H	H	H	19.3		18.9		-36.2		-45.6
Cl	H	H	H	20.1		19.5	19.6	-35.0		-44.9
H	H	H	H	20.2	19.0	19.5	19.6	-34.7	-42.8	-45.6
CH ₃	H	H	H	20.7		20.8	20.0	-33.8		-43.2
OH	H	H	H	20.9		20.8	20.3	-33.3		-43.7
NH ₂	H	H	H	21.3		21.1		-32.4		-42.2
N(CH ₃) ₂	H	H	H	21.5	19.5	21.3	20.7	-31.8	-40.8	-41.3
SO ₃ ⁻	H	H	H	22.6		20.9		-28.9		-44.1
S ⁻	H	H	H	21.4 (ΔG)						
O ⁻	H	H	H	24.0		22.0	21.0	-20.0		-37.9
NH ₂	OH	H	H	22.6		20.1		-31.4		-43.4
NH ₂	OH	OH	H	23.9		18.6		-25.8		-41.6
NH ₂	O ⁻	H	H	19.9		19.5		-25.9		-39.6
NH ₂	CH ₃	H	H	19.6		19.1		-34.1		-44.2

^aSee <2003CEJ5511>.

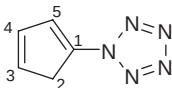
The solvation data were calculated for solvation in methanol <2004PCA7463>.

The *para*-substituted compounds are more stable than *ortho*- or *meta*-substituted compounds. Addition of one or two electron-donating OH-groups in *ortho*-position increases the activation barrier for the decomposition of *p*-aminophenylpentazole, but only slightly. The *p*-oxophenylpentazole anion has the highest activation barrier with 24.0 kcal mol⁻¹, which is still 3 kcal mol⁻¹ lower than the activation energy for the decomposition of the pentazole anion. The pentazol anion has the highest calculated activation barrier for the decomposition of a pentazole compound. The calculated data for the free activation enthalpy for the decomposition of arylpentazoles in solution agree well with values obtained from NMR measurements and range between 17.9 and 22.0 kcal mol⁻¹.

6.18.2.4 Pentazole Attached to Azoles

The first evidence for pentazoles not attached to substituted phenyl rings was provided for tetrazolypentazole, which decomposes at -50 °C <2002IC906>. A comprehensive computational study of all possible tetrazolypentazoles shows that, similar to substituted phenylpentazoles, pentazoles with electron-donating substituents are more stable than pentazoles with electron-withdrawing substituents. The energy for the decomposition reaction to form the corresponding azide and dinitrogen as well as the activation energy are loosely correlated to the number of nitrogen atoms of the substituent (Table 3). The decomposition energy increases for an increasing number of nitrogen atoms in the five-membered ring system and the activation energy decreases. Thus dipentazole, which contains only nitrogen atoms, is the least stable azolypentazole and a pyrrolylpentazole is the most stable azolypentazole. A cyclopentadienylpentazole has an even higher activation barrier for the decomposition than pyrrolylpentazole.

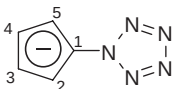
Table 3 Activation energies and decomposition energies for the decomposition of azolypentazoles at the CCSD(T)/cc-pvDZ / MP2(full)/6-311+G(d) level of theory in kcal mol⁻¹ <2003CEJ5511>



1	2	3	4	5	E_{act}	ΔE_{dec}
CH	CH	CH	CH	CH	16.3	-32.2
C	NH	CH	CH	CH	14.5	-35.0
C	CH	NH	CH	CH	16.5	-32.4
C	NH	N	CH	CH	14.0	-35.4
C	N	NH	CH	CH	14.4	-38.0
C	CH	NH	N	CH	15.9	-33.7
C	NH	CH	N	CH	13.8	-36.3
C	N	CH	NH	CH	13.5	-37.6
C	NH	CH	CH	NH	12.7	-36.3
C	NH	N	N	CH	13.4	-38.9
C	N	NH	N	CH	13.4	-37.9
C	N	N	NH	CH	12.8	-37.1
C	NH	N	CH	N	12.2	-43.3
C	N	NH	CH	N	12.7	-41.3
C	N	N	CH	NH	12.0	-38.1
C	NH	N	N	N	11.4	-40.5
C	N	NH	N	N	11.7	-42.6
N	N	N	N	N	5.2	-45.2

The azolypentazoles are acidic. Removal of a proton leads to the azolypentazoles which have lower decomposition energies and higher activation energies for the decomposition than the neutral compounds due to the higher electron densities in the pentazole ring. The order of stability is the same as for the neutral compounds (Table 4). An increasing number of nitrogen atoms in the azole leads to a decreasing activation barrier for the decomposition of the pentazole.

Table 4 Activation energies and decomposition energies for the decomposition of azolypentazoles at the CCSD(T)/ cc-pvDZ/MP2(full)/6-311+G(d) level of theory in kcal mol⁻¹ <2003CEJ5511>



1	2	3	4	5	E_{act}	ΔE_{dec}
C	CH	CH	CH	CH	20.6	-18.2
C	N	CH	CH	CH	18.6	-21.6
C	CH	N	CH	CH	20	-19.6
C	N	N	CH	CH	18.3	-23.5
C	CH	N	N	CH	19.5	-20.3
C	N	CH	N	CH	18	-22.4
C	N	CH	CH	N	18.3	-25.3
C	N	N	N	CH	17.7	-24.1
C	N	N	CH	N	17.9	-26.9
C	N	N	N	N	17.7	-28.1

Further substitution of pyrrolylpentazole with an electron-donating amino group (Figure 2) decreases the activation energy slightly by ca. 0.1–0.3 kcal mol⁻¹ compared to the unsubstituted compounds, proving that further substitution of the pyrrole ring system with electron-donating substituents does not significantly increase the stability of the pentazole compound.

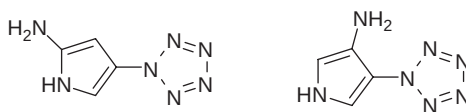


Figure 2 Further substitution of pyrrolylpentazole.

6.18.2.5 Pentazoles with Nonaromatic Substituents

Quantum-chemical calculation of the decomposition of methylpentazole has shown that methylpentazole is as stable as aromatic pentazole derivatives <2003CEJ5511>. In the reaction of ¹⁵N-labeled diazomethane with hydrazoic acid at -80°C , which leads to methyl azide, no methylpentazole intermediate has been detected <1932G716, 1958HCA1823>. Therefore, methylpentazole can only be synthesized by using a different route. Other substituents like CN, F, or NH₂ lead to pentazoles with lower activation barriers (Table 5) than the known arylpentazoles.

Table 5 Activation and decomposition energies in kcal mol⁻¹ for the decomposition of nonaromatic R-N₅ pentazoles to the corresponding R-N₃ azides and dinitrogen N₂

<i>R</i> -N ₅	<i>E</i> _{act}	ΔE_{dec}	Reference
F ^a	6.7	-46.7	CCSD(T) <2003CEJ5511>
CH ₃ ^a	17.4	-31.4	CCSD(T) <2003CEJ5511>
CN ^a	8.7	-47.8	CCSD(T) <2003CEJ5511>
NH ₂ ^b	12.6		MBPT(2) <1992JA8302>

The endothermic reaction of the pentazole anion N₅⁻ with HN₃ leads to an azidopentazole N₈H⁺ with a decomposition barrier of 26 kcal mol⁻¹ at the MP2 level. The proton of N₈H⁺ is attached to the nitrogen atom next to the azide chain on the pentazole ring <2002PCA1872>.

6.18.2.6 Complexation

The question of whether metal complexes of pentazoles similar to ferrocene are stable has been discussed since extended Hückel calculations predicted the stability of these complexes 20 years ago (Figure 3) <1985POL1721, 1988AIC171>.

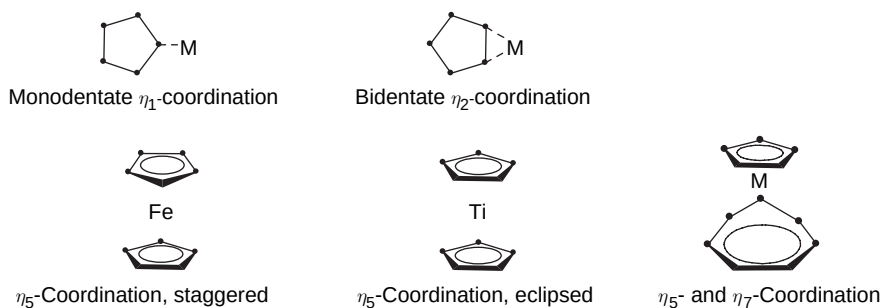


Figure 3 Different coordination modes in pentazole complexes.

In lithium pentazolate, lithium is coordinated to two nitrogen atoms. The dissociation to LiN₃ and N₂ has a calculated activation energy of 16.2 kcal mol⁻¹ <1992JA8302> at the MBPT(2) level and a calculated dissociation energy of -33.5 kcal mol⁻¹ <1993JPC8200>. The dissociation energy of lithium pentazolate to the respective ions was estimated to be 136.2 kcal mol⁻¹ <2004PCP895>. The global minimum structures of the Na⁺, K⁺ pentazolate, and the Mg²⁺,

Ca^{2+} dipentazolate salts were calculated to be bidentate structures at the MP2 level of theory, while the monodentate structures are 4.6, 5.5, 12.6, and 23.3 kcal mol⁻¹ higher in energy. For Zn^{2+} dipentazolate, a monodentate structure was found to be favored by 14.1 kcal mol⁻¹ over a bidentate structure. No minima were found for ferrocene-like structures for the Na^+ , K^+ , Mg^{2+} , Ca^{2+} , and Zn^{2+} pentazolate salts <2001J(P2)1679>. The alkaline earth metal MN_5^+ cations ($\text{M} = \text{Be}$ to Ba) also have minimum structures with a planar, bidentate coordination of the pentazole ring. The ferrocene-like pyramidal structures are also local minima on the potential energy surface but higher in energy than the bidentate structures and kinetically unstable with isomerization barriers from 0.9 to 4.5 kcal mol⁻¹ at the CCSD(T) level. The monodentate structures are transition states for the transfer of the metal around the pentazole ring. The dissociation barriers for the bidentate structure were found to be range from 1.2 to 18.7 kcal mol⁻¹ from beryllium to barium, showing an increase of kinetic stability from lighter to heavier atoms <2004IJQ485>.

The cyclopentadienyl ligand forms very stable complexes with transition metals where every carbon atom of the ligand is bound to the transition metal (η^5 -coordination). Thus an iron bispentazole $\text{Fe}(\eta^5\text{-N}_5)_2$, which is isoelectronic to ferrocene, might be a very stable compound. Analysis of vibrational modes has led to the conclusion that an iron bispentazole, which has a staggered conformation of the pentazole rings, might be more stable than the known phenylpentazole compounds <2001CEJ4155>. The dissociation leading to Fe^{2+} and two N_5^- has a calculated energy of 109 kcal mol⁻¹, only about 30 kcal mol⁻¹ less than for the decomposition of ferrocene. The metal–ligand bond is about half ionic and half covalent, the same as for ferrocene <2001JOM9>. More detailed studies of $\text{Fe}(\text{N}_5)_2$ and $\text{FeCl}(\text{N}_5)$ with the CI (configuration interaction) method show that bidentate structures, similar to the alkaline and alkaline earth metal pentazolates, are the most stable structures for both complexes. The spin state of these complexes also has to be considered. A quintet state is the lowest state for both $(\text{N}_5)_2$ and $\text{FeCl}(\text{N}_5)$ <2004CC1082>.

Optimization of the titanium bispentazole dianion $[\text{Ti}(\eta^5\text{-N}_5)_2]^{2-}$ led to a triplet structure with an eclipsed conformation of the pentazole rings <2003IC2504>. Complexes of the type $\eta^5\text{-N}_5\text{-metal-}\eta^7\text{-N}_7$ with the metals Ti, Zr, Hf, and Th are locally stable at the B3LYP level <2003PCA4690>. N_5ThN_7 , which has an activation energy of 15 kcal mol⁻¹ for the opening of an N–N bond of the N_7 ring and lies 177 kcal mol⁻¹ above $\text{Th} + 6\text{N}_2$, was reported to be the most stable. N_5HfN_7 has an activation energy of 21.5 kcal mol⁻¹ for the opening of an N–N bond of the N_7 ring and lies 132 kcal mol⁻¹ above $\text{Hf} + 6\text{N}_2$. While cationic N_5VN_7^+ is not stable, the anionic N_5ScN_7^- can be formed via a barrierless reaction from N_5^- and ScN_7 . Cationic $\text{Sc}(\text{N}_5)_2^{2+}$ also has a stable minimum <2001JA9700>. Interactions between nitrogen atoms in η^2 -pentazolato complexes with hydrocarbon ligands may be responsible for distortions of the structure <2005IC4894>.

6.18.2.7 Basicity

At the RHF level, the preferred site for protonation of pentazole is the N-3 position with a protonation energy of 191.6 kcal mol⁻¹. The protonation energy for the protonation at N-2 is 170.9 kcal mol⁻¹ <1986JPC5597>. At the more reliable B3LYP level of theory, the proton affinity of the pentazole anion was calculated to be 316.5 kcal mol⁻¹. In dimethyl sulfoxide (DMSO) solution, this corresponds to a pK_a of 2.1 <2005MP209>.

The energy difference between methylpentazole and its protonated form was calculated to be 201.5 kcal mol⁻¹, 20 kcal mol⁻¹ less than for 2-methyltetrazole. This corresponds to a pK_a of roughly –8.9, the highest in the methylazole series <1993MRC791>. Addition of chlorosulfonic acid with a pK_a of about –12 leads to the complete protonation of *p*-chlorophenylpentazole and *p*-methoxyphenylpentazole <2004TL1977>.

The gas phase basicities ΔG^0 of HN_5 for protonation at the N-2 and N-3 positions are 157.3 and 174.1 kcal mol⁻¹, respectively at the B3LYP level <1998IJM51>. The basicity of the azoles is correlated to the σ -ionization potential of the azoles <1991JPC7694>.

6.18.2.8 Aromaticity

Aromaticity is a useful concept that has not yet been defined quantitatively. Physically observable criteria for aromaticity are bond lengths between a single and a double bond, high stability and a ring current. Aromaticity indices for the structural, energetic, and magnetic criteria include similar information and show significant collinearity <2005PCA3711>. In early attempts, resonance energies <1966JCP759, 1975PAC767> and uniformity of the bond orders of the ring periphery <1985T1409> were used to quantify the aromaticity of pentazole. Later, more characteristics for aromaticity were included in the calculations <1990JPR885>. After introduction of the nucleus-independent chemical shift (NICS) <1996JA6317> at the ring center as an indicator for ring aromaticity, many reports tried to quantify the aromaticity <1998JOC2497, 2001T5715, 2003T1657, 2005MI83, 2004MI145> of the

azole series and the importance of the respective criteria for aromaticity <1998JOC5228, 2004JCP1670, 2002CEJ433>. The NICS value for the pentazole anion is -16.5 compared to a NICS value of -10 for benzene. Since the NICS value decreases with more aromatic systems, the pentazole anion is 'more aromatic' than benzene when studied by the NICS value <2003CCR93>.

All calculations agree that the 'aromatic stabilization' increases in the azole series from pyrrole to pentazole with an increasing number of nitrogen atoms. While no reason for this behavior is given, it is quite logical that the delocalization of π -electrons increases when the ring atoms have the same electronegativity. Thus the all-nitrogen pentazole ring has a higher electron delocalization than the other azoles even though the electronegativity of nitrogen is higher than the electronegativity of carbon.

6.18.3 Experimental Structural Methods

6.18.3.1 Molecular Dimensions

The pentazole ring system is planar (Table 6). The N–N bond distances in the pentazole system are roughly equal and about 132 pm in *p*-dimethylaminophenylpentazole <1983CC910> and in phenylpentazole <2002ZFA1933>. The N(1)–N(2) and N(3)–N(4) bonds are slightly longer, indicating an aromatic delocalization of the electrons. In the electron-poor *p*-sulfonatophenylpentazole, the bond distances show larger differences between 121 pm for the N(1)–N(2) and N(4)–N(5) bond, which is the range of an N–N double bond, and 143 pm for the N(3)–N(4) bond, which is in the range expected for an N–N single bond <2004ZFA787>. Calculations of electron-poor and electron-rich pentazole compounds do not show differences of the N–N bonds lengths in this magnitude <2003CEJ5511>.

Table 6 Geometrical parameters from X-ray diffraction of different pentazole compounds

<i>p</i> -R-C ₆ H ₄ -N ₅	R = NMe ₂	R = H	R = K(18crown6) ⁺ O ₃ S [−]
C–N(1) (pm)	143.8	143.7(5)	142.5(6)
N(1)–N(2) (pm)	132.1	132.2(1)	121.4(6)
N(2)–N(3) (pm)	130.9	130.8(2)	129.1(4)
N(3)–N(4) (pm)	134.7	133.7(6)	143.3(1)
N(4)–N(5) (pm)	130.9	130.7(8)	124.2(3)
N(1)–N(5) (pm)	132.1	132.2(1)	126.6(4)
N(1)–N(2)–N(3) (°)	105.1	105.3(1)	112.07(1)
N(2)–N(3)–N(4) (°)	108.8	108.9(1)	103.15(1)
N(3)–N(4)–N(5) (°)	108.8	109.0(1)	103.16(1)
N(4)–N(5)–N(1) (°)	105.1	105.3(1)	113.01(1)
N(2)–N(1)–N(5) (°)	112.1	111.5(1)	108.35(1)
Reference	1983CC910	2002ZFA1933	2004ZFA787

6.18.3.2 NMR Spectroscopy

The electron-withdrawing effect of pentazole is similar to a nitro group and the ¹H NMR shifts of nitrophenyl and pentazolylphenyl compounds are similar <2002ZFA1933>. The π -electron densities calculated by the Hückel molecular orbital (HMO) method show a linear correlation with ¹H, ¹³C, and ¹⁴N NMR chemical shifts in the azole series <1977IJB168>. The ¹⁵N NMR chemical shifts of the following compounds have been reported: cesium/tetramethyl ammonium (TMA) pentazolylphenolate ($\delta = -81.1$ (N-1), -29.7 (N-3/N-4), 1.9 (N-2/N-5)) <2002AGE3051>; *p*-dimethylaminophenylpentazole in CDCl₃ ($\delta = -80.0$ (N-1), -27.1 (N-2/N-5), $+4.9$ (N-3/N-4)) <1985AG515>; *p*-oxophenylpentazole in CD₃OD/D₂O ($\delta = -28.7$ (N-2/N-5), 3.6 (N-3/N-4)) <2002JOC1354>; *p*-hydroxyphenylpentazole ($\delta = -81.6$ (N-1), -27.6 (N-2/N-5), 4.2 (N-3/N-4)) <2002AGE3051, 2002JOC1354>, and tetrazolylpentazole in CH₃OH/Et₂O ($\delta = -29.7$ (N-2/N-5), 7.7 (N-3/N-4)) <2002IC906>. For *p*-chlorophenylpentazole in CD₃OD/D₂O ($\delta = -82.7$ (N-1), -25.6 (N-2/N-5), 4.6 (N-3/N-4)), *p*-methoxyphenylpentazole in CD₂Cl₂ ($\delta = -26.9$ (N-2/N-5), 4.9 (N-3/N-4)) the ¹⁵N shifts of the N-3 protonated compounds have also been measured by addition of chlorosulfonic acid to a solution of the compounds in a CD₂Cl₂/CD₃OD mixture (*p*-ClC₆H₄N₅ protonated at N-3: $\delta = -27.5$ (N-2/N-5), -55.1 (N-3/N-4), *p*-MeOC₆H₄N₅ protonated at N-3: $\delta = -27.9$ (N-2/N-5), -55.1 (N-3/N-4)) <2004TL1977>.

6.18.3.3 Mass Spectrometry

The molecular peak of *p*-NMe₂-C₆H₄-N₅ can be detected using electrospray ionization (ESI) <2002MI1>. For the successful generation and mass spectrometric detection of the pentazole anion, *p*-hydroxyphenylpentazole was employed. In this *para*-substituted phenylpentazole, the maximum negative charge is maximized and the C–N bond connecting the pentazole with the phenyl ring is weakened <2002AGE3051>. With negative-ion electrospray ionization mass spectrometry (ESI-MS), a [parent-H][−] peak at *m/z* 162 was detected and mass selected for further MS-MS studies. Addition of pyridine increased the concentration of the *p*-pentazolylphenolate anion. With low collision voltages the parent compound then stepwise loses two molecules of N₂ and a CO molecule, producing intense peaks at *m/z* 134 for the azidophenolate ion [OC₆H₄N₃][−], at *m/z* 106 for the deprotonated quinone-imine [O=C₆H₄=N][−], and at *m/z* 64 [C₅H₄][−]. With a high collision voltage of about −75 V a peak at *m/z* 72 was detected that represents the pentazole anion N₅[−], which loses N₂ to form the azide anion at *m/z* 42. ¹⁵N labeling of the *p*-pentazolylphenolate anion confirmed the decomposition pattern.

The pentazole anion can also be generated with laser desorption ionization (LDI) from *p*-dimethylaminophenylpentazole in a time-of-flight (TOF) mass spectrometer using a negative detection mode. Double ¹⁵N labeling of *p*-dimethylaminophenylpentazole confirmed the decomposition of the pentazole peak at *m/z* 72 to the azide ion by detection of peaks at the expected *m/z* ratios of 42, 43, and 44. Even at higher laser powers, no mixed anionic fragments due to cleavage of the nitrogen ring were detected, indicating that the reaction mechanism is highly selective toward the cleavage of the C–N bond linking the pentazole ring with the phenyl ring. The detected azide ions are almost exclusively formed by the decomposition of the pentazolate anion. A relatively high pentazolate:azide ratio in the mass spectrum indicates a high stability of the pentazolate anion.

The homolytical cleavage of the C–N bond linking the pentazole ring with the phenyl ring in *p*-dimethylaminophenylpentazole to form a pentazole radical is highly endothermic by 118 kcal mol^{−1} at the B3LYP level and thus unlikely. The cleavage of the C–N bond of the *p*-dimethylaminophenylpentazolate radical anion, which is likely formed by electron attachment to *p*-dimethylaminophenylpentazole, is only endothermic by 18 kcal mol^{−1} with an activation energy of 25 kcal mol^{−1} and a much more likely mechanism. The low pressure in the mass spectrometer probably even makes it an exergonic process. Competing decomposition reactions include the elimination of N₂ from both *p*-dimethylaminophenylpentazole and its radical anion to form the corresponding azides. Both are exothermic by about 35 kcal mol^{−1} and have activation energies of about 20 kcal mol^{−1}. C–N bond cleavage should therefore only be observed in small amounts. The experimental observation of the C–N bond cleavage suggests that other processes like excitation of special vibrational modes are also involved <2003CPL539>. Complete active space self-consistent field (CASSCF) and CISD calculations show that the barrier for C–N bond cleavage in the closed shell *p*-pentazolylphenolate is much higher than the barrier for N₂ extrusion. Here the reaction involves an electron transfer to the pentazole ring, while in the C–N bond cleavage of *p*-dimethylaminophenylpentazole no electron transfer is necessary. For the open shell radical anion of *p*-dimethylaminophenylpentazole, the reaction barriers for C–N bond breaking and N₂ extrusion are similar. The yet unknown HN₅[−] radical anion is expected to show a similar reaction pattern <2004PCA11715>.

6.18.3.4 IR and UV Spectra

The ultraviolet (UV) spectra of several substituted phenylpentazoles measured by Ugi <1958CB2324> were reported to be similar to the UV spectra of the corresponding tetrazoles. The pentazole substituent behaves similar to a nitro group with strong interactions between electron donation *p*-substituents and the pentazole ring.

Raman and infrared (IR) spectra of pentazoles are difficult to measure. The main problem is the separation of the pentazole from impurities of the azide decomposition products that are almost impossible to remove quantitatively in the synthesis and can be formed even during the measurement at low temperatures. In Table 7, an overview is given over the principal vibration modes of the pentazole anion at the CCSD level of theory.

6.18.4 Decomposition Temperatures and Decomposition Rates

The onset of decomposition of arylpentazoles is difficult to determine. Even freshly prepared samples can contain impurities of the corresponding azides, which increase during heating. Therefore the decomposition temperature cannot be determined exactly. The most stable pentazoles include *p*-dimethylaminophenylpentazole and the *p*-oxophenylpentazole anion (Table 8). The experimentally determined activation energies are not in total agreement with the observed stabilities due to different measurement methods.

Table 7 Vibrational frequencies of the pentazole anion at the CCSD level of theory

Symmetry	Mode description	ν^a (cm ⁻¹)	ν^b (cm ⁻¹)	IR intensity ^b	Raman intensity ^b	Depolarization ratio ^b
E'' ₂	Bend	739	782.7	0	0	0.75
E' ₂	Bend	1001	1059.5	0	3.6	0.75
E' ₂	NN stretch	1078	1124.2	0	2.0	0.75
A' ₁	NN stretch	1141	1222.4	0	47.8	0.04
E' ₁	NN stretch	1202	1286.1	27.2	0	0.75

^a2004JA834.

^b1999CPL381.

Table 8 Decomposition temperatures and experimentally determined activation enthalpies for the decomposition of substituted phenyl azides

R-N ₅	T _{dec} (°C)	E _{act} (exp.) (kcal mol ⁻¹)	References
Phenyl	-5	21.3	1958CB2324, 1956AG705
<i>p</i> -Tolyl	+2		1958CB2324
<i>p</i> -Chlorophenyl	+8	20.8	1958CB2324, 1998J(P1)2243
<i>p</i> -Methoxyphenyl	+13		1958CB2324
<i>p</i> -Ethoxyphenyl	+26	ΔH _{dec} (exp) = 5.4	1958CB2324
<i>p</i> -Dimethylaminophenyl	+50		1958CB2324
K[18-crown-6] ⁺ <i>p</i> -O ₃ S-phenyl	-30	23.5	2004ZFA787
<i>p</i> -Hydroxyphenyl		ΔG _{act} = 19.7	2002JOC1354
<i>p</i> -O ⁻ -Phenyl		ΔG _{act} (CD ₃ OD) = 20.6	2002JOC1354
		ΔG _{act} (CD ₂ Cl ₂) = 20.6	

The solvent has a strong influence on the rate of decomposition of the arylpentazoles (Table 9). Solvents with lower polarity increase the rate of decomposition. This suggests that the transition state for the decomposition is less polar than the ground state of the pentazole, which was confirmed by quantum-chemical calculations <2003CEJ5511>. The decomposition of phenylpentazoles is not influenced by acids or bases <1957CB2914>. The rate of nitrogen evolution is also independent on the concentration of azide ions at -40 °C.

Table 9 Reaction constants for the decomposition of phenylpentazole in different solvents <1958CB2324>

PhN ₅	k (dec) (×10 ⁴ sec ⁻¹)
<i>n</i> -Hexane	45.2(6)
CCl ₄	34.0(9)
<i>n</i> -Butanol	16.9(2)
Toluene	12.4(3)
THF	14.4(1)
Methanol	9.8(2)
	<i>t</i> _{1/2} (0 °C) = 13 min
Chloroform	8.9(2)
Acetone	7.7(3)
Acetonitrile	4.06(3)
Formic acid	2.3(1)
CCl ₄ /CH ₃ CN	
80:20	15.1(2)
60:40	11.2(1)
40:60	8.0(1)
20:80	7.1(2)
Methanol/water 50:50	5.6(1)
Acetic acid/water 75:25	5.8(1)

Some of the rate constants were determined by monitoring the ^1H NMR spectra of the respective pentazole derivatives in a 1:1 mixture of $\text{CD}_2\text{Cl}_2/\text{CD}_3\text{OD}$; the other rate constants were determined by observation of the nitrogen evolution during the decomposition. The values correspond to the Hammett equation with ρ values of +0.87 <2002JOC1354>, +1.01 <1958CB531>, to +1.25 ($\rho=0.989$) <1996J(P2)801>. The evaluation of the data for *p*-chlorophenylpentazole leads to an activation energy of $21.5 \text{ kcal mol}^{-1}$, a reaction enthalpy ΔH of $20.9 \text{ kcal mol}^{-1}$, and a reaction entropy difference ΔS of 19.9 J K^{-1} .

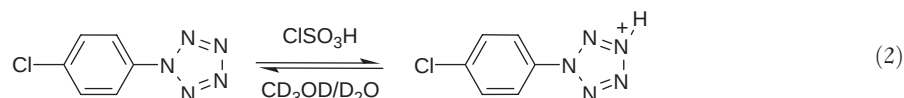
The decomposition rates in methanol in Table 10 also show the influence of the position of the electron-withdrawing substituent. The decomposition of *m*- NO_2 -phenylpentazole is slower than the decomposition of the *para*-substituted compound. Otherwise, substitution in *ortho*- or *meta*-position increases the decomposition rate compared to the *para*-substituted compounds, in case of the *ortho*-substitution drastically. The dipentazole compound 1,4-bis(*p*-pentazolylphenyl)butane has a decomposition constant of $12.7(1) \cdot 10^{-4} \text{ s}^{-1}$ and a half-life of 9.1(1) min in CDCl_3 solution at 0°C . The resulting decomposition product with one pentazole ring and an azide group decomposes with a reaction constant of $5.40(1) \cdot 10^{-4} \text{ s}^{-1}$ and a half-life of 21.4 min to the diazide and dinitrogen.

Table 10 Decomposition constants of substituted phenylpentazoles in methanol at 0°C <1958CB531>

$R\text{-C}_6\text{H}_4\text{-N}_5$	$k \text{ (dec)} (\times 10^4 \text{ sec}^{-1})$
<i>p</i> - Me_2N -	51(3)
<i>p</i> - MeO -	2.1
<i>p</i> - Me -	2.7
<i>m</i> - Me -	7.6(0.5)
<i>o</i> - Me -	31(3)
<i>p</i> - H -	8.4(2)
<i>p</i> - Cl -	9.2
<i>p</i> - Cl - (263 K)	4.3
<i>p</i> - Cl - (270 K)	12.0
<i>m</i> - Cl -	23(1.5)
<i>o</i> - Cl -	86(7)
<i>p</i> - OH	3.2(1)
<i>p</i> - O^-	0.91(3)
<i>p</i> - NO_2 -	59(5)
<i>m</i> - NO_2 -	36(4)
<i>o</i> - NO_2 -	92(9)
$\text{K}[18\text{-crown-6}] \text{ } p\text{-O}_3\text{S-}$	
CD_3OD	
-45°C	$t_{1/2} = 850 \text{ h}$
-20°C	0.357(8)
	$t_{1/2} = 5.4 \text{ h}$
0°C	10.5(5)
	$t_{1/2} = 11.0 \text{ min}$

6.18.5 Reactivity of Fully Conjugated Rings

Pentazoles are extremely sensitive to light. Light exposition leads to quick decomposition or even explosion <2002MI1>. Arylpentazoles are very basic compounds; the ^{15}N NMR spectra of *p*-chlorophenylpentazole in a 1:1 mixture of trifluoroacetic acid and trifluoroacetic anhydride only show a low percentage of protonation at the N-3 nitrogen atom in β -position to the pyrrole-type nitrogen atom. In chlorosulfonic acid with a $\text{p}K_a$ of about -12 the pentazole is fully protonated. Thus a $\text{p}K_a$ of about -9 is estimated experimentally. Chlorosulfonic acid also fully protonates *p*-methoxyphenylpentazole <2004TL1977>. The protonation is reversible by dilution or neutralization of the solution (Equation 2).



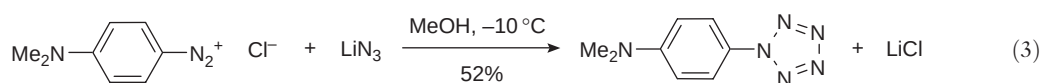
The addition of butyllithium to a solution of phenylpentazole in tetrahydrofuran (THF) at -30°C leads to a deep red solution without gas evolution. The red solution is stable for more than 25 days at -30°C and is supposed to contain a pentaazadiene anion: $\text{Li}^+ [\text{p-C}_6\text{H}_4\text{-N=N=N-N=N-C}_6\text{H}_5]^-$. After leaving the solution to warm up to room temperature, *N,N*-dibutyl-*N'*-phenylhydrazine and lithium azide are formed. The hydrazine can be separated by extraction with an ether/petrol ether mixture <2004ZN351>. A cleavage of the C–N bond between the phenyl and the pentazole ring was not observed. A report of the successful cleavage of the C–N bond in *p*-dimethylaminophenylpentazole with ceric(IV) ammonium nitrate (CAN) and the NMR spectroscopic identification of a zinc pentazolate salt in solution <2003CC1016> was later shown to be misinterpreted <2005CC1607>, while earlier attempts to cleave the carbon–nitrogen bond by ozonolysis and reduction with a sodium/ammonia mixture had failed.

6.18.6 Ring Syntheses from Acyclic Compounds

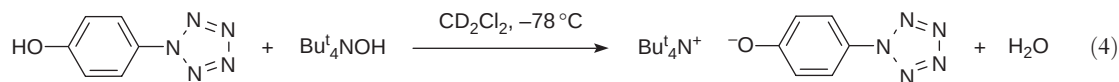
Great care has to be taken in the preparation of pentazole compounds. Pentazoles are extremely sensitive toward shock, friction, temperature, light, and electrostatic impact. This is true even for the most stable pentazoles, while less stable pentazoles like *p*-nitrophenylpentazole exploded at every attempt at their isolation. Several explosions of pentazoles without apparent reason have also been reported, especially for large-scale preparations. Thus appropriate safety measures (protection of face, ears, body, and hands) have to be taken at all times during these reactions. The smallest possible amounts should be used <1994HOU796>.

The first phenylpentazoles were synthesized from the reaction of the respective phenyldiazonium salts with sodium or lithium azide at temperatures lower than -30°C in methanol/petrol ether solvent mixture. Lithium azide is the better reagent due to its higher solubility <1957CB2914>. As the diazonium compounds are very sensitive, it is often easier to prepare them *in situ*. Solubility problems may be encountered with a sodium nitrite/HCl mixture; therefore, isoamyl nitrite is advantageous for small-scale reactions <2003CEJ5511>. Pentazoles are soluble in 1:1 mixtures of methanol and dichloromethane <1975MI137>. Often the arylpentazole crystallizes and can be filtered off. The isolated arylpentazoles contain impurities of the respective aryl azides of about 10%. They are very sensitive and can spontaneously lose nitrogen. Therefore, special care has to be taken in their handling (small scale, face shield, leather gloves, protective clothing, blast shields, ear protection). Most arylpentazoles, either in solution or in the crystalline state, are only stable below -20°C . Pentazoles stable at room temperature include *p*-dimethylaminophenylpentazole, which decomposes at about 50°C , *p*-hydroxyphenylpentazole, and its anion.

The preparation of *p*-dimethylaminophenylpentazole can be used as example for the isolation of a pentazole compound (Equation 3) <1994HOU796>. In this procedure, 550 mg (3.0 mmol) *p*-dimethylaminobenzene diazonium chloride in 10 ml methanol at -10°C were reacted with a 1 M solution of lithium azide in methanol. The pentazole immediately crystallizes as pale yellow plates. After filtration and washing with a small amount of methanol, 294.8 mg (52%) 1-(4-dimethylaminophenyl)pentazole were isolated.

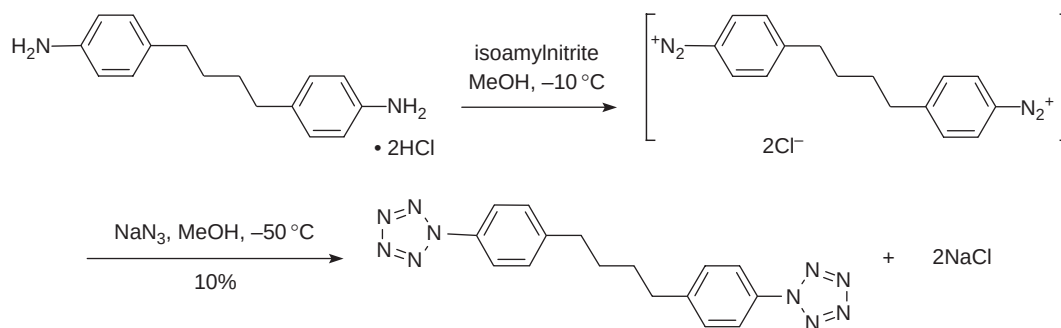


The *p*-pentazolyphenolate anion could not be prepared by direct synthesis from *p*-diazobenzoquinone and was obtained by the reaction of *p*-hydroxyphenylpentazole with tetrabutylammonium hydroxide (Equation 4) <2002JOC1354>. Both *p*-hydroxyphenylpentazole and the *p*-pentazolyphenolate anion are more stable in mixtures of CD_2Cl_2 and CD_3CN than in mixtures containing CD_3OD <2002AGE3051>. Substituents in *meta*- and *ortho*-position favor the decomposition of the pentazoles. No *ortho*- or *meta*-substituted arylpentazoles were isolated so far.

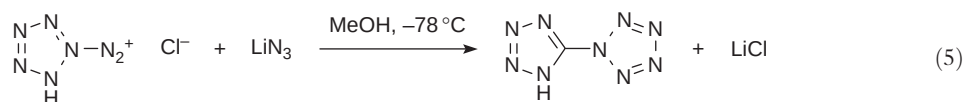


1,4-Bis(*p*-pentazolyphenyl)butane was synthesized as shown in Scheme 5 <2004ZNB716>. NMR spectroscopic investigation showed a product mixture of dipentazole to azidopentazole to diazide of 10:30:60.

For the synthesis of tetrazolypentazole (Equation 5), a solution of lithium azide in methanol at -78°C is slowly added to an ethereal solution of tetrazolediazonium chloride at -78°C . Tetrazolypentazole was detected NMR-spectroscopically in the reaction mixtures up to temperatures of -50°C <2002IC906>. Utmost care has to be taken for this reaction as tetrazolediazonium chloride is not very soluble and can form a second phase in the reaction mixture, which will almost inevitably lead to an explosion.



Scheme 5



6.18.7 Important Compounds and Applications

In recent years, pentazole compounds were investigated more closely than at any time since their first synthesis, especially due to the progress in computational chemistry. Due to these new insights, several new classes of pentazole compounds have been identified and synthesized.

The reason for the renewed interest in pentazoles is the need for environmentally friendly materials that can store huge amounts of energy. For use as energy storage materials the activation energy for the decomposition of pentazole compounds has to be increased significantly to ensure safe handling during use.

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